Title: CLINICAL RESPONSE TO INO-3107 IN RECURRENT RESPIRTORY PAPILLOMATOSIS IS IRRESPECTIVE OF PAPILLOMA MICROENVIRONMENT AND MOLECULAR SUBTYPE

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Introduction: Recurrent respiratory papillomatosis (RRP) is a chronic disease of the airway caused by Human Papillomavirus (HPV) infection. The current standard of care consists of repeat surgeries that can result in airway damage and impaired vocal function. Treatments that minimize or eliminate surgery while targeting the underlying etiology of RRP are needed. High viral load, cytokine expression and molecular subtype have immune suppressive/regulatory activity, which may hinder immune therapy efficacy. Here, we report successful clinical treatment of RRP irrespective of this activity in a Phase 1/2 trial of INO-3107, a DNA therapy designed to target HPV-6/HPV-11 (NCT04398433).

Methods: INO-3107 was administered at Day 0, Weeks 3, 6 and 9. Formalin-fixed paraffin-embedded papilloma tissue obtained pre-treatment was assessed by RNA sequencing and analyzed by Gene Set Enrichment Analysis (GSEA). Patients were classified as clinical responders if surgery frequency during the 52-week trial was lower than the 52-week pre-treatment period.

Results: The overall clinical response for the trial was 81.3%. Pre-treatment papilloma tissue exhibited diverse HPV-6/HPV-11 viral loads, and reductions in surgical interventions were observed irrespective of HPV type or viral replication. GSEA did not identify significant elevations of Hallmark Interferon Alpha signaling or Inflammatory modules in clinical responders compared to non-responders. Neither cytokine (e.g. IL-1β, IL-15 and IL-18) nor chemokine (e.g. CXCL9, CXCL10) expression showed elevations specific to clinical responders. Regression analyses of VEGFA and PD-L1 expression versus change in surgical intervention did not reveal a significant correlation. Molecular subtyping into basal (immune permissive) or differentiated (immune exclusionary) did not trend with clinical benefit.

Conclusions: Reduction in surgical interventions after INO-3107 treatment was not contingent on low viral loads, a pre-inflamed papilloma or reduced expression of VEGFA or PD-L1. A differentiated subtype did not preclude clinical efficacy. These data indicate that INO-3107 effectively reduced surgical burden irrespective of papilloma microenvironment and molecular subtype.