289 PGV-001: A PHASE 1 TRIAL OF A PERSONALIZED NEOANTIGEN PEPTIDE VACCINE FOR THE TREATMENT OF MALIGNANCIES IN THE ADJUVANT SETTING

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Background The efficacy of T cell directed immunotherapies relies on adequate priming of T cells to tumor-specific neoantigens, which some studies have augmented with synthetic neoantigen vaccines. This is the first report of a personalized genomic vaccine (PGV-001) in multiple histologies in the adjuvant setting.

Methods Tumor and germline RNA and DNA were sequenced, and neoantigen peptides were selected using our OpenVax custom computation pipeline that identifies and ranks mutant sequences by a combination of predicted MHC-I binding affinity and neoantigen abundance within tumor. Up to 10 peptides were synthesized per patient and were administered over the course of 27 weeks in combination with the poly-ICLC. Primary objectives were to determine 1) the safety and tolerability; 2) the feasibility of PGV-001 production and administration; and 3) the immunogenicity of PGV-001. Secondary objectives included immunophenotyping neoantigen-specific T cells in peripheral blood, and characterization of peripheral blood lymphoid, myeloid and humoral responses. We report here for the first time on the primary endpoints.

Results Vaccine was synthesized for 15 patients. A mean of 1619 somatic variants (range 521–5106) were detected. Our pipeline identified a mean of 67.1 neoantigens/patient (range 8–193) and 9.7 peptides/patient were synthesized (range 7–10). 13 patients received PGV-001 (11 patients received all 10 doses and 2 patients received at least 8 doses) while 2 had progressive disease before vaccine initiation. Transient grade 1 injection site reactions were seen in 31% of patients, and one patient experienced grade 1 fever. There were no other significant adverse events. Ex vivo ELISpot analysis of patient blood demonstrated significant induction of T cell responses following receipt of 10 vaccines that were not present after the 6th vaccine, supporting the need for a prolonged dosing schedule. Robust responses were seen in both CD4 and CD8 T cells by intracellular cytokine staining for TNF-a, IFN-a, and IL-2 following in vitro expansion in the presence of vaccine antigens. Additional studies are ongoing to define the most immunogenic antigens.

Conclusions A personalized neoantigen vaccine of synthetic mutant peptides and adjuvant poly-ICLC was successfully synthesized for 15 patients and administered successfully to 87% patients over the course of 27 weeks. The vaccine was well tolerated, and T cell expansion and reactivity to synthetic neoantigens confirms immunogenicity of neoantigens identified with OpenVax.

Trial Registration NCT02721043

Ethics Approval This study was approved by the IRB of The Mount Sinai Hospital in accordance with Federal law. HSM #15-00841.

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290 CYTOKINE AND IMMUNE SUBSET SIGNATURES IN PATIENTS WITH VARIOUS SOLID AND HEMATOLOGICAL MALIGNANCIES TREATED WITH ONCOLYTIC VACCINA VIRUS DELIVERED BY AUTOLOGOUS STROMAL VASCULAR FRACTION CELLS

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Background The development of oncolytic viruses for the treatment of cancer has been significantly hampered by their rapid clearance in circulation due to complement and antibody-mediated neutralization. In our recent first-in-human Phase I clinical trial, we evaluated the safety and feasibility of our approach to enhance virus delivery and improve tumor targeting by utilizing an autologous stromal vascular fraction (SVF) based cell delivery system. Patient sample analysis demonstrated that patients could be stratified based on the level of vaccinia virus amplification in vivo, as evidenced by analysis of persistent viral DNA in the blood.

Methods In the current study, we evaluated the immunomodulatory potential of vaccinia virus delivered by autologous stromal vascular fraction (SVF)-derived cells and attempted to identify immunological correlates of successful vaccinia virus amplification in vivo. To this end, we performed an extensive time-course analysis of cytokines in patients’ plasma as well as various peripheral blood immune subpopulations using Luminex multi-analyte profiling and multi-parameter flow cytometry, respectively. We also analyzed the impact of this therapeutic approach on the innate and adaptive immune subpopulations, including NK cells, myeloid cells, as well as effector, regulatory and memory T cells.

Results Therapy with SFV-delivered oncolytic vaccinia virus induced a coordinated activation of cytokine, T cell and NK cell responses in patients as early as 1 day after treatment, which peaked around 1-week and lasted for up to 1-month post treatment. The ability of the oncolytic virus to effectively amplify in cancer patients correlated with significant changes of multiple innate (NK) and adaptive (T cell) immunological parameters. Interestingly, patient stratification into groups with transient versus persistent viral DNA was linked to opposing and mutually exclusive patterns of robust activation of NK versus T cell responses, respectively. Our study also identified intriguing cytokine and immune subset frequency signatures present at baseline and associated with successful amplification and persistence of oncolytic vaccinia virus in vivo.

Conclusions Overall, this study establishes the timeline of treatment-related immunological changes and identifies biomarkers present at baseline and potential immunological correlates associated with the persistence of virus amplification in vivo. Therefore, our findings provide new insights into the role of interpatient immunological variability and will contribute to the proper evaluation of the therapeutic potency of oncolytic virotherapy in future clinical trials.

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