Contact:

Association of ultra-sensitive ctDNA assay to identify actionable variants and response to immune checkpoint inhibitor (ICI) therapy in metastatic melanoma





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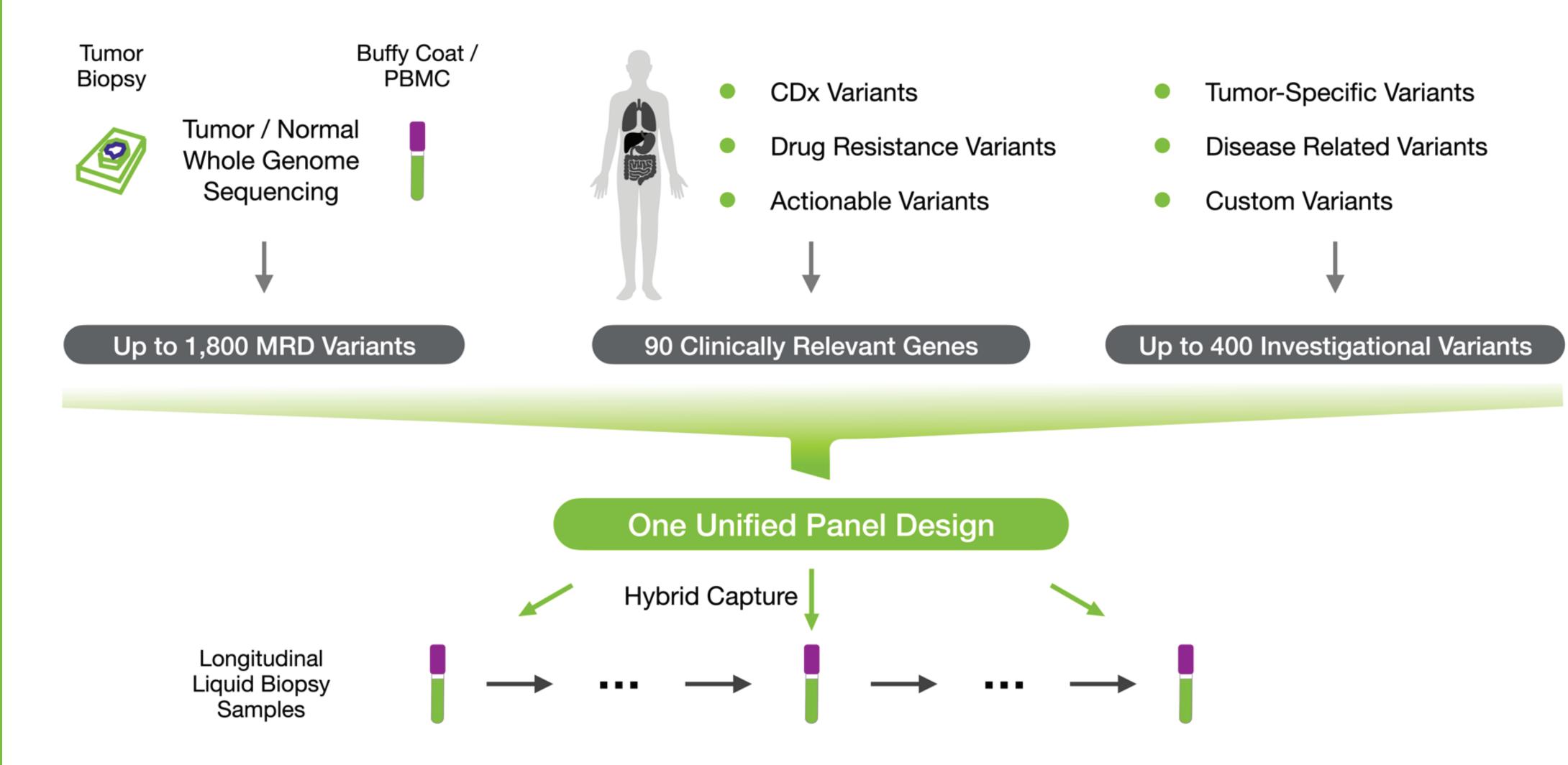
BACKGROUND

Detection of tumor burden via circulating tumor DNA (ctDNA) can identify therapeutic response or resistance months in advance, and monitoring clinically actionable variant dynamics may be important for guiding treatment. Despite this, adoption has been slow due to the reduced sensitivity and reproducibility of current approaches. Here, we profile melanoma patients receiving ICI over several years using an ultra-sensitive tumor-informed ctDNA platform, and correlate the findings with clinical outcome.

