453 PERSONALIZED DNA NEOANTIGEN VACCINE (GNOS-PV02) IN COMBINATION WITH PLASMID IL-12 AND PEMBROLIZUMAB FOR THE TREATMENT OF PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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Background Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death. Immune checkpoint inhibitors targeting PD-1 have limited activity in HCC as monotherapy, with response rates ranging from 14–17%. Tumor neoantigens derived from tumor-specific mutations can be incorporated into personalized therapeutic cancer vaccines to generate tumor-specific T cell immunity, potentially priming the immune system for anti-PD1 therapy. DNA vaccines have been shown to elicit strong CD8 and CD4 T cell responses in preclinical and clinical trials. GNOS-PV02 is a personalized DNA vaccine, encoding up to 40 patient-specific neoantigens. In the GT-30 trial, it is used in combination with INO-9012 (plasmid-encoded IL-12) and pembrolizumab for the treatment of advanced HCC.

Methods GT-30 is a single-arm phase I/II clinical trial to assess the safety, immunogenicity, and preliminary efficacy of GNOS-PV02 in combination with INO-9012 and pembrolizumab in patients with advanced HCC. Twenty-four patients are anticipated to be enrolled. Patients are recruited upon diagnosis or during first-line treatment with tyrosine kinase inhibitors (TKI). Tumors are biopsied for exome and transcriptome sequencing, and peripheral blood collected for germline sequencing and histogenetics. The tumor specific vaccine is designed, optimized and manufactured during first-line therapy. Each vaccine encodes up to 40 neoantigens. After progression or intolerance with first-line therapy, patients commence concurrent personalized vaccine and pembrolizumab. GNOS-PV02 + INO-9012 are administered Q3w for the first 4 doses and Q9w thereafter. Pembrolizumab is delivered Q3w.

Results We performed a data cut-off on the first 12 patients. The median age was 66 years (range 55–75 years). GNOS-PV02 + INO-9012 with pembrolizumab has had no reported DLTs or drug related SAEs. The most common treatment-related AE were grade 1 fatigue (25%) and grade 1 injection site reactions (17%). By including up to 40 epitopes in the vaccine we were able to target all neoantigens present in 83% of the patients. The objective response rate was 25% (3/12 partial response, 5/12 stable disease, 4/12 progressive disease). Analysis of the TCR repertoire in peripheral blood and tumor tissue identified novel and significantly expanded T cell clones post-vaccination in all patients analyzed. Many of the novel peripheral T cell clones were also identified to have trafficked to the TME at week 9, potentially mediating the observed tumor regressions.

Conclusions These data demonstrate the potential of GNOS-PV02 + INO-9012 with pembrolizumab to target multiple neoepitopes, and provide initial support for the safety and efficacy of this regimen in patients with advanced HCC.

Trial Registration NCT04251117

Ethics Approval The study obtained IRB approval (IRB) and all patients signed informed consent prior to taking part in the clinical trial. NZCR EC: 20/NTA/6; JHU: IRB00227771; Mount Sinai: HS#: 20–00076

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