Trial in Progress: First-in-Human Immunotherapy-Trio for Advanced Head and Neck Squamous Cell Carcinoma

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Background: Glucocorticoid-Induced Tumor Necrosis Factor Receptor-related protein (GITR) is a co-stimulatory pathway that when triggered has potent effects on T-cell memory, proliferation and anti-tumor activity. Preclinical models identified significant synergy between anti-GITR agonist therapy and cancer vaccines to generate stronger tumor-specific CD8 T cell responses. DPV-001 is an "off-the-shelf" multivalent autophagosome vaccine generated by in vitro manipulation of the autophagy pathway in human cancer cell lines. The vaccine delivers short-lived proteins (SLiPs) and defective ribosomal products (DRiPs) which are likely the dominant epitopes directly presented by MHC class I of tumor cells; but because of proteosomal degradation, are normally unavailable for cross-presentation, hence the delivery via vaccine. We hypothesize that addition of aGITR to DPV-001 vaccine will augment expansion of reactive CD4 and CD8 T cells, attenuate contraction of this response, and improve the therapeutic effect of treatment, and will result in the development of a coordinated T and B cell response to some of the same proteins, detectable using a cutting-edge seromics approach, as a window to TCR target identification for immunodynamic tracking of induced anti-cancer responses at an advanced level.

Methods: Patient recruitment began in August 2022, for this first-in-human immunotherapy-trio study of DPV-001, with sequenced checkpoint inhibition (aPD-1 mAb; retifanlimab), with or without aGITR agonist mAb (INCAGN-1949), in recurrent or metastatic HNSCC (NCT04470024). Patient population to include HPV-positive or HPV-negative, ECOG 0-2, with therapy continued until confirmed progression (RECIST 1.1), up to 2 years. Primary objective is safety, DLT ≤ 33%, with secondary efficacy objectives of ORR (PR+CR) and 2 year OS. Initial safety lead-in (n = 3+3 per arm), will be followed by phase Ib expansion of one/both arms if immunologically promising, 28 patients per arm, futility if <4/15 responses.

Study Drugs	Cyclophosphamide 300mg/m2 IV, priming Day (-2) only Vaccine (DPV-001)- Day 1 intranodal US bilateral inguinal- Days 8,15 intradermal, then q2wks to week 22- Thereafter q4wks until progression, up to 2 years aPD-1 (retifanlimab) 500mg IV q4wks, start Day 15 (Arms 1 & 2) aGITR (INCAGN01876) 300mg IV q2wks, start Day 1 (Arm 2 only)
Response(RECIST 1.1)	CT weeks 8 and 12, then q3mos
ImmunologicMonitoring	PBL and sera are collected regularly and PBL are evaluated by flow cytometry. Biopsies obtained at baseline, Day 15 and Day 57, analyzed by mIF and 10x scRNA-Seq. Sera analyzed by phage immunoprecipitation (PhIP) sequencing for reactivity against thehuman proteome. Immune monitoring modifications that allow for improved characterization of immune cell subsets will be presented.

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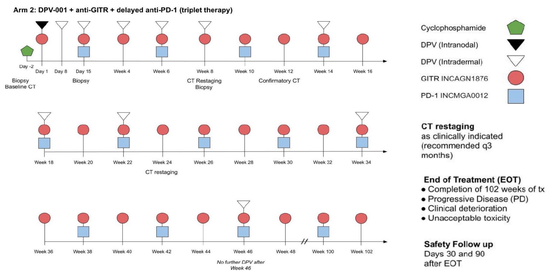
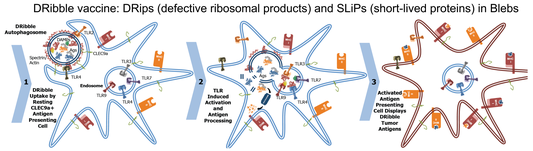
Clinical Trial Design