METHODS

Ultra-sensitive ctDNA quantification with NeXT Personal

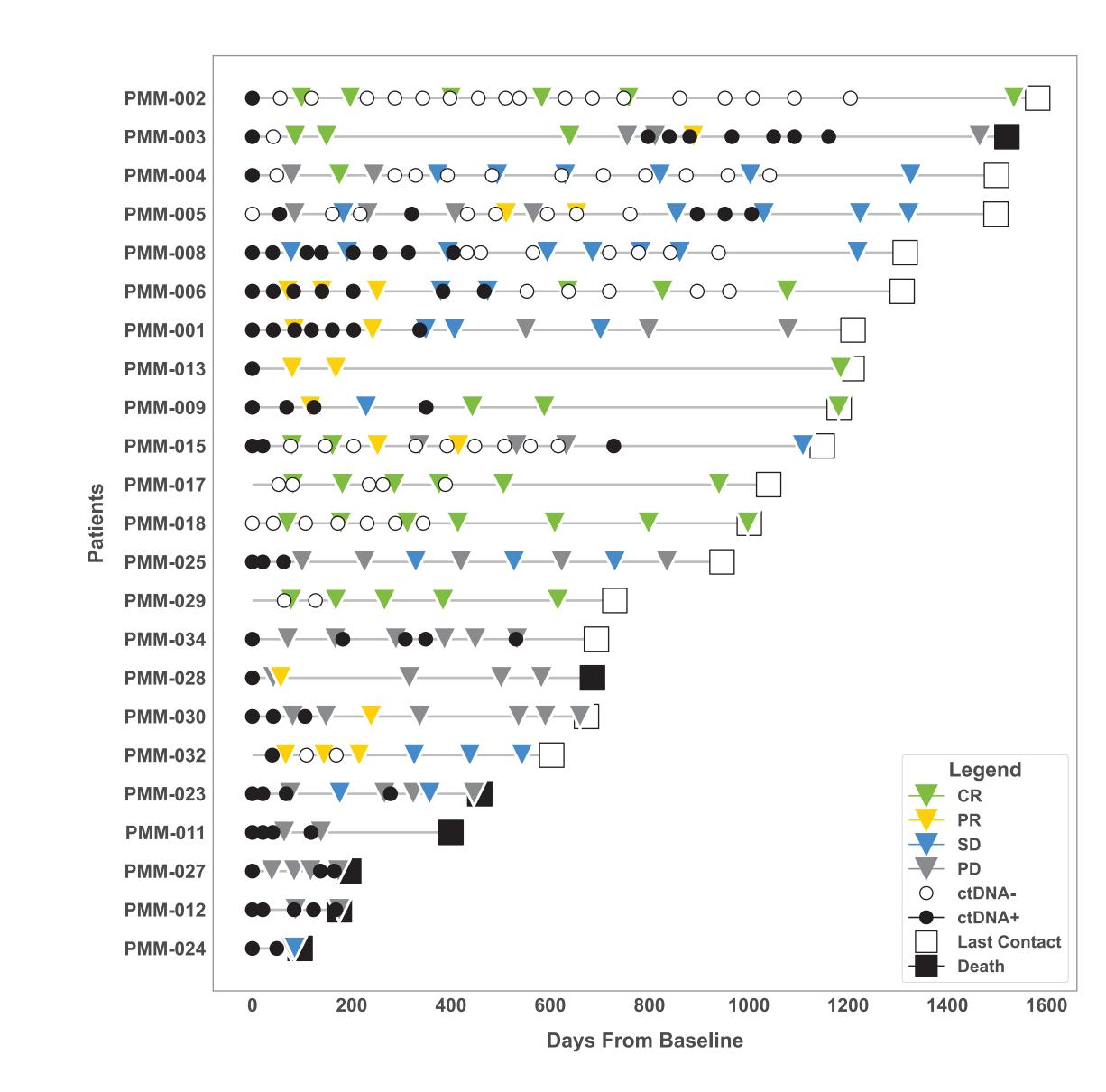
Over 150 plasma samples from 23 advanced melanoma patients were collected during ICI treatment (up to 1,200 days) and profiled with NeXT Personal®, a tumor-informed ctDNA assay that leverages whole-genome sequencing of tumor/normal samples to generate personalized liquid biopsy panels. Each bespoke panel consists of up to 1,800 selected variants which enable ultra-sensitive ctDNA detection (molecular / minimal residual disease; MRD variants), and a fixed set of 90 known clinically actionable and resistance loci for detection of variants emerging under therapeutic pressure. ctDNA signal and variant dynamics were then correlated with RECIST assessments and outcome.



