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Circulating tumor DNA analysis of genomic alterations in metastatic urothelial carcinoma from NCT03113266 study

Haige Chen[1], Ruiyun Zhang[1], Feng Xie[2], Yue Zhang[2], Yiqiu Wang[1], Jingyu Zang[1], Pan Du[2], Shidong Jia[2], Guanglei Zhang[1], Yiran Huang[1]
[1]Department of Urology, Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China and [2]Huidu Shanghai Medical Sciences Ltd, Shanghai, China

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INTRODUCTION

Recent studies have suggested the predictive value of liquid biopsies for immune checkpoint inhibitors. NCT03113266 is a multicenter phase II trial to evaluate the safety and efficacy of toripalimab (anti-PD-1) in metastatic urothelial carcinoma (mUC). Here we report the initial circulating tumor DNA (ctDNA) analysis of genomic alterations 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 protocols permitting biomaterial collection and genetic sequencing.

Tumor tissue samples were collected from **primary lesion**. Plasma samples were obtained before treatment.

The 600-gene PredicineATLAS liquid biopsy assay was applied to assess somatic variants and blood tumor mutational burden (bTMB). NGS assays were completed at the Huidu Laboratory in Shanghai, China.

Figure 1. PredicineATLAS workflow

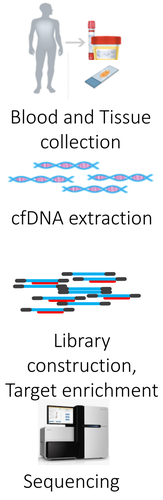


Fig.1a: NGS workflow

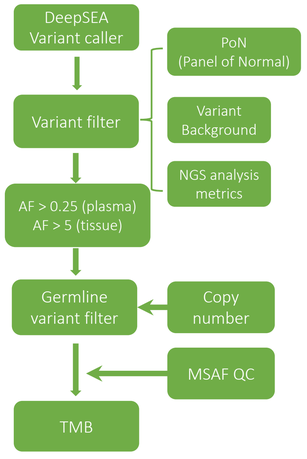


Fig.1b: TMB analysis

RESULTS

The ctDNA analysis was performed successfully for 100% of the baseline samples (n = 27) with average read depth of 24,389 (range 14,000-31,700). A total of 571 non-synonymous mutations were identified, demonstrating prevalent aberrations in *TP53* (63%), *TERT* promoter (30%), *KDM2D* (26%), *PPM1D* (26%), and *KDM6A* (26%). *FGFR3* variants were detected in 5 patients, including 6 missense sites and 4 *FGFR3-TACC3* fusion events. TMB estimation revealed one case with an exceptionally high bTMB (62.6 mutations/Mb) and genomic features of microsatellite instability (MSI).

Figure 2. Concordant mutation profiles between 27 matched pairs of bladder tumor and plasma.

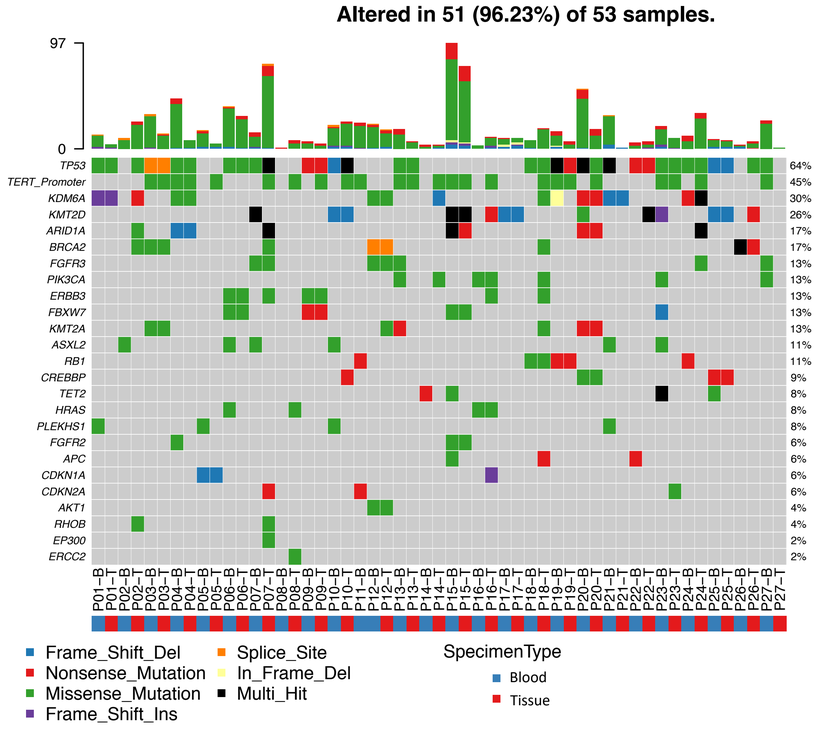
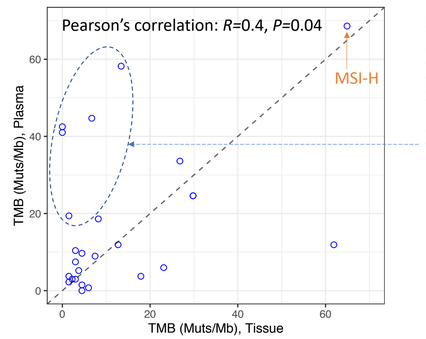


Figure 3. TMB concordance study using matched blood and tissue samples. Concordant TMB scores were observed in matched blood and tissue samples. Distinct TMB scores between tumor tissue and plasma samples were detected in several patients (dots in the circle), indicating potential tumor heterogeneity and variation across primary and metastatic sites and across collection time points. The H&E staining images demonstrated the tumor content (TC) of patients in the circle.



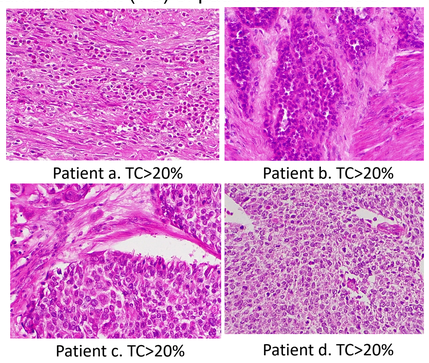
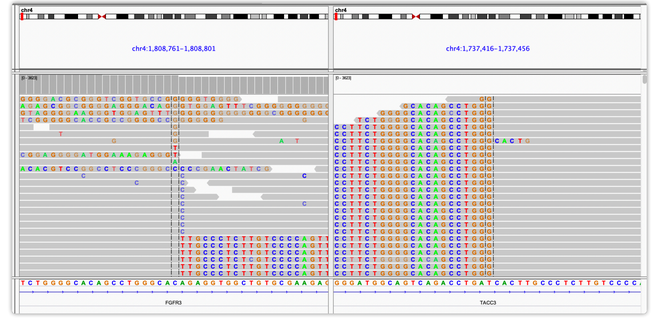


Figure 4. *FGFR3-TACC3* fusions detected in mUC.



CONCLUSIONS

- Using the PredicineATLAS NGS platform, we observed concordant mutation profiles between 27 matched pairs of bladder tumor and plasma samples.
- Further investigation is underway to correlate genomic alterations, ctDNA kinetics and clinical outcome associated with toripalimab treatment in mUC patients.