Abstract No. 3535

Longitudinal circulating tumor DNA profiling of metastatic urothelial carcinoma in the POLARIS-03 trial

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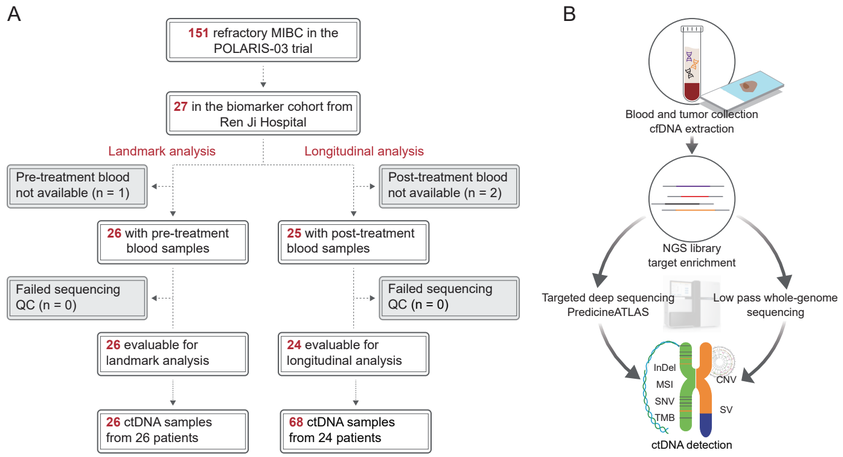
INTRODUCTION

Noninvasive biomarkers for immune checkpoint inhibitors remain a compelling unmet medical need. POLARIS-03 is a multicenter phase II trial to evaluate the safety and efficacy of toripalimab (anti-PD-1) in refractory metastatic urothelial carcinoma (mUC). We assessed the predictive utility of longitudinal circulating tumor DNA (ctDNA) analysis from a single-institution biomarker cohort.

METHODS

Twenty-seven mUC patients receiving toripalimab (3 mg/kg Q2W) at Ren Ji Hospital were enrolled and consented to Institutional Review Board-approved protocol. Serial plasma specimens were obtained at baseline and then every two cycles during treatment. The 600-gene panel (PredicineATLAS) liquid biopsy assay was applied to probe somatic variants and tumor mutational burden (TMB) by sequencing paired tissue and blood samples. Low-pass whole genome sequencing (LP-WGS) was used to identify chromosomal abnormality scores. Genomic aberrations were correlated with clinical outcomes.

Figure 1. Study design and next-generation sequencing workflow.



CONCLUSIONS

This study demonstrates the feasibility and effectiveness of tTMB/bTMB as a potential biomarker for mUC patients undergoing immunotherapy, and supports the clinical application of PredicineATLAS liquid biopsy assay as a minimally invasive tool for treatment stratification, efficacy prediction and dynamic monitoring in mUC.

RESULTS

Figure 2. Clinical characteristics and immunotherapeutic efficacy of 27 patients.

A

Characteristic	n (%)
No. of patients	27
Age at entry, yr	
Mean (SD)	64.8 (8.30)
Median (Min-Max)	66 (43 - 82)
Gender	
Male	15 (55.6%)
Female	12 (44.4%)
Stage at entry	
IIIb	0
IV	27 (100%)
Stage at diagnosis	
I	6 (22.2%)
II	3 (11.1%)
III	9 (33.3%)
IV	8 (29.6%)
unknown	1 (3.7%)
PD-L1	
positive	6 (22.2%)
negative	20 (74.1%)
unknown	1 (3.7%)
Location of primary tumor	
Upper urinary tract	9 (33.3%)
Lower urinary tract	18 (66.7%)
others	0
Metastasis sites	
Lymphatic metastasis only	4 (14.8%)
Visceral metastasis	23 (85.2%)
Liver	3 (11.1%)
Lung	8 (29.6%)
Bone	11 (40.7%)
Response	
CR/PR	10 (37.0%)
SD/PD	17 (63.0%)

