GNOS-PV02, a personalized DNA neoantigen vaccine, in combination with INO-9012 and pembrolizumab for the treatment of advanced hepatocellular carcinoma (GT-30)

Tumor neoantigens are epitopes derived from tumor-specific somatic mutations that are presented on MHC molecules. Neoantigens have emerged as promising targets for personalized cancer immunotherapy due to their frequency in cancer, lack of central tolerance and lack of expression in healthy tissues. There is increasing interest in priming CD8 T cells against tumor neoantigens using personalized vaccines, however early clinical and preclinical studies using peptides and RNA platforms have reported immune responses predominantly driven by CD4 T cells. New synthetically designed DNA vaccines have recently shown strong CD8 and CD4 T cell responses in clinical trials. In preclinical studies, DNA-encoded neoantigen vaccines have shown induction of CD8 T cells against 50% of predicted high affinity epitopes with the ability to impact tumor growth. GNOS-PV02 is a personalized DNA vaccine, encoding up to 40 patient-specific neoantigens. It is used in combination with INO-9012, an IL-12 plasmid, to augment T cell responses.

In preclinical models, the inclusion of up to 40 neoantigens in a single neoantigen vaccine did not result in antigen interference. Furthermore, immunization using a single relevant epitope exerted similar anti-tumor effect when delivered together with 11, 23, or 59 irrelevant epitopes.

We are now performing a first in human phase I/IIA, open-label, multi-center trial to evaluate the safety, immunogenicity and preliminary clinical efficacy of GNOS-PV02 + INO-9012 delivered by intradermal injection followed by electroporation in participants with advanced hepatocellular carcinoma (HCC). HCC is the fourth most common cause of cancer-related death, and the incidence of HCC is rising in the US. Checkpoint inhibitors targeting programmed cell death protein 1 (PD1) such as pembrolizumab are approved in 2nd line HCC, however response rates to anti-PD1 as monotherapy are in a range of 14-17%, underscoring a need for combination approaches to immunotherapy in HCC. We hypothesize that the personalized DNA vaccine GNOS-PV02 in combination with INO-9012 and pembrolizumab will generate CD8 and CD4 T cells specific for the tumor, will be safe, and will result in enhanced over what would be seen in response to pembrolizumab alone in patients with HCC.

Twelve patients are anticipated to be enrolled in this study. Patients are recruited upon diagnosis or during 1st line treatment with tyrosine kinase inhibitors (TKI). Tumors are biopsied for exome and transcriptome sequencing and tumor specific vaccine is manufactured during 1st line therapy. Study treatment begins upon progression or intolerance to TKI. GNOS-PV02 + INO-9012 is administered Q3w for the first 4 doses and Q9w thereafter until disease progression. Pembrolizumab will be delivered Q3w until disease progression.

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Neoantigen DNA vaccine for HCC