A PHASE 1A/B STUDY OF IK-175, AN ORAL AHR INHIBITOR, ALONE AND IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH LOCALLY DVANCED OR METASTATIC SOLID TUMORS AND UROTHELIAL CARCINOMA

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Background Aryl Hydrocarbon Receptor (AHR) is a transcription factor that regulates the activity of multiple innate and adaptive immune cells after binding to several endogenous and exogenous ligands, including kynurenine, generated from tryptophan by IDO1 and TDO2. Binding of kynurenine to AHR leads to a net immunosuppressive tumor microenvironment, making AHR an attractive therapeutic target in multiple cancer types. IK-175 is a selective, small molecule AHR inhibitor being developed as an oral (PO) agent. In human T-cells, IK-175 induces an activated T-cell state, interleukin (IL)-22 gene expression, and leads to an increase in proinflammatory cytokines, such as IL-2 and IL-9. IK-175 demonstrates antitumor activity as a single agent or in combination with checkpoint inhibitors in multiple mouse tumor models.¹ AHR immunohistochemistry (IHC) tumor microarray analysis across 15 different tumor types revealed that bladder cancer has the highest level of AHR protein expression and AHR nuclear localization, an indicator of active AHR signaling. Therefore, nuclear AHR in urothelial carcinoma tumors is being investigated for potential predictive clinical benefit with IK-175.

Methods This is a first-in-human, phase 1a/b, open-label, multicenter, dose-escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of IK-175 administered PO daily in 21 or 28 day-cycle as a single agent, and in combination with nivolumab, 480 mg q4w on Day 1 of every cycle, in 93 adult patients with advanced solid tumors (dose escalation) and urothelial carcinoma (dose expansion) in both treatment arms. Key eligibility criteria include patients with histologically confirmed solid tumors (including urothelial carcinoma) who have locally recurrent or metastatic disease that have progressed on or following all standard of care therapies deemed appropriate by the treating physician. Primary endpoints include dose-limiting toxicities and treatment-emergent adverse events. Key secondary endpoints include IK-175 PK profile on both treatment arms, PD of IK-175, and preliminary efficacy. The study will explore tumor AHR nuclear localization by IHC as a predictive biomarker in patients with urothelial carcinoma in both treatment arms. A minimum of 10 patients having a positive AHR nuclear localization test (cutoff for positive AHR is 65% tumor cells positive for 2+/3 + nuclear AHR by a validated IHC assay) will be enrolled in the combination arm. Exploratory biomarkers of IK-175 mediated PD effects, PK-PD correlations, and correlative analyses of predictive and PD measurements with response and resistance will be performed. The study started in January 2