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Resistance to immune checkpoint inhibitor (ICI) therapy in metastatic melanoma is revealed by deep circulating tumor DNA tracking in concert with tumor immune profiling

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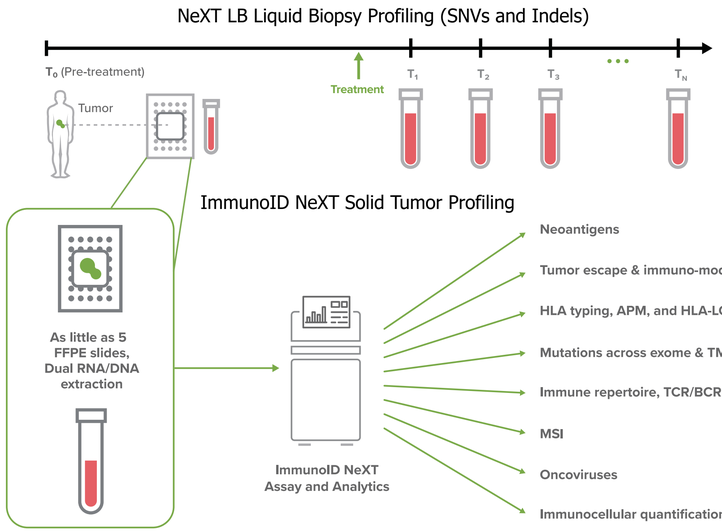
BACKGROUND

Circulating tumor DNA (ctDNA) has emerged as a promising noninvasive biomarker for monitoring response to immune checkpoint blockade (ICB) therapy in cancer patients. However, the clinical utility of ctDNA across different tumor types treated with ICB remains to be fully established. Here, we broadly profile melanoma patients receiving ICI over several years, beginning with extensive tumor mutational and immune profiling followed by deep, whole-exome ctDNA monitoring.

METHODS

Deep ctDNA monitoring and tumor immune profiling

Tumor informed exome-scale cfDNA profiling of 66 matched serial plasma samples from 23 advanced stage melanoma patients that were collected throughout ICI treatment was performed using the NeXT Liquid Biopsy® (NeXT LB) platform. NeXT LB leverages a hybrid capture approach that augments difficult to sequence genomic regions yielding uniform, high average depth coverage (2000X) across the exome, with boosted coverage (5000X) for 247 clinically relevant genes to achieve sensitive, exome-scale variant detection. The ImmunoID NeXT Platform® was used to broadly profile solid tumor tissue; including gene expression quantification, HLA profiling (typing, mutation, and loss of heterozygosity), T-cell receptor and tumor microenvironment profiling, and neoantigen prediction. ctDNA dynamics and tumor immunity were correlated with clinical outcome.



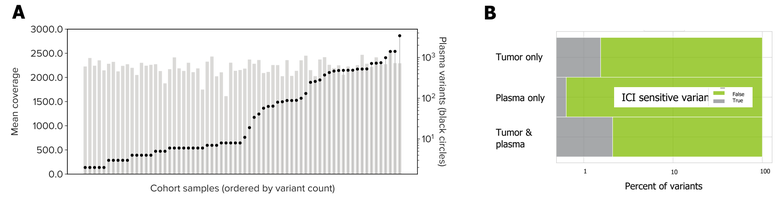
RESULTS

Patient demographics

This study included patients with advanced-stage melanoma (III-IV) who received ICI treatment for up to 41 cycles (median: 10 cycles). The majority (15/23) of patients were male, with a median age of 55 years at the start of treatment. Patients were monitored for up to 1582 days with a median follow-up time of 1183 days. Response was evaluated using standard RECIST criteria. Overall, the cohort had a survival rate of 70% (16/23), with 40% (9/23) achieving progression-free survival, and 10 patients attaining complete responses by the end of the surveillance period.

