Title: Successful Treatment of Recurrent Respiratory Papillomatosis with INO-3107 is Irrespective of Papilloma Microenvironment and Molecular Subtype

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Introduction: Recurrent respiratory papillomatosis (RRP) is a chronic disease of the airway characterized by recurrent papilloma growth caused by Human Papillomavirus (HPV) infection. The current standard of care consists of multiple surgeries, which often lead to lasting damage to the airway and impaired vocal function. Treatments that minimize or eliminate the necessity for these surgeries while ideally targeting the known etiological agents of RRP (HPV-6 and/or HPV-11) are thus an area of need. Various molecular aspects of papilloma tissue are known to have immune suppressive/regulatory activity, inclusive of high viral load, cytokine/chemokine expression profiles and molecular subtype status. Such aspects may present hurdles to efficacy of an immune therapy based on T cell activity. Here we report successful clinical treatment of RRP irrespective of these variables in a Phase 1/2 trial of INO-3107, a DNA therapy designed for the treatment of adults with RRP (NCT04398433).

Methods: INO-3107 was administered on study Weeks 0, 3, 6 and 9. Formalin-fixed paraffin-embedded papilloma tissue obtained prior to INO-3107 treatment was assessed by RNA sequencing. Data analyses were performed via R and Gene Set Enrichment Analysis (GSEA) platforms. Patients were classified as clinical responders if the frequency of required surgery during the 52-week trial was lower than the 52-week period prior to treatment.

Results: The overall clinical response for the trial was 81.3%. Pre-treatment papilloma tissue exhibited diverse viral loads in both HPV-6 and/or HPV-11 infected patients, and reductions in surgical interventions were observed irrespective of either HPV type or viral replication. GSEA driven assessment of pre-treatment papilloma tissue did not identify significant elevations of hallmark Interferon Alpha (IFNα) signaling or Inflammatory modules in patients who responded clinically as compared to those who did not. Likewise, individual assessment of cytokines such as IL-1β, IL-15 and IL-18 did not show elevations specific to patients who exhibited clinical responses, nor did expression of chemokines such as CXCL9 or CXCL10. Regression analyses of VEGFA and PD-L1 expression versus change in surgical intervention while on trial did not reveal a significant correlation. Additionally, categorization of pre-treatment papilloma tissue into Basal (immune permissive) or Differentiated (immune exclusionary) molecular subtypes did not trend with clinical benefit.

Conclusions: Reduction in surgical interventions for the management of RRP after treatment with INO-3107 were not contingent on low viral loads, a pre-inflamed papilloma status or reduced expression of modulators such as VEGFA or PD-L1. Presence of a Differentiated molecular papilloma subtype did not preclude clinical efficacy. Taken together these data indicate that INO-3107 was able to effectively reduce surgical burden in RRP patients irrespective of papilloma microenvironment and molecular subtype.