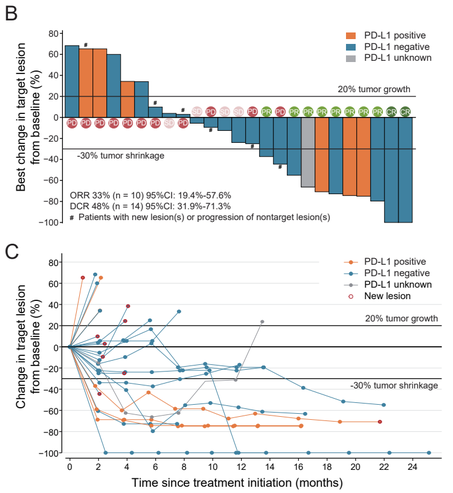


Figure 3. Mutation landscape of tumor and plasma samples in 27 patients. Mutation frequencies were compared in the right, referring to The Cancer Genome Atlas[1] or the German Cancer Research Center for *TERT* promoter mutations.[2]

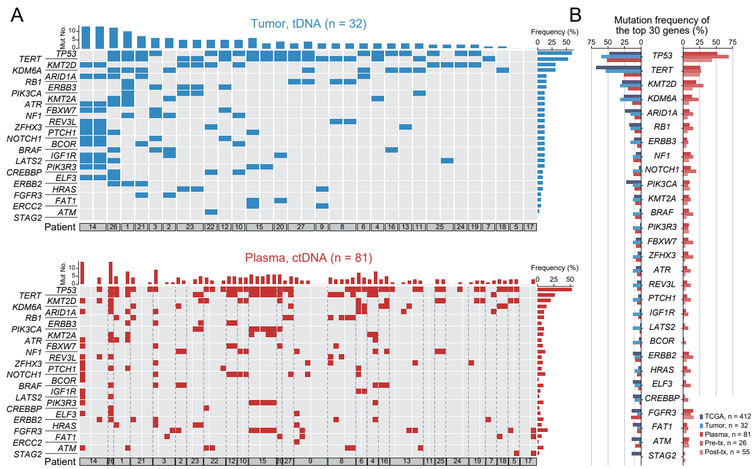


Figure 4. TMB inferred by ctDNA in blood (bTMB) was correlated with that measured by matched tumor samples (tTMB). High bTMB and tTMB were associated with better response.

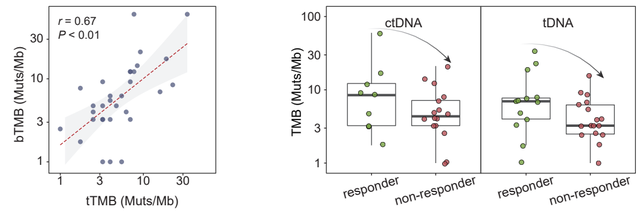


Figure 5. Early ctDNA clearance identified anti-PD-1 responders. C2D1 samples of immunotherapy responders showed significant decrease in cancer cell fraction (CCF), maximum somatic allelic frequency (MSAF), median VAF and chromosomal abnormality score measured by low-pass whole genome sequencing.

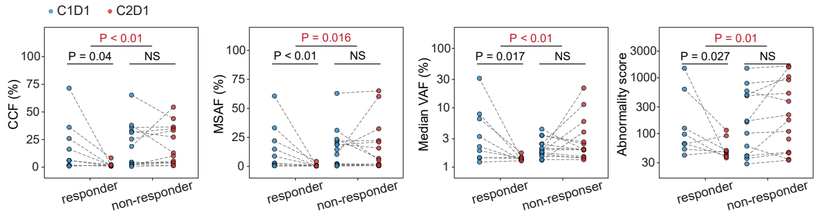
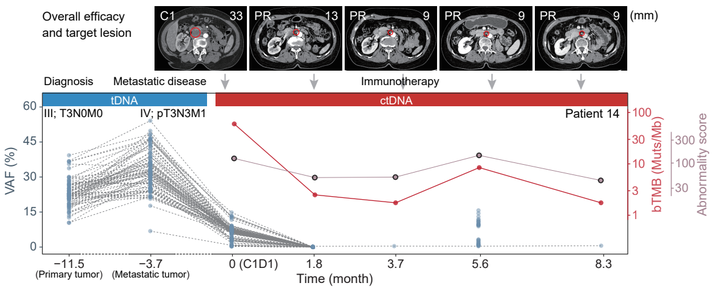


Figure 6. One patient with an exceptionally high bTMB (59 Muts/Mb) and genomic features of microsatellite instability (MSI) experienced a rapid disease improvement.



Reference
1.Robertson AG, Kim J, Al-Ahmadie H et al: Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell 2017; 171: 540.
2.Rachakonda PS, Hosen I, de Verdier PJ et al: *TERT* promoter mutations in bladder cancer affect patient survival and disease recurrence through modification by a common polymorphism. Proc Natl Acad Sci U S A 2013; 110: 17426.