Title: Loss of Detectable HPV-6 Following Induction of Emergent T cells in Patients with Durable Complete Clinical Response to Treatment for Recurrent Respiratory Papillomatosis using INO-3107

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Introduction: Recurrent respiratory papillomatosis (RRP) is a debilitating chronic disease of the airway caused by infection with Human Papillomavirus (HPV) Types 6 and/or 11 characterized by recurrent, benign tumor growth with the potential for malignant transformation. The current standard of care consists of multiple surgeries, which often lead to lasting damage to the airway and impaired vocal function. Here we describe the viral, immunological and clinical results in two patients who exhibited loss of detectable HPV-6 in a Phase 1/2 trial of INO-3107, a DNA therapy designed to target HPV-6 and HPV-11 for the treatment of adults with RRP (NCT04398433).

Methods: INO-3107 was administered on study Weeks 0, 3, 6 and 9. Peripheral blood mononuclear cells (PBMCs) were assessed by multiparametric flow cytometry and TCRβ sequencing. Formalin-fixed paraffin-embedded papilloma tissue obtained prior to INO-3107 treatment as well as at the end of the 52-week study was assessed by RNA and TCRβ sequencing as well as the SPF10 LiPA25 algorithm for HPV type. Complete Response was defined as the absence of need for surgical intervention for the treatment of RRP in the 52 weeks following treatment with INO-3107.

Results: HPV-6 infection was detected in pre-treatment papilloma tissues for both patients. Activated HPV-specific CD4+ and CD8+ T cells, inclusive of cytotoxic lymphocytes, were elevated in PBMCs following treatment with INO-3107. Infiltration of new T cell clonal populations, confirmed as INO-3107-induced Emergent T cells that trafficked from circulation, were observed in airway tissue biopsies obtained one year after treatment from the same anatomical locations as pre-treatment samples. Further assessment of these tissues confirmed increases in CD4+ and CD8+ T cell signatures, inclusive of both Central and Effector Memory populations while viral assessment yielded a negative result for HPV-6. Laryngoscopic examination of the airway resulted in RRP anatomical severity (Derkay) scores of zero for both patients. Both patients have maintained Complete Response status continuing for over 1,000 days, which amounts to a 3- to 10-fold increase in surgery-free days as compared to the year prior to INO-3107 treatment.

Conclusions: Immune and viral assessments of two patients from the RRP-001 trial revealed the induction of Emergent T cells in circulation as well as CD4+ and CD8+ T cell responses in airway tissues after treatment with INO-3107. These immune responses were observed in the context of loss of HPV-6 positivity in tissue biopsy and site disease scores of zero. Clinical monitoring confirms patients remain surgery-free continuing over 1,000 days each, confirming the ability of INO-3107 to induce HPV-specific immune responses and drive long-term relief from surgical intervention for the treatment of RRP.