RESULTS

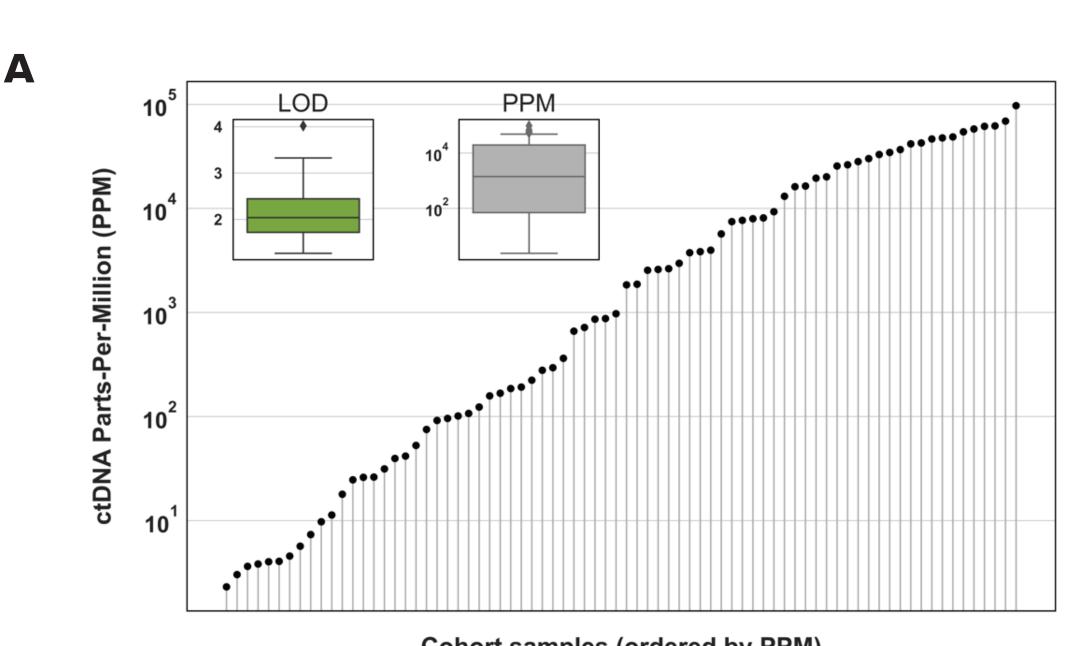
Patient demographics

Patients with advanced-stage melanoma (III-IV) receiving ICI treatment for up to 41 cycles (median 10 cycles) were enrolled in this study. The majority (15/23) of the patients were male, with a median age of 55 at the beginning of treatment. During treatment, patients were monitored for up to 1582 days using standard RECIST criteria, with a median follow-up of 1183 days. Overall, the cohort had a 70% survival rate (16/23), with 40% (9/23) attaining progression-free survival by the end of observation. Complete responses were attained by 10 patients.

