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A PHASE 1B OPEN-LABEL, SINGLE-ARM DOSE EXPANSION STUDY OF IK-175, AN ORAL AHR INHIBITOR, IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH PRIMARY PD-1 INHIBITOR RESISTANT ADVANCED HEAD AND NECK CANCER

Trupti Lingaraj*, Marissa Timothy, Nerymar Ortiz-Otero, Wilmin Bartolini, Katherine Kacena, Karim Malek, Sergio Santillana. *Ikena Oncology, Boston, MA, USA*

Background Despite recent advances with immunotherapy in head and neck squamous cell carcinoma (HNSCC), many patients progress and develop resistance to checkpoint inhibitors. Aryl hydrocarbon receptor (AHR) is a ligand-activated nuclear transcription factor that regulates the activity of multiple innate and adaptive immune cells. Kynurenine, a ligand generated from tryptophan by IDO1 and TDO2, binds AHR and leads to a net immunosuppressive tumor microenvironment. HNSCC has been found to have high prevalence of nuclear AHR protein expression, indicative of active AHR signaling, making AHR an attractive therapeutic target. IK-175 is an oral selective, small molecule that is being developed as potential first-in-class AHR inhibitor for the treatment of cancer. Given the role of AHR in mediating immunosuppression, IK-175 may overcome the immunosuppressive effects driving resistance to PD-1 inhibitors in HNSCC and improve the clinical activity of nivolumab.

Methods This is a phase 1b, open-label, multicenter, dose-expansion study of IK-175 in combination with nivolumab in adult patients with primary programmed cell death-1 (PD-1) inhibitor resistant metastatic or locally incurable, recurrent head and neck squamous cell carcinoma (HNSCC). IK-175 is administered orally at a dose of 600mg QD (Cohort 1) or 450mg q12h (Cohort 2) in 28 day-cycles in combination with nivolumab (480 mg q4w on Day 1 of every cycle). AHR nuclear localization is being studied as a potential predictive biomarker in patients with HNSCC. The study will enroll unselected HNSCC patients as well as an enriched population that includes patients with AHR + tumors as determined by immunohistochemistry. Key eligibility criteria include patients with histologically confirmed advanced HNSCC that have progressed within 12 weeks of initiation of a PD-1 inhibitor, whether administered alone or in combination with chemotherapy. The primary objectives are to determine the safety, tolerability, and preliminary antitumor activity (ORR, DCR, and DOR) of IK-175 in combination with nivolumab. Secondary objectives are to evaluate the pharmacokinetics of IK-175 and its active metabolites and to assess additional parameters of preliminary antitumor activity (PFS). Key exploratory objectives are to evaluate pharmacodynamic effects on paired tumor biopsies and peripheral immune cells, to assess candidate baseline biomarkers, and correlative analyses of tumor AHR nuclear localization with disease response. Estimated enrollment is approximately 54 patients; the study started in July 2022.

Trial Registration NCT05472506

Ethics Approval The study was approved by Advarra Central IRB, approval number MOD01366597

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