Background Tumor immune editing and escape are key mechanisms of cancer progression and metastatic dissemination. However, immune editing in response to therapeutic cancer vaccines has been challenging to demonstrate in patients. Neoantigens derived from tumor-specific mutations are promising targets for immunotherapy. They can be incorporated in personalized cancer vaccines (PCV) to prime T cell activation. Here, we report evidence of immune editing in a patient treated with a therapeutic neoantigen DNA PCV from the ongoing GT-30 advanced hepatocellular carcinoma single-arm open-label multi-center phase Ib/IIa trial.

Methods A 74 yo white male, having progressed on multiple prior lines of therapy including ablation, TACE and lenvatinib, was enrolled in the GT-30 study. Following WES and transcriptome analysis of the primary liver tumor biopsy, a DNA PCV encoding 29 neoantigens (GNOS-PV02) was manufactured. GNOS-PV02 (1mg) and pIL12 (0.3mg) were administered intradermally Q3w x 4 doses; Q9w thereafter. Pembrolizumab 200mg IV was administered Q3w. Treatment response was evaluated Q9w by RECIST 1.1. Pre-treatment and on-treatment biopsy samples and periodic blood samples were evaluated retrospectively for neoantigen repertoire, immune responses and ctDNA.

Results GNOS-PV02+pIL12+pembrolizumab treatment resulted in a partial response, with target lesion reduction of -36% at w9 deepening to -59% at w54 by RECIST1.1. TCR/TIL analysis of w9 biopsy versus screening biopsy samples revealed the expansion and infiltration of multiple new T-cell clones post-vaccination. PBMC analysis by IFNg ELISpot detected strong T-cell response to 4/29 vaccine epitopes. Flow cytometry analysis showed antigen-specific, activated (CD69+, Ki67+) CD8 and CD4 T-cells at high frequency. A new, distal adrenal lesion was detected at w18 that increased in size by w54. Sequencing of the adrenal lesion at w54 identified 25 neoantigens, including 16 shared with the primary liver lesion. However all 4 of the vaccine epitopes with strongest ELISpot responses were absent in the adrenal lesion, consistent with neoantigen loss resulting from immune editing and subsequent clonal escape. ctDNA analysis was consistent with complete response of the liver-specific tumor clone by w21 persisting through w57 but showed an increasing frequency of the adrenal specific tumor ctDNA over time.

Conclusions We documented evidence of PCV immune pressure induced clonal escape via the emergence and growth of a new distal lesion despite the primary lesion showing continued and deepened response. Such ongoing analysis of immune response and ctDNA for monitoring tumors offers a means to dynamic cancer therapy, whereby therapeutic vaccines with evolved neoantigen panels may be designed against new, or newly unresponsive, lesions.

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.