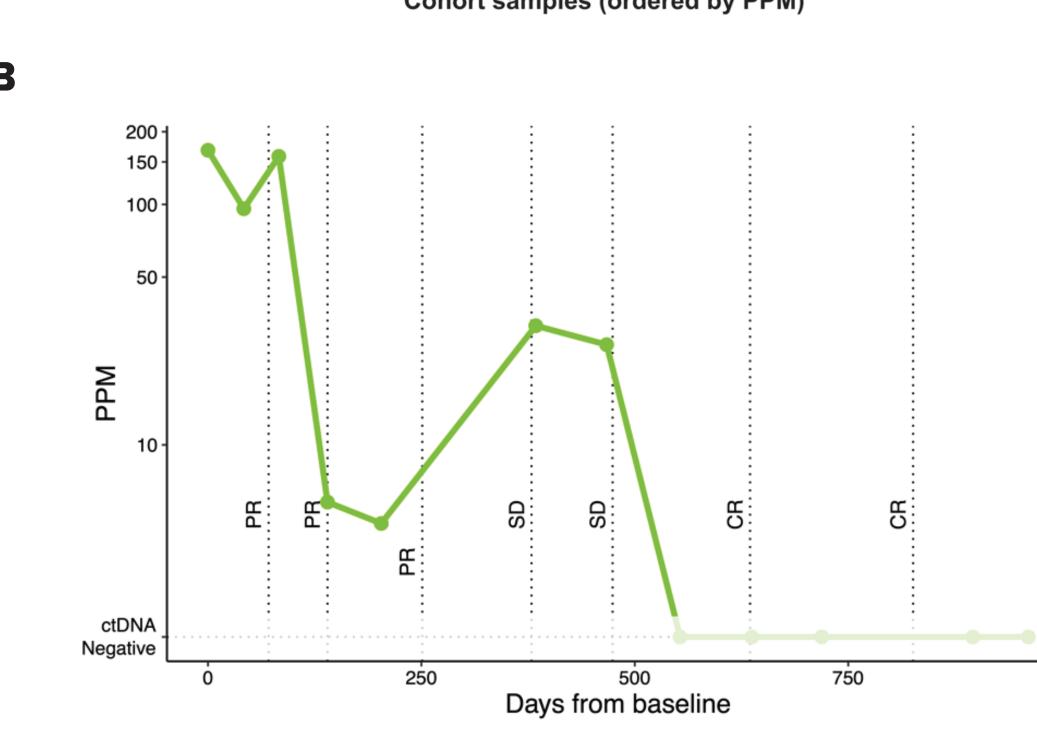


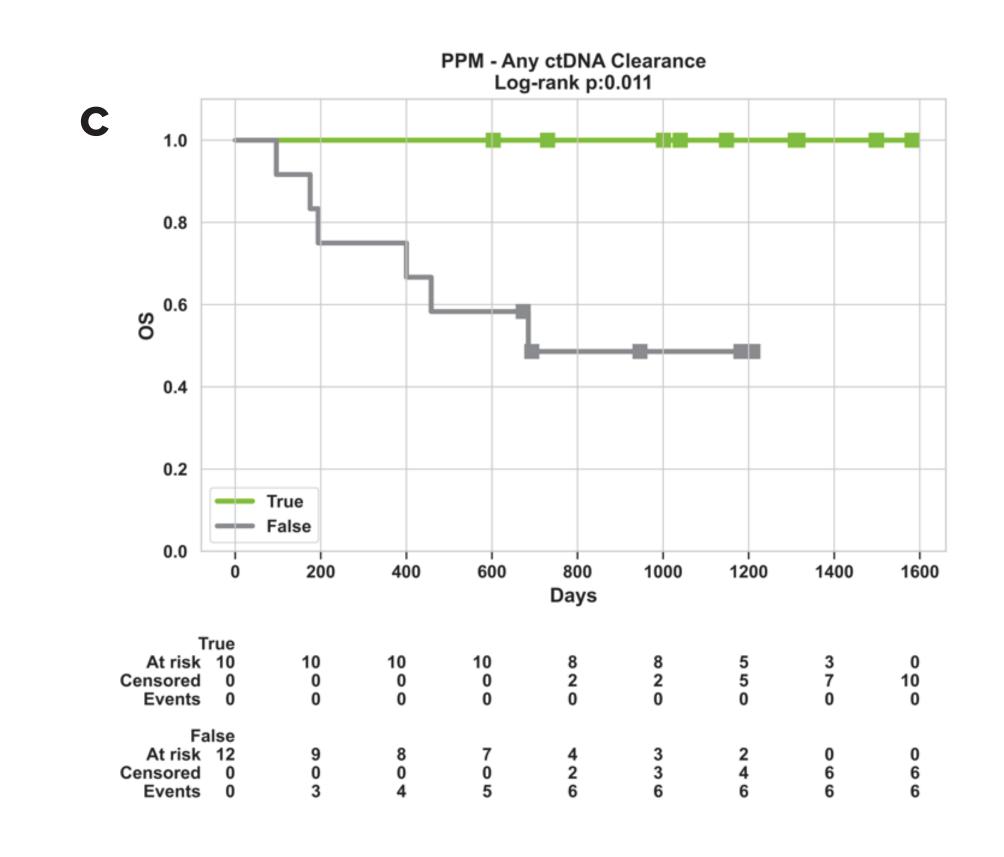
Highly sensitive ctDNA detection down to parts-per-million resolution is associated with clinical response

ctDNA was detected across a broad dynamic range, from approximately 100,000 PPM down to 2.3 PPM, with a median limit of detection (LOD) of 1.97 PPM (**A**). High assay sensitivity was reflected in a significant number of positive ctDNA detections at low PPM levels, with 37% (19/51) of positive, on-treatment detections occurring below 100 PPM and 31% (16/51) occurring below 50 PPM. (**B**; example patient time course and RECIST



