1361 NEOADJUVANT CD40 AGONISM REMODELS THE TUMOR IMMUNE MICROENVIRONMENT IN LOCALLY ADVANCED ESOPHAGEAL/GASTROESOPHAGEAL JUNCTION CANCER

[1]Bridget P Keenan*, [2]Maira Soto, [2]Erin L Filbert, [1]Hai Yang, [1]Stephanie Starzinski, [1]Alec Starzinski, [1]Marissa Gin, [1]Brandon Chen, [1]Phi Le, [1]Tony Li, [1]Brandon Bol, [1]Alexander Cheung, [1]Li Zhang, [2]Frank J Hsu, [1]Andrew H Ko, [1]Lawrence Fong. [1]*University of California San Francisco, San Francisco, CA, USA*; [2]*Apexigen, Inc., San Carlos, CA, USA*

Background Sotigalimab (sotiga) is an agonistic anti-CD40 monoclonal antibody that can stimulate anti-tumor immune responses. In a phase II clinical trial of sotiga combined with neoadjuvant chemoradiation (CRT) in patients with locally advanced esophageal/gastroesophageal junction (E/GEJ) cancer, we saw pathologic complete responses (pCR) in 38% of patients.[1] We performed high dimensional single cell profiling of intratumoral and circulating immune responses induced with sotiga.

Methods Samples were collected from patients with E/GEJ cancer treated on the phase II trial of neoadjuvant sotiga with CRT, including longitudinal assessments of the tumor and peripheral blood mononuclear cells. Biopsies were conducted at baseline and after a single dose of sotiga monotherapy. We used high dimensional techniques, including multiplexed ion beam imaging by time of flight (MIBI-TOF) and multi-omic single cell RNA sequencing (scRNAseq), to investigate the mechanism of action of sotiga.

Results A single dose of sotiga dramatically re-models the tumor immune microenvironment (TME) with upregulation of antigen-processing pathways and modification of metabolic pathways in antigen-presenting cells. Concomitant with these changes in myeloid cells, we also find that sotiga treatment primes new T cell clonotypes and induces an increased frequency and density of activated T cells with enhanced effector function. Treatment also induced a decrease in the frequency of Tregs. Clinical responses were associated with both baseline and treatment-induced T cell states.

Conclusions Treatment with sotiga induced the activation of antigen presentation leading to the downstream generation of novel T cell clonotypes and enhanced T cell activation. The high rates of clinical response with this treatment are associated with both pre-existing and treatment-induced T cell populations. Sotiga can therefore mediate the conversion of an immune-suppressive ('cold') to immune-activated ('hot') TME.

Trial Registration Related to trial #NCT03165994

REFERENCE

1. Ko A NM, Chao J, Sohal DPS. A Multicenter Phase 2 Study of Sotigalimab (CD40 Agonist) in Combination with Neoadjuvant Chemoradiation for Resectable Esophageal and Gastroesophageal Junction (GEJ) Cancers. ESMO Annual Conference. September 9–13, 2022.

Ethics Approval This study was approved by UCSF institutional review board #17–21833.

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