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CIRCULATING TUMOR DNA ANALYSIS OF ADVANCED HEPATOCELLULAR CANCER (HCC) PATIENTS TREATED WITH NEOANTIGEN TARGETED PERSONALIZED CANCER DNA VACCINE (GNOS-PV02) IN COMBINATION WITH PLASMID IL-12 (PIL12) AND ANTI-PD1 (PEMBROLIZUMAB)

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Background Recent advances in circulating tumor DNA (ctDNA) analysis have enabled the non-invasive detection of mutations that lead to resistance mechanisms and therapeutic and disease monitoring in cancer patients. Improvements in whole exome sequencing with high sensitivity and specificity has made it feasible to interrogate a large number of genes simultaneously. We sought to evaluate the clinical utility of ctDNA analysis for longitudinal tracking of cancer neoantigen targets and for monitoring of disease status in advanced cancer patients being treated with aDNA personalized cancer vaccine (PCV). Our results also inform the kinetics of somatic variants included in the PCV (neoantigen vaccine targets) as well as the larger set of all variants identified in the tumor (MRD targets).

Methods Patients with unresectable or metastatic HCC with progression on, or intolerance to, first-line therapy with tyrosine kinase inhibitors were enrolled into the Phase Ib/IIa GT-30 study [NCT04251117]. Tumors were biopsied for exome and transcriptome sequencing and a patient-specific neoantigen DNA vaccine (GNOS-PV02) was designed. Patients were treated with GNOS-PV02 (1mg) and DNA plasmid encoded IL-12 (0.34mg) in combination with pembrolizumab (200mg). Treatment response was evaluated by RECIST 1.1. Prospectively collected pre- and post-treatment samples from 17 patients were batched and analyzed by personalized ctDNA assays. Somatic mutation calls were made using Personalis ACE[®] exome data from tumor tissue biopsies. Capture probe panels were designed for the two sets of targets. ctDNA was extracted from the plasma samples; up to 50ng was used as input for deep sequencing. Advanced noise suppression, mutation calling, aggregate tumor tracking and MRD calling was performed using NeXT ctDNA technology.

Results Pre-treatment ctDNA magnitude varied widely across patients for both neoantigen targets and MRD targets. Although analyzed retrospectively, changes in ctDNA magnitude over time correlated well with disease status in most patients. ctDNA broadly tracked with MRI scans for monitoring objective responses (CR and PR). In patients with tumor recurrence and/or emergence of de novo metastatic lesions, an increase in target copy number or mean tumor molecules/ml was detected prior to confirmation by MRI. Patient level data from the ongoing GT-30 clinical trial will be discussed at the meeting.

Conclusions Our analysis indicated that ctDNA can be a useful tool for monitoring disease in a patient specific manner. The ease of sample handling and analysis, and rapid availability of data, could enable the use of ctDNA monitoring to allow real time clinical treatment decision making for personalized cancer immunotherapy.

Trial Registration NCT04251117

Ethics Approval For GT-30 trial, the protocols were approved by Johns Hopkins Medicine Review Boards (CR00039002/IRB00227771), Icahn School of Medicine-Program for the Protection of Human Subjects (20-00076 GCO#1), and Northern A Health and Disability Ethics committee (Ethics ref: 20/NTA), respectively. Written informed consent was obtained from each patient prior to the patient participating in the trial.

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