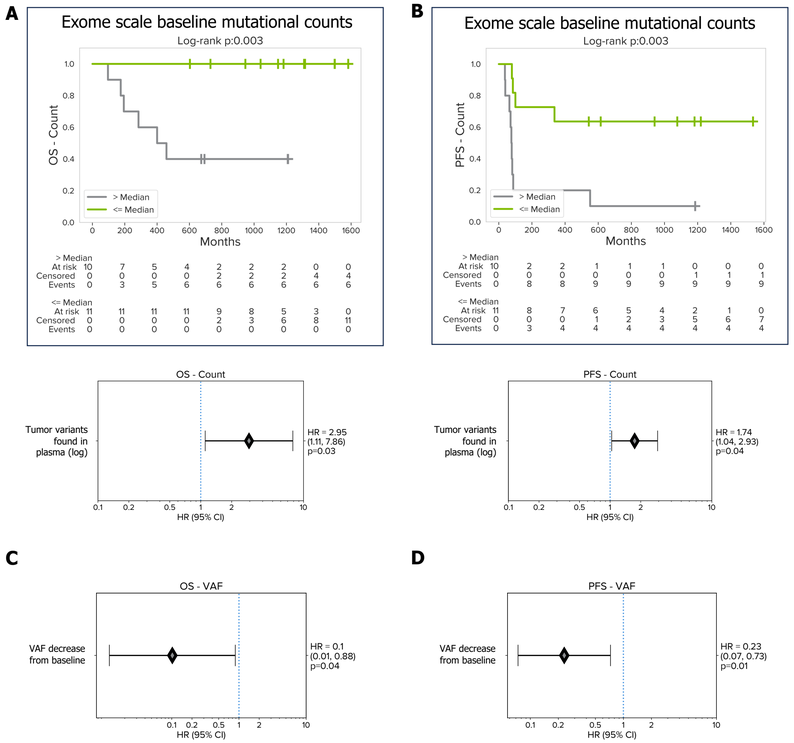
Deep sequencing of ctDNA variants

Somatic variants were detected a broad range (4-4081 mutations/time point) in plasma, with an average coverage of 2260X (SD +/-157) (**A**). Overall, 10% (4277) of all variants were de novo mutations observed only in the plasma. De novo variants were less likely to emerge in genes conferring sensitivity to ICI therapy (**B**, mixed-model; p<0.001).



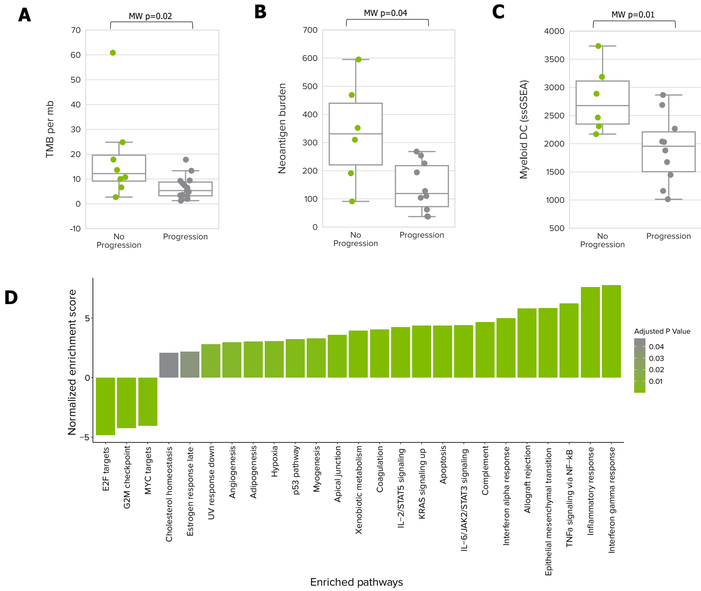
Plasma variant burden and VAF dynamics are prognostic of ICI resistance and overall survival

The number of on-treatment tumor variants detected in plasma predicted increased hazard for OS (**A**, Kaplan-Meier (KM) p=0.0003; HR=2.95, Wald p=0.03) and disease progression (**B**, KM p=0.0003; HR=1.74, Wald p=0.04). Dynamic shifts in allelic fraction between baseline and the first available on-treatment timepoint predicted increased OS hazard (**C**, HR=3.02, Wald p=0.05) and progression hazard (**D**, HR=2.90, Wald p=0.02).



Solid tumor derived immune factors predict ICI resistance

Patients who progressed had lower tumor mutational burden (**A,** TMB, Mann-Whitney (MW); p=0.02), and lower neoantigen burden (**B**, MW; p=0.04). Responding tumors were enriched for myeloid dendritic cells (**C**, mDC's, MW; p=0.01), and interferon gamma and inflammatory signaling (**D**, Wald; adjusted p<0.01), as measured by baseline RNA expression profiling, suggesting improved immune surveillance in responding patients.



A combination of immune and ctDNA factors are prognostic of ICI resistance

Multivariable Cox models of progression free survival that combine immune features with ctDNA measures have increased accuracy for predicting ICI resistance compared to univariable assessment.

	Univariable model			Multivariable model adjusted for ctDNA burden			Log-likelihood ratio test between models with and without ctDNA
	log-likelihood	p-value	HR	log-likelihood	p-value	HR	p-value
Myeloid DC's	4.0533	0.0441	0.163	6.6057	0.0368	0.25	0.024
Neoantigen Burden	9.6178	0.0019	0.17	11.6453	0.003	0.18	0.044
CD8 T cells	3.9206	0.0477	<0.01	6.4836	0.0391	<0.01	0.024

CONCLUSIONS

We used a WES-based liquid biopsy platform to profile tumor immunity and track existing and emerging ctDNA variants over the course of ICI treatment. We demonstrate that, even though counts of on-treatment ctDNA variants were sufficient for significant risk stratification, deep profiling of both tumor immunity and ctDNA dynamics provided broader understanding of ICI resistance. Subsequent studies will further explore clinical significance of combined exome-scale ctDNA profiling and solid tumor immune profiling.