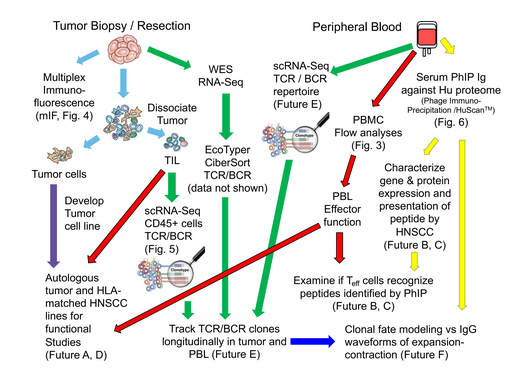


DRibble vaccine: DRips (defective ribosomal products) and SLiPs (short-lived proteins) in Blebs



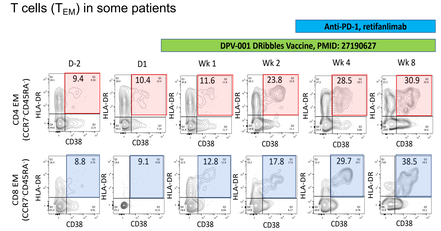
DPV-001 DRibble Vaccine contains 5 TLR/NOD agonists, 15 DAMPs & molecular chaperones, >300 proteins for genes overexpressed in HNSCC, and non-canonical alternative cancer neoantigens (Dark Matter), packaged in a spectrin and actin coated microvesicle targeted to CLEC9A+ DCs

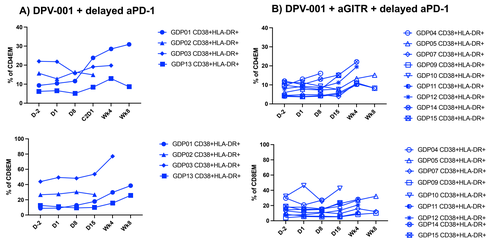
Immunological Monitoring Strategy



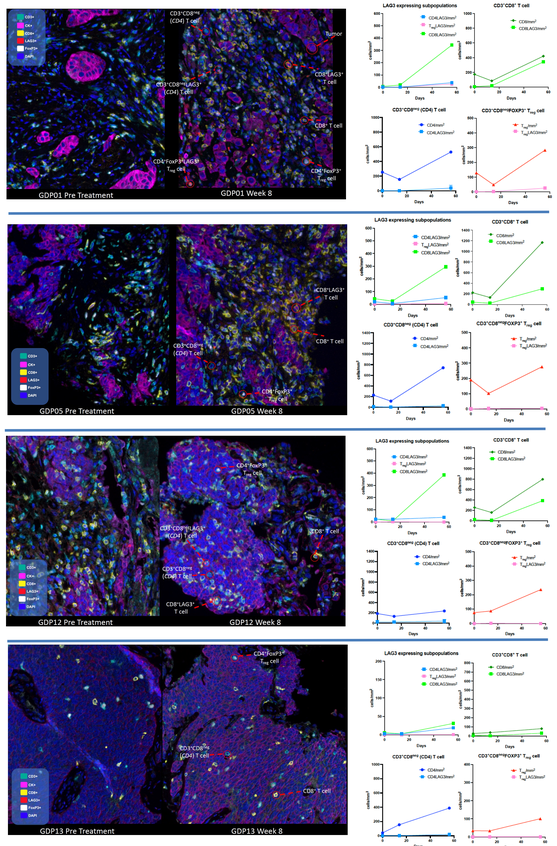
Flow Cytometric Analyses (Blood)

Increases in activated (HLA DR+ / CD38+) CD4 and CD8 effector memory T cells (T_{EM}) in some patients

