SYNERGISTIC EFFECTS OF A THERAPEUTIC CANCER VACCINE, AN IMMUNOCYTOKINE, AND AN HDAC INHIBITOR IN AN HPV TUMOR MODEL

Lisa K Poppe*, Nicholas Roller, Miriam Marlene Medina-Enríquez, Jeffrey Schlom, Caroline Jochems Frohlich. National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Background HPV-associated cancers continue to present a major health concern despite the development of prophylactic vaccines. Currently checkpoint inhibition is the only FDA-approved immunotherapy available for HPV-associated cancers, and the response rate remains low. PDS0101 is a liposomal nanoparticle HPV16-specific therapeutic vaccine that has previously been shown to generate strong HPV-specific responses in pre-clinical and clinical studies. We assessed the efficacy of PDS0101 in combination with two other immune-modulating agents. PDS0301 (previously designated NHS-IL12, M94241) is a tumor-targeting immunocytokine composed of the histone binding NHS76 antibody fused to two molecules of IL-12. The epigenetic modifier Entinostat (ENT), a class I histone deacetylase (HDAC) inhibitor, has been shown to increase tumor cell susceptibility to cytotoxic T cell mediated killing and increase necrosis.

Methods The TC-1 murine carcinoma, which expresses HPV16 E6 and E7 but lacks PD-L1, was used in a syngeneic mouse model to evaluate the anti-tumor effects, survival, and changes to peripheral immune cells and the tumor microenvironment induced by combination treatment with PDS0101, PDS0301, and ENT. Tumor infiltrating lymphocytes (TILs) were assessed via flow cytometry, immunohistochemistry, and single cell RNA sequencing. Serum and tumor supernatant analytes were evaluated via ELISA and cytometric bead array.

Results Superior anti-tumor activity and prolonged survival were observed when all three drugs were used in combination, and elevated levels of HPV-specific T cells in the tumor correlated strongly with decreased tumor size. PDS0101 was the primary driver of HPV-specific T cells. PDS0301 reduced M2 macrophages in the tumor and increased effector memory CD8 T cells, and ENT decreased CD4 T cells in the tumor. All three agents were necessary for optimal tumor infiltration of granzyme B+ T and NK cells.

Conclusions These data provide rationale for the combination of therapeutic cancer vaccines, immune-activating tumor targeting cytokines, and HDAC inhibitors in the clinical setting, especially in checkpoint refractory HPV-associated cancers.

Ethics Approval All animal procedures reported in this study that were performed by NCI-CCR affiliated staff were approved by the NCI Animal Care and Use Committee (ACUC) and in accordance with federal regulatory requirements and standards.

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