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Ultra-sensitive tumor-informed ctDNA assay predicts survival in advanced melanoma patients treated with immune checkpoint inhibition

Laura Keller[1], Isabel Heidrich[1], Julian Kött[1], Charles W. Abbott[2], Sean M. Boyle[2], Jason Pugh[2], Richard O.Chen[2], Glenn Geidel[1], Ronald Simon[1], Stefan Schneider[1], Christoffer Gebhardt[1], Klaus Pantel[1]

1. Institute for Tumor Biology | University Cancer Center Hamburg | University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246, Hamburg, Germany
2. Personalis, Inc. | 6600 Dumbarton Cir, Fremont, CA 94555

Contact:
charles.abbott@personalis.com
sean.boyle@personalis.com
pantel@uke.de

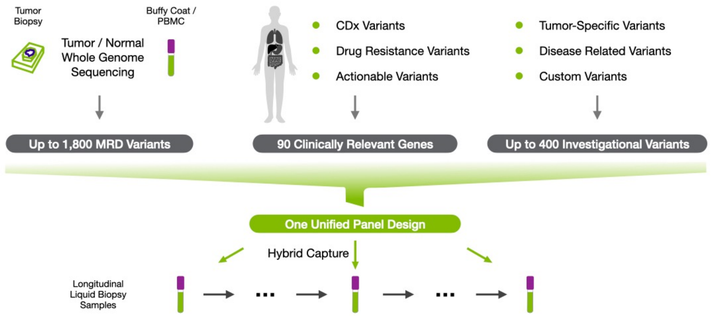
BACKGROUND

Immune checkpoint inhibition (ICI) elicits clinical benefit in a subset of cancer patients[1,2] and monitoring of circulating tumor DNA (ctDNA) in peripheral blood might improve our ability to predict responses or resistance to immunotherapy earlier than imaging[3,4]. In this poster, we present results from long-term monitoring of ctDNA in a cohort of melanoma patients, using a novel tumor-informed ctDNA platform, and correlate the findings with the clinical outcome of each patient.

METHODS

Ultra-sensitive ctDNA quantification with NeXT Personal

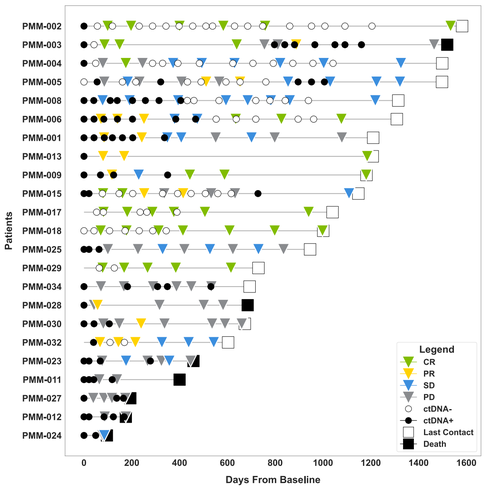
We analyzed 150 plasma samples from a preliminary group of 23 advanced melanoma patients was collected at ICI treatment cycles and retrospectively profiled using NeXT Personal® in this research study. NeXT Personal is a tumor-informed liquid biopsy assay that leverages whole-genome sequencing of tumor/normal samples to generate a personalized liquid biopsy panel for each patient consisting of up to 1,800 selected somatic variants, enabling ultra-sensitive minimal residual disease (MRD) detection down to 1-3 parts per million (PPM). Each bespoke panel also includes a tumor-agnostic set of 90 clinically relevant and resistance genes for detecting important cancer mutations that may emerge under therapeutic pressure. NeXT Personal results were compared with imaging assessments and outcomes for each patient.



RESULTS

Patient demographics

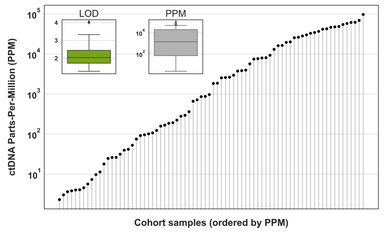
This study recruited advanced-stage melanoma (III-IV) patients receiving ICI treatment for up to 41 cycles (median 10 cycles). Median age at the start of treatment was 55, and 65% (15/23) of patients were male. Patient responses were defined using standard RECIST criteria, and surveilled for a maximum of 1582 days following treatment, with a median follow up of 1183 days. Overall, 70% of the cohort survived (16/23), 40% (9/23) attained progression-free survival by the end of observation, and 10 patients attained complete response to therapy.



Highly sensitive ctDNA detection down to parts-per-million resolution

We demonstrated a broad dynamic range of ctDNA detections, from ~100,000 PPM down to 2.3 PPM, with a median limit of detection (LOD) of 1.97 PPM (A). The high sensitivity of the assay was reflected in a significant number of positive detections at low PPM levels, with 29% (22/76) of positive detections occurring below 100 PPM and 24% (18/76) occurring below 50 PPM. We also observed strong concordance with imaging findings, with 100% of ctDNA$^+$ detections presenting correlated findings via RECIST which confirmed presence of tumor even at the lowest PPM levels. Similarly, 100% (39/39 timepoints) of complete responses (CR) assessed via RECIST were ctDNA negative for all corresponding plasma timepoints (B; example patient time course and RECIST shown). Excluding patients with previous immunotherapy immediately prior to enrollment, 94% (16/17) of baseline samples were ctDNA$^+$ including all patients who progressed on treatment.