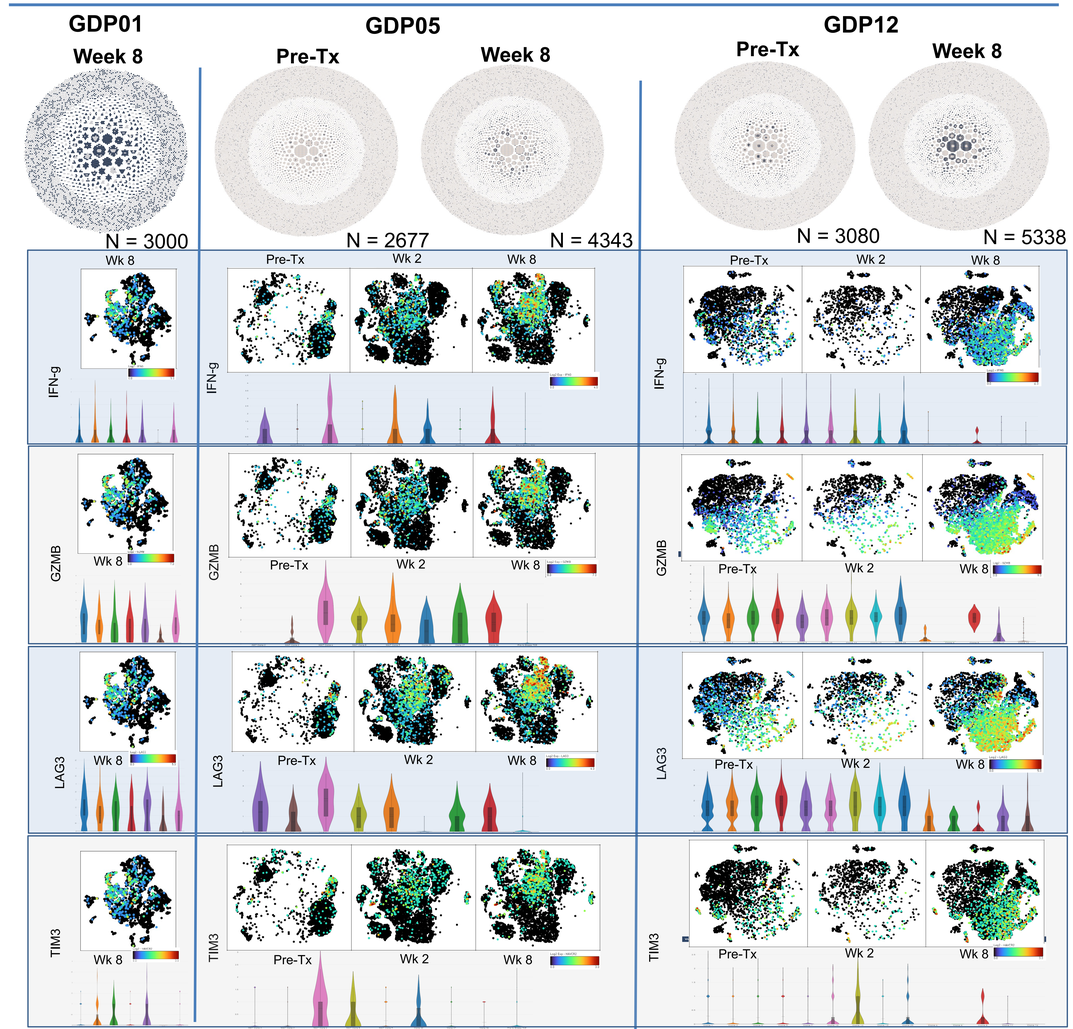




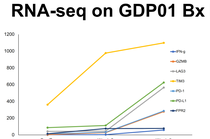
Multiplex IF: Tx increased TIL and LAG3+ CD8+ TIL



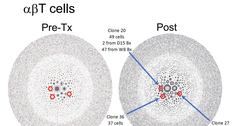
scRNA-seq and TCR-seq Analyses of Tumor Biopsies (Bx)