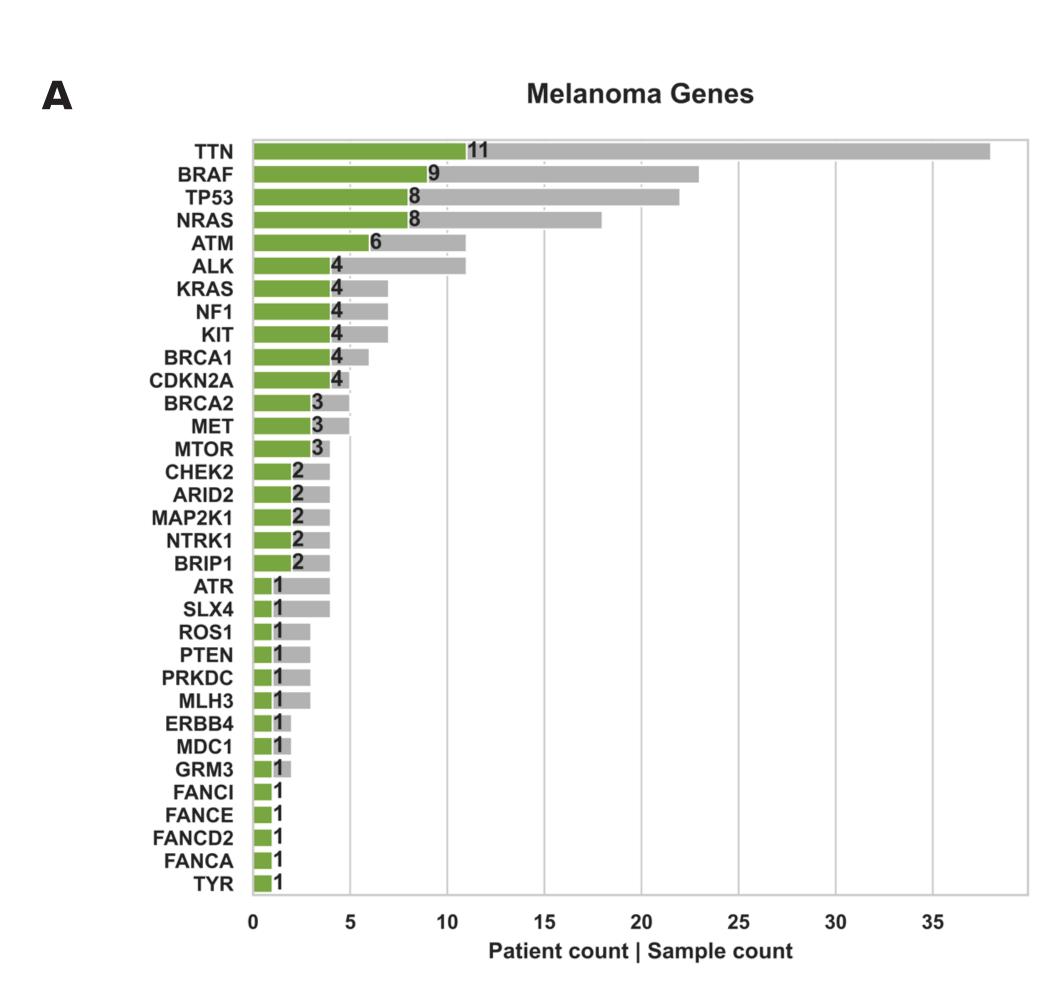
shown). Excluding patients with previous immunotherapy immediately prior to study enrollment, 94% (16/17) were ctDNA+ including all patients who progressed on treatment. We assessed the ability of NeXT Personal ctDNA detection status to predict patient survival. Attaining ctDNA clearance (ctDNA-) during the study was significantly associated with increased duration of overall survival (OS) (C; Kaplan-Meier (KM) log-rank p value = 0.01).

