PERSONALIZED DNA NEOANTIGEN VACCINE (GNOS-PV02) IN COMBINATION WITH PLASMID IL-12 AND PEMBROLIZUMAB AS SECOND-LINE (2L) TREATMENT FOR ADVANCED HEPATOCellular CARCINOMA (HCC)

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Background Hepatocellular carcinoma (HCC) is a low TMB tumor with largely immune-excluded phenotype. Anti-PD1 monotherapy for 2L HCC has response rates of 12-18%. Therapeutic cancer vaccines targeting neoantigens can generate tumor-specific T-cell immunity, potentially enhancing responses to anti-PD1 therapy. GNOS-PV02 is a personalized cancer DNA vaccine encoding up to 40 patient-specific neoantigens. GT-30 trial is an ongoing single-arm open-label multi-center phase Ib/IIa study to evaluate safety, immunogenicity, and efficacy of GNOS-PV02 administered in combination with plasmid-encoded IL-12 (pIL12) and pembrolizumab.

Methods Patients with unresectable or metastatic HCC and progression or intolerance on first-line therapy with tyrosine kinase inhibitors (sorafenib or lenvatinib) are enrolled. Tumors are biopsied for exome and transcriptome sequencing, peripheral blood is collected for germline sequencing, and a patient-specific vaccine is designed, optimized and manufactured, all in 6-8 weeks. GNOS-PV02 (1mg) and pIL12 (0.34mg) are administered via intradermal injection and electroporation Q3w x 4 doses, Q9w thereafter. Pembrolizumab 200mg is administered IV Q3w. Treatment response is evaluated Q9w by RECIST 1.1. Blood samples are collected pre-treatment, Q3w until w12, then Q12w for immunological analyses. Tumor biopsy is obtained at w9 for TME assessment.

Results As of cutoff date of June 30, 2022, 24 patients were enrolled with median age 66.5 years (range 40-78 years). There were no DLTs, GNOS-PV02+pIL12 related SAEs, or Grade 3 or 4 AEs reported. Two cases of hypothyroidism and immune nephritis, likely immune-mediated were noted, however no increase in irAEs or SAEs was seen with the combination therapy relative to previously known pembrolizumab monotherapy data. ORR (mITT) per RECIST 1.1 was 29.2% (7/24). Disease control rate was 54.2% (13/24) consisting of 2 CR, 5 PR, 6 SD, 10 PD. One patient early-terminated due to a non-treatment-related SAE six days after their sole PCV dose and was deemed unevaluable but included in the mITT analysis. One patient with a radiological PR after five PCV doses achieved secondary resectability, and discontinued therapy to pursue resection without disease recurrence. Novel and expanded T cell clones, predominantly CD8+ with activated phenotype, were identified in all evaluated patients via pre-/ post-vaccination analysis of TCR repertoire in peripheral blood and tumor tissue. These clones trafficked to the TME by w9, potentially mediating the observed tumor regressions.

Conclusions GNOS-PV02 + INO-9012 combined with pembrolizumab in the 2L setting was well tolerated and induced tumor-neoantigen-directed CD8+ T cells and TILs. Data to date suggest clinical benefit relative to PD1 monotherapy in patients with advanced HCC.

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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