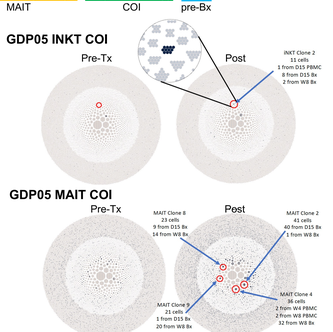


RNA-seq on GDP01 Bx FFPE

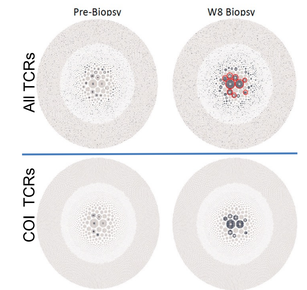


GDP05 Clones Of Interest (COI)



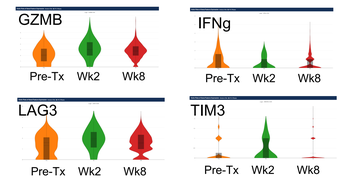


GDP12: T cell Clones of Interest - Enriched in the Wk 8 Bx



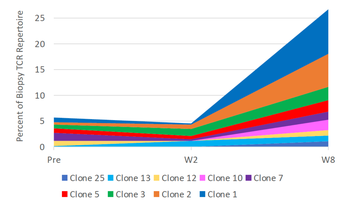
GDP12 COI were selected based on level of expansion in the week 8 biopsy. Top right figure circles the 9 COI identified. Each dot is a single T cell. Clusters of dots enumerate the number of T cells identified for that clone at the specified time point.

GDP12 COI Respond to Tx



scRNA-seq data for 9 COI identified in GDP12 tumor biopsies were pooled and evaluated for specified gene expression in pre-treatment, week 2, and week 8 biopsies.

GDP12 COI - Expansion



GDP12 COI are enriched in the week 8 biopsy. The colors labelling each clone in the Alluvial Plot match the colors used to identify the same clones in the GDP12 clone violin plots (left) presented under the t-SNE plots for GDP12. GDP12 COI expressed increased LAG3, IFN-γ and GZMB compared to other TCR clones present in the tumor.

Preliminary Conclusions

BLOOD
- Flow cytometric analyses of PBMC documented increases in activated (HLA DR+ / CD38+) CD4 and CD8 effector memory T (T_{EM}) cells in some patients. Preliminary evaluation TCR and BCR analyses of blood samples not shown.

TUMOR
- mIF documented increased intra-tumoral T cell from baseline to week 8 biopsies in 3 of 4 patients evaluated. These same 3 patients expressed increased numbers of LAG3+ T cells.
- Two patterns of clonal TCR expansion were seen in pts. 1) Proliferation of previously undetected clones in the tumor, and 2) Expansion of clones in the tumor that predated treatment. The first scenario resulted in a diverse set of pheno/genotypically distinct αβ T cell, iNKT and MAIT cells. The second involved a group of pheno/genotypically similar αβ T cell clones that show signs of activation in the tumor at week 2 (Wk 2) and expanded to become the dominate clones in the tumor at week 8 (Wk 8).
- Biopsies show evidence of increasing IFNG, GZMB, LAG3 and TIM3 in the tumor during treatment. The GDP12 COI demonstrate increased GZMB, TIM3, and LAG3 at week 2, suggesting an early impact of treatment.

Future Plans

- Functional studies characterizing whether clones recognize autologous or HLA-matched HNSCC cell lines are underway and includes an evaluation of neoantigens, TAAs, and non-canonical peptides (Dark Matter – Ref 1).
- Evaluation of humoral immunity to human proteome and whether there is a coordinated B and CD8 T cell response
- Increased expression of LAG3 by T cells that infiltrate the tumor, and have expand in the tumor, provide a rationale for adding anti-LAG3 to this immunotherapy strategy.

Reference: 1) https://doi.org/10.1158/1078-0432.CCR-23-0422