Tracking MRD and neoantigen targets using a tumor-informed liquid biopsy platform in HCC patients treated with personalized cancer vaccine and pembrolizumab

ctDNA analysis has enabled non-invasive detection and monitoring of potentially actionable mutations, and can identify therapeutic response/resistance prior to confirmation by radiographic imaging. Little is known about ctDNA in the neoantigen-targeted personalized cancer DNA vaccine setting, potentially due to the limited sensitivity of current ctDNA assays. We used an ultra-sensitive, tumor-informed ctDNA platform to longitudinally track tumor neoantigen targets and monitor molecular residual disease (MRD) in advanced HCC patients (pts) being treated with a DNA personalized therapeutic cancer vaccine (GNOS-PV02).

Pts with unresectable or metastatic HCC with progression on, or intolerance to, first-line therapy with TKI were enrolled into the Phase 1b/2a GT-30 study [NCT04251117]. GNOS-PV02 was designed based on whole exome/transcriptome tumor sequencing. Pts were treated with GNOS-PV02 (1mg; Q3W x 4, Q9W) and plasmid-encoded IL-12 (0.3mg; Q3W x 4, Q9W) in combination with pembrolizumab (200mg; Q3W). Response was evaluated by RECIST 1.1 at baseline (bl) and Q9W.

Over 100 prospective bl and on-treatment (ot) plasma samples were collected and analyzed using NeXT Personal®, a tumor-informed ctDNA assay that leverages whole genome sequencing of tumor/normal samples to generate personalized liquid biopsy panels. Each panel included personalized neoantigen targets, up to 1,800 selected variants for ultra-sensitive detection of MRD, and a fixed set of 2,100 known clinically actionable and resistance loci for detection of variants emerging under therapeutic pressure.

ctDNA was detected across a broad dynamic range (3-100,000 PPM; minimum limit of detection = 2.5 PPM) with frequent positive detections below 100 PPM. Bl ctDNA was detected in 100% (12/12) of patients. Ot changes in ctDNA relative to bl correlated with disease status. ctDNA tracking of a patient with a target liver lesion reduction of 36% at W9 deepening to -59% at W54 by RECIST1.1 showed ctDNA clearance of all liver-specific neoantigen targets between W12 to w21. New adrenal lesions were observed on W18 by MRI and retrospective ctDNA analysis revealed an increase of adrenal-specific ctDNA measures by W9. These data indicate ctDNA can be used to track tumor neoantigens and provide important data supporting immune pressure-induced tumor escape.

Highly sensitive tracking of MRD and neo-antigenic variants over the course of therapy was achieved using a single assay. We show that ctDNA can sensitively monitor disease status non-invasively, potentially leading to accurate clinical outcome prediction. Additionally, the ease of sample handling, analysis, and rapid availability of data could enable the use of ctDNA monitoring to allow real-time dynamic personalized cancer immunotherapy.

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