A



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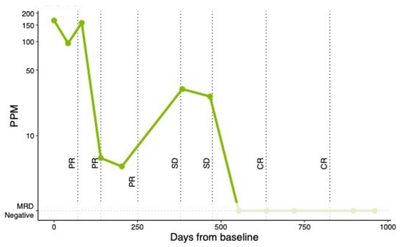
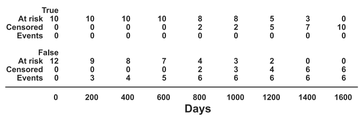


ctDNA clearance predicts survival

We assessed the ability of NeXT Personal ctDNA detection status to predict patient survival. Attaining ctDNA clearance (ctDNA$^-$) during the study was significantly associated with increased duration of overall survival OS (C; Kaplan-Meier (KM) log-rank p value = 0.01).



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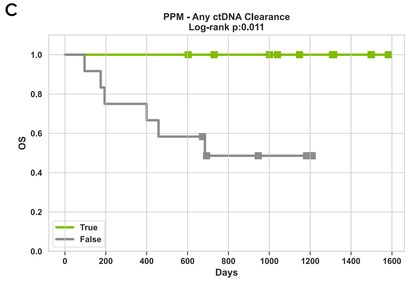
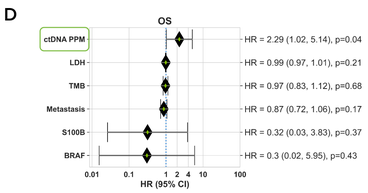


Cox models establish prognostic value of ctDNA for OS and PFS

Time-varying multivariable cox models including ctDNA level, and baseline clinical and tumor covariates (serum S100B, serum LDH, tumor mutational burden, extent of metastasis, and protein-coding BRAF mutations) were significant for OS (D; log-likelihood test p-value = 0.03, Concordance 0.93 +/- 0.087) and PFS (Fig 2; log-likelihood test p-value = 0.03, Concordance 0.85 +/- 0.066). ctDNA level was an independently negative prognostic factor, yielding a hazard ratio (HR) of 2.29 for OS (95% CI 1.02-5.14, Wald test p value = 0.04), and 1.95 for PFS (E; 95% CI 1.05-3.62, Wald test p value = 0.04). In both OS and PFS models, ctDNA provided the only significant independent hazard among all covariates investigated in this patient set.

D



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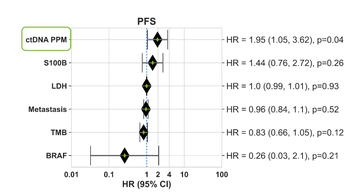
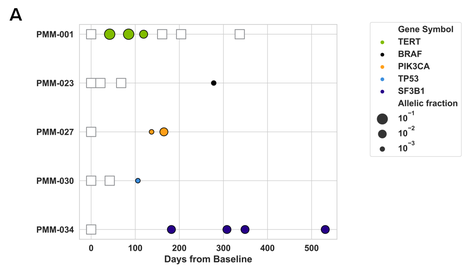


Detection of evolving clinically actionable variants and tumor-specific variants changing under therapeutic pressure

At each plasma timepoint we also looked for clinically actionable variants that may be evolving under therapeutic pressure. Here, analysis showed dynamic variant allele frequency changes in 21 variants including therapeutic targets such as BRAF V600E. In five patients, a clinically actionable variant was detected on-treatment, but not at baseline, suggesting potential tumor evolution in response to treatment (A, hollow squares represent additional sampling timepoints with no signal detection, and filled circles indicate detection with a p value <= 10^{-6}). We also assessed variants detected in the primary tumor, and evaluated how they changed in response to treatment (B; example of the 20 most dynamic variants among 50 detected in an example patient case). Note the dynamic shifts of variant subpopulations in the first 140 days.

A



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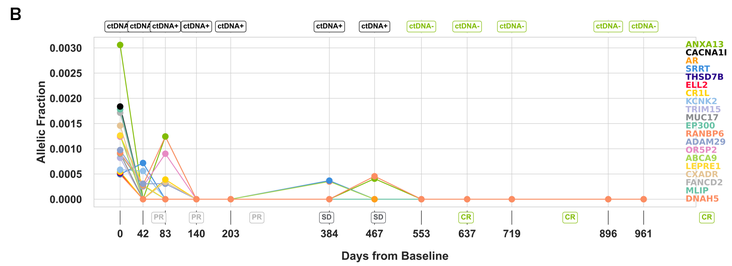

CONCLUSIONS

We demonstrate that low ctDNA levels are commonly observed, even in late stage disease, with positive ctDNA detections in this study occurring as low as 2.3 PPM. Detections down to low PPM levels correlate strongly with imaging and RECIST-derived classifications of response. Our results further suggest that without the ultra-sensitive ctDNA detection achieved using NeXT Personal, patient MRD status would have been misclassified at a significant number of time points in this cohort. Sensitive detection of ctDNA down to these low levels is critical for accurate prediction of patient outcomes, including overall survival. Additionally, we demonstrate the potential for future clinical use of a unique aspect of our tumor-informed MRD platform which identifies and tracks clinically actionable variants arising or changing in response to therapeutic pressure. The results presented here suggest the importance of ultra-sensitive ctDNA-based therapy monitoring which will be further validated as we expand the patient set.

References:

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3. Lee RJ *et al.* Circulating tumor DNA predicts survival in patients with resected high-risk stage II/III melanoma. Ann Oncol. 2018 Feb 1;29(2):490-496.
4. Marsavela G et al. Circulating Tumor DNA Predicts Outcome from First-, but not Second-line Treatment and Identifies Melanoma Patients Who May Benefit from Combination Immunotherapy. Clin Cancer Res. 2020 Nov 15;26(22):5926-5933.