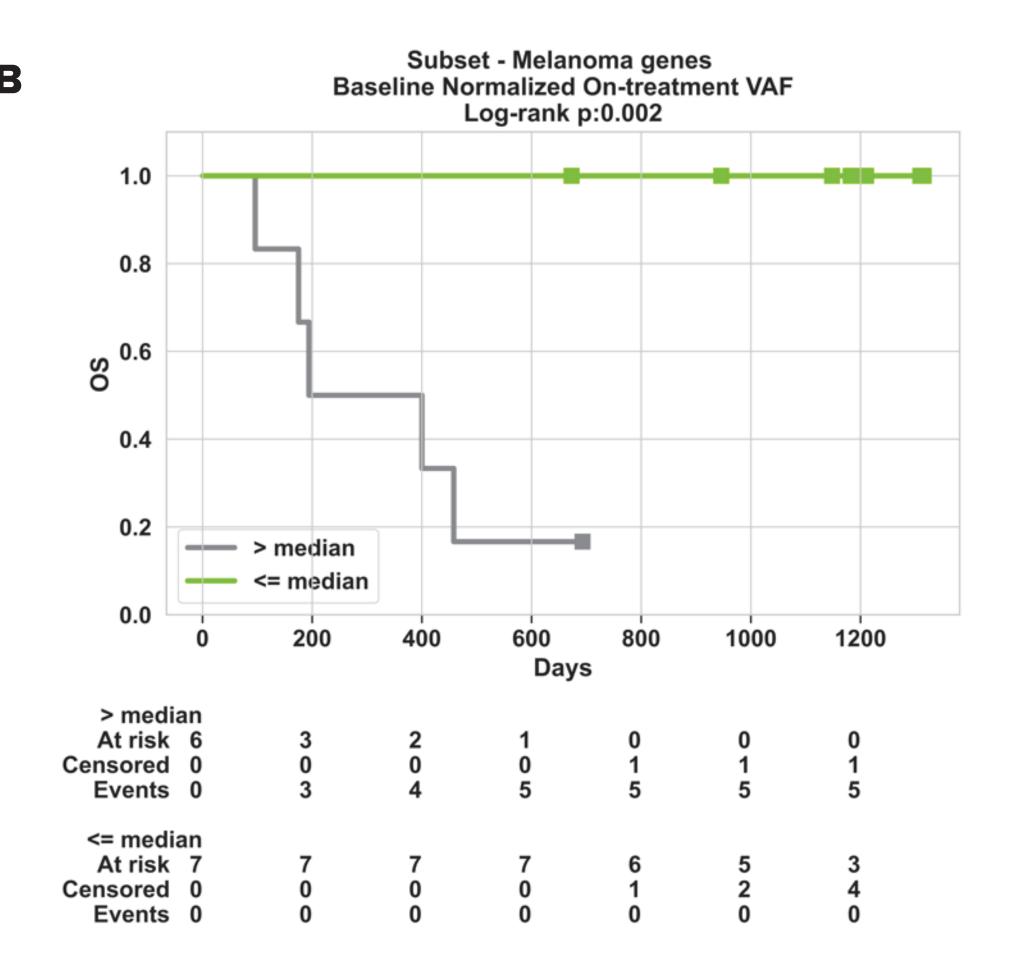




Changes in allelic fraction predict OS, specifically among key melanoma driver genes

