Abstract No. # 551

Blood-based Detection of Copy Number Loss and Its Clinical Implication in Prostate Cancer

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INTRODUCTION

Liquid biopsy is increasingly used to profile genomic alterations in circulating tumor DNA, yet the low sensitivity for detecting gene copy loss remains a challenge. This limits the interrogation of critical tumor suppressor gene deletion events during cancer progression and treatment. We developed a next generation sequencing (NGS)-based cfDNA test that detects copy loss with high sensitivity in blood samples. Here we describe its application to detect copy loss in 2 independent cohorts of metastatic prostate cancer patients to demonstrate: i) high concordance of this assay with orthogonal tissue-based whole genome sequencing (WGS) and immunohistochemical analyses for detecting copy loss in metastatic castrate resistant prostate cancer (mCRPC) patients, ii) robust detection of PTEN, RB1 and TP53 deletions in a mCRPC patient cohort, and iii) correlation of PTEN, RB1 and TP53 loss with poor patient outcomes.

METHODS

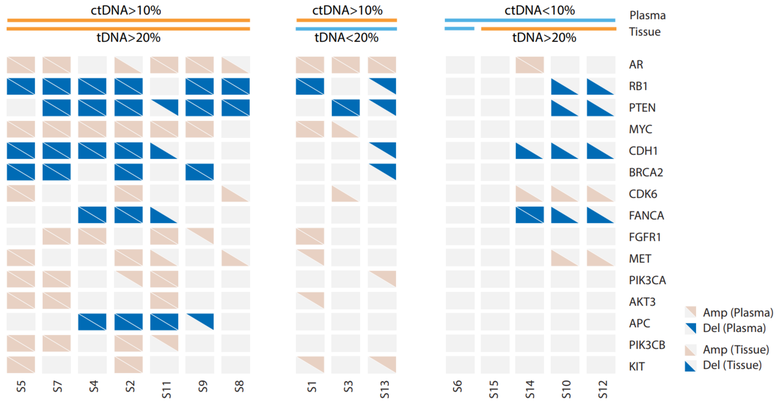
Patients & sample collection:
Concordance of genomic aberrations between plasma and tissue was assessed in a prospective cohort of 15 ARPI-resistant mCRPC patients at the Second Hospital of Tianjin Medical University, China (NCT03786848). Each patient underwent imaging-guided core needle biopsy sampling from an accessible metastatic lesion. Paired collection of peripheral blood was obtained on the day of tissue biopsy. To evaluate patient outcomes in association with blood-based copy number loss, plasma samples were collected from 52 prostate cancer patients prospectively enrolled in the Mayo Clinic, Rochester Minnesota, between September 2009 and March 2014, with either biochemically or radiographically progressive mCRPC. Samples were collected following progression on androgen deprivation therapy (ADT), prior to commencement of chemotherapy. Study approval was acquired from the human research ethics committee, with all participants providing written informed consent prior to sample collection. Median follow-up time for non-deceased patients was 80.7 months.

NGS assays
The 152-gene PredicineCARE™ liquid biopsy assay was used for somatic alteration identification in tissue-based tumor DNA (tDNA) and blood circulating tumor DNA (ctDNA). Low-pass whole genome sequencing assay was applied to the 15 pairs of matched tissue-blood samples in the validation group.

Workflow for PredicineCARE™ - a targeted NGS assay for tissue and blood.

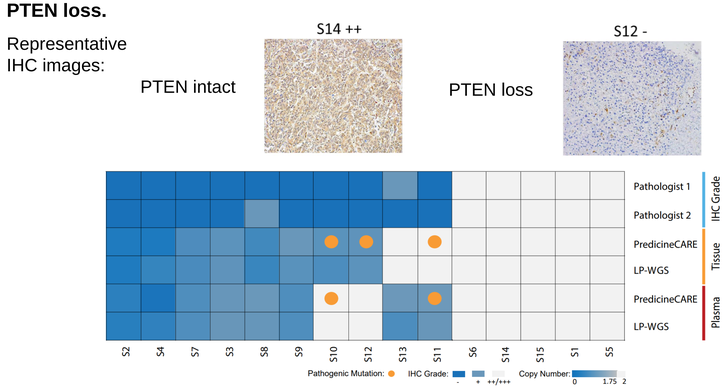
RESULTS

Figure 1. Concordance between PredicineCARE™ blood and tissue biopsy assays in detecting gene copy number variation.



Paired tumor tissue and blood samples were collected from 15 metastatic castration-resistant prostate cancer patients and analyzed by PredicineCARE™ target-capture based NGS assay. Among genes covered by the assay, those altered in greater than 10% of the samples are shown. ctDNA fraction was estimated by LP-WGS assay. Percentage of ctDNA represents the proportion of ctDNA in all cfDNA in a sample.

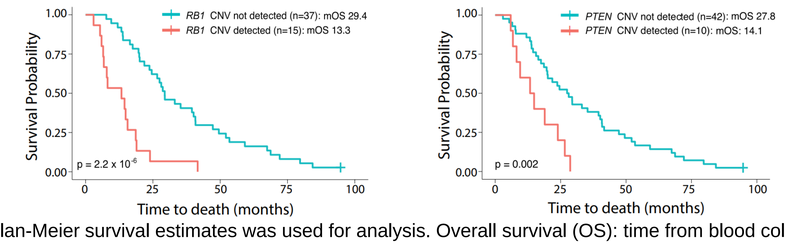
Figure 2. Concordance between IHC and next generation sequencing assays in detecting PTEN loss.



"IHC grade" columns show PTEN tissue expression by immunohistochemical staining, independently reviewed by two pathologists. IHC grades "-" and "+" indicate PTEN expression loss and expression-intact, respectively. *PTEN* gene copy loss was evaluated in tissue samples and their matching blood samples using the PredicineCARE™ assay (panel) and low pass whole genome sequencing assay (LP-WGS).

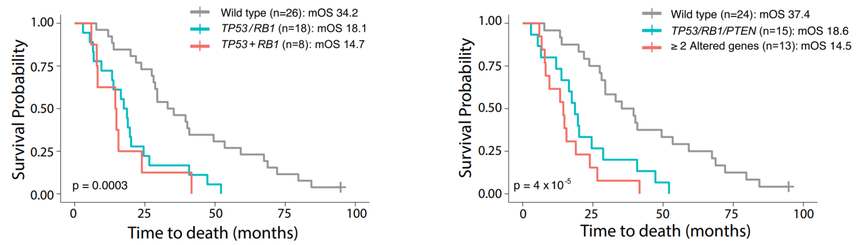
Figure 3. Landscape of ctDNA-based alterations detected in the TP53, RB1 and PTEN genes by PredicineCARE™ liquid biopsy across 52 mCRPC patient blood samples.

Figure 4. *PTEN* and *RB1* gene loss detected in blood samples was associated with shorter patient overall survival.



Kaplan-Meier survival estimates was used for analysis. Overall survival (OS): time from blood collection until death from any cause.

Figure 5. Detection of multiple copy number loss events among the *PTEN*, *RB1* and *TP53* genes was associated with shorter patient overall survival compared to single gene alteration.



CONCLUSIONS

PredicineCARE™ liquid biopsy assay detected prevalent gene copy loss events from blood samples that were confirmed by tissue biopsy NGS assay and IHC staining, and with a level of sensitivity that enabled analysis of patient outcomes in association with PTEN, RB1 and TP53 gene loss. The sensitive detection of copy loss biomarkers in liquid biopsy samples constitutes an important addition to the precision medicine toolbox.