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Program Speaker – Mark S. Chambers

Title
Oral Premalignant Lesion Transformation and Prevention Measures with Monoclonal Antibody Therapy – An MD Anderson Experience

Abstract
Background: Oral Potentially Malignant Disorders (OPMDs) encompass a diverse group of oral mucosal diseases, including the prevalent oral leukoplakia (OL), serving as precursors to transform to invasive oral squamous cell carcinoma (OSCC). OL exhibits an annual malignant transformation rate ranging from 0% to 36%, with distinct risk variations among dysplasia grades. Despite the breadth of research on OPMD the standard-of-care remains local pharmacotherapeutics, surgery or observation. This study aims to evaluate the safety, tolerability, pharmacokinetics, and efficacy of intralesional injections of Nivolumab in patients with OPMDs. Choosing intralesional injection over systemic administration of Nivolumab is motivated by the desire to minimize severe immune-related adverse events associated with systemic exposure to PD-1 inhibitors, and preclinical evidence suggesting that localized, high concentrations of anti-PD-1 antibody in the tumor microenvironment may effectively trigger anti-tumor immune responses.

Objectives: The primary objective is to characterize the safety and tolerability of intralesional Nivolumab, while secondary objectives include assessing objective response rate, pathologic complete response rate, cancer free survival and systemic exposure. We hypothesize that intralesional Nivolumab will be well tolerated and induce clinical responses in patients with high-risk oral premalignant tumors.

Methods: This phase 1, single-arm, open-label, dose-escalation pilot study involves intralesional injections of Nivolumab (index lesion(s)) in patients with high-risk oral premalignant lesions every 3 weeks (total of 4 doses, i.e., 12 weeks). Non-index oral lesion(s) were also documented and monitored. This dose escalation study includes two dose cohorts (10 mg and 20 mg) to assess maximally tolerated dose with a 3 + 6 dose-escalation design. Adverse events are reported according to NCI CTCAE Version 5.0. Serial biopsies before treatment and up to 8 weeks, as well as efficacy evaluated by the change in composite score (size and degree of dysplasia) following treatment of index lesion(s) (major response [MR]: >80% decrease in score; partial response: 40%-80% decrease). Freshly frozen tumors were subjected to RNA sequencing for immune cells abundance and gene pathway analysis to identify biomarkers of response or progression.

Results: In this Interim Analysis, thirteen patients have been recruited, both dose levels were well tolerated. Adverse events included diarrhea, fatigue, and skin rash. By composite score, 22.5% demonstrated a major response, 50% exhibited a partial response , and 37.5% showed stable disease. One patient progressed to invasive SCC in a non-index lesion. RNA sequencing based immune phenotyping revealed increased immune infiltration and CD8 signature in index lesions on-treatment. Pathway analysis from the differentially expressed genes comparing before and after treatment revealed significant alterations in immune pathways: cell mediated immunity, humoral immunity, Natural killer cell signaling and immunoregulatory pathways. Spatial transcriptome analysis and pharmacokinetics data are pending. [ASCO 2024]

Conclusions: This immune checkpoint therapy trial shows that intralesional nivolumab is well tolerated in OPMD and suggests potential biological and clinical activity. A randomized phase II trial to assess cancer-free survival with extended follow-up is recommended to determine the efficacy in preventing cancer progression.

Biography

Dr. Mark S. Chambers is a tenured Professor and clinical investigator in the Departments of Head and Neck Surgery and Radiation Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas. He holds the Susan and Christopher Damico Chair in Viral Associated Malignancies. He also serves as Deputy Chair for the Department of Head and Neck Surgery and Chief of the Section of Oral Oncology and Maxillofacial Prosthodontics. He serves as the Executive Chair of the Institutional Review Board of MD Anderson. Dr. Chambers is recognized nationally and internationally as an oral oncologist and clinical investigator with a focus on developing novel therapeutic approaches in managing the oral sequelae of cancer therapy. His funded clinical research efforts include the conduct of several novel clinical trials evaluating peptides, secretogogues, mucoprotectants, cytokines, and small molecules in the management of treatment-induced salivary dysfunction, mucosal injury, and bone necrosis. Additional interests include biomarker analyses and the oral microbiome influence on cancer development. He and his wife, RoseMarie, have an equine sports business raising and training American Saddlebred horses.

**Has disclosed Affiliation/Financial Interest with the following companies: NIH/NIDCR, MD Anderson Cancer Center, RiboX Therapeutics*