INTRATUMORAL SOTIGALIMAB WITH PEMBROLIZUMAB ACTIVATES ANTIGEN-PRESENTING CELLS AND INDUCES LOCAL AND DISTANT ANTI-TUMOR RESPONSES IN FIRST-LINE METASTATIC MELANOMA: RESULTS OF A PHASE I/II STUDY

Salah-Eddine Bentebibel*, Daniel Johnson, Barbara Pazdrak, Daniel McGrail, Srisuda Lacagompom, Cara Haymaker, Dolia Y Duose, Khalida Wani, Heather Sonnemann, Houseein Saof, Jared K. Burks, Patrick Hwu, Cho Sungnam, Chantale Bernatchez, Suhendan Ekmekcioglu, Gregory Lizée, Adi Diab. The University of Texas MD Anderson, Houston, TX, USA

Background Checkpoint inhibitors (CPI) provide significant clinical benefits for patients with metastatic melanoma (MM). However, the majority of patients do not respond or develop resistance after initial tumor regression. In this ongoing phase I/II study, we assessed intratumoral sotigalimab, a CD40 agonistic antibody in combination with systemic pembrolizumab in CPI treatment naïve MM.

Methods As of May 15, 2022, thirty-two patients were enrolled. Patients received sotigalimab every 3 weeks for a total of 4 doses. The primary objectives include safety and tolerability, determination of the recommended phase 2 dose (RP2D), and assessment of the overall response rate (ORR) by RECIST v1.1. Biomarker analyses of blood and tumor samples were performed to measure immune activation using imaging mass cytometry, TCR sequencing, and a cross-cohort comparison of gene expression data (sotigalimab plus pembrolizumab versus anti-PD-1 monotherapy). Single-nucleus ATAC and RNA sequencing are being performed to determine cell-type-specific chromatin accessibility and transcriptional profiles associated with clinical response.

Results The combination therapy has been well-tolerated, and there were no study discontinuations or death due to treatment-related adverse events, most common treatment-related adverse events were injection-site reactions. Efficacy analysis of thirty patients with disease evaluations demonstrated an ORR of 50% in distant lesions and a disease control rate of 67%. The ORR at the RP2D of 10 mg is 55% (12/22). Responses were observed in PD-L1 negative patients and those with elevated LDH. Multi-omics analysis of peripheral blood mononuclear cells and tumor biopsies demonstrate that sotigalimab effectively engaged CD40 pathway. In comparison to anti-PD-1 monotherapy, the combination therapy significantly increased expression of genes associated with antigen presentation and effector T-cells in local lesions accompanied by an increase in T cell activation genes at distant lesions. Additionally, combination therapy resulted in an increase in clonality with expansion of new clones shared between local and distant lesions. All these immunologic changes were correlated with clinical response. Findings were recapitulated in B16 melanoma preclinical model, which demonstrated that intratumoral CD40 activation synergizes with systemic anti-PD-1 therapy and suppress tumor growth. Therapeutic efficacy was associated with increases in intratumoral conventional type 1 dendritic cells (cDC1), CD8+ T cells, and an increased ratio of intratumoral CD8+ T cells to myeloid-derived suppressor cells.

Conclusions This combination therapy is well tolerated and has a notable clinical response rate, accompanied by broad innate and adaptive immune activation at both local and distant lesions. More biomarker and clinical response data are anticipated in November.

Trial Registration NCT02706353

Ethics Approval The study was approved by FDA and the Institutional Review Board