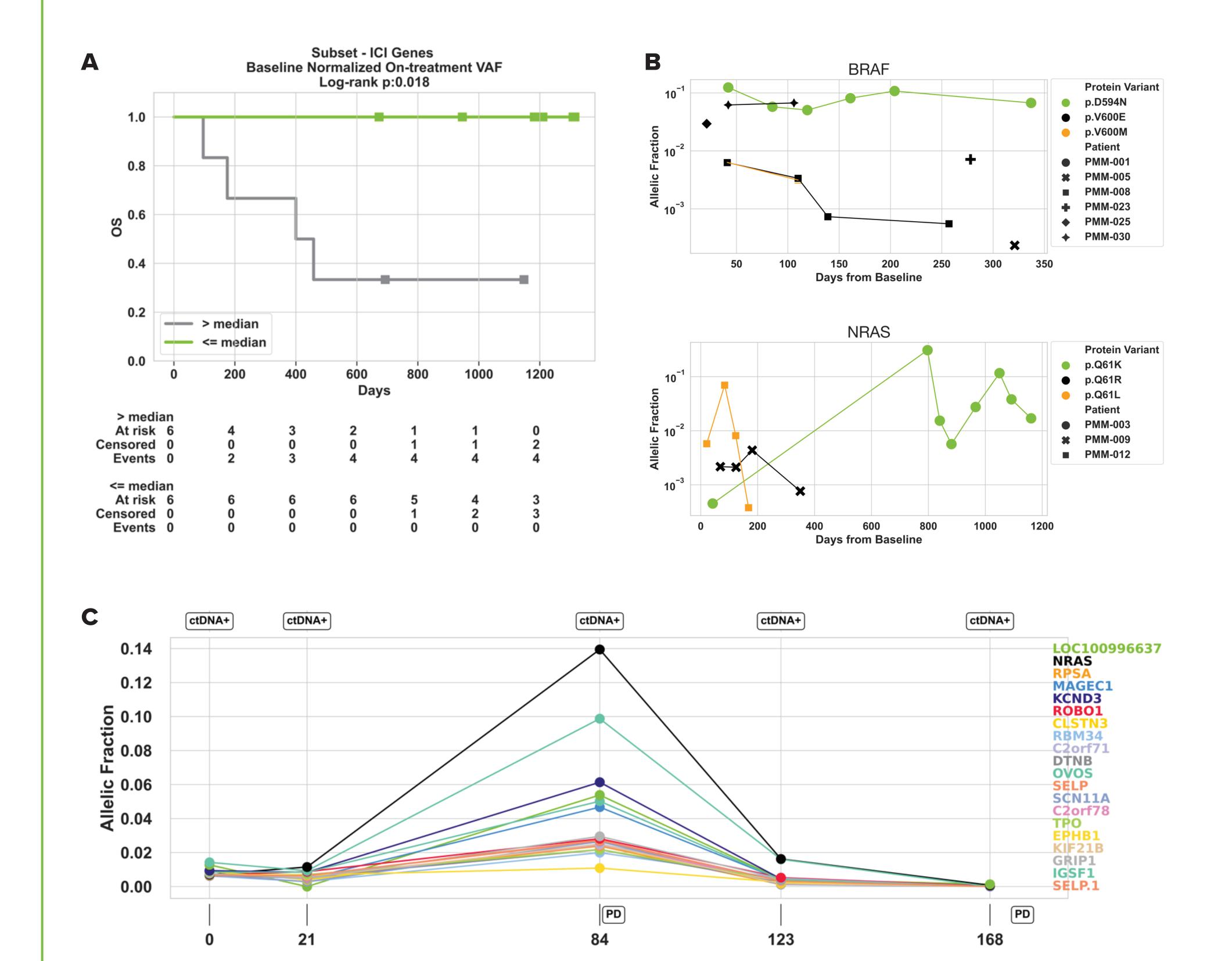
We examined changes in the variant allele frequency (VAF) of melanoma driver genes, including those that are current therapeutic targets. These genes include BRAF, NRAS, CDKN2A, KIT, and MAP2K1, among others (**A**, green bars = patient counts; grey bars = sample counts). Among these genes, the mean on-treatment VAF change from baseline was closely associated with overall survival (**B**, KM log-rank p value = 0.002).





Detection and tracking of investigational variants informing ICI and targeted therapies

Among genes known to impact ICI, on-treatment VAF predicted shortened OS (**A**, KM log rank p = 0.018). Dynamic changes were detected on-treatment in BRAF variants sensitive to BRAF/MEK inhibitors (top), and NRAS variants sensitive to Binimetinib5 (bottom) (**B**). An example of investigational variant tracking shown in (**C**) highlights the 20 most dynamic variants in patient PMM-0012, out of 366 investigational variants detected, including NRAS p.Q61L. PPM measures derived from MRD variants (up to 1800) are also shown at each timepoint. Notably, this patient passed away seven days after the final plasma sample, which may have appeared as ctDNA clearance in a less sensitive assay.



CONCLUSIONS

We found that low ctDNA levels were commonly observed, even in late stage disease, with positive ctDNA detections occurring as low as 2.3 PPM in this study. Detections down to low PPM levels correlate strongly with RECIST-derived classifications of response. Further, our results suggest the need for ultra-sensitive ctDNA detection for accurate classification of ctDNA status and patient outcomes, including overall survival. Additionally, we demonstrate the potential for future clinical use of a unique aspect of our tumor-informed ctDNA platform: identification and dynamic VAF tracking of clinically actionable and resistance variants, which correlate with response. The results presented here highlight the importance of ultra-sensitive ctDNA-based treatment monitoring, and will be further validated as the patient set is expanded.

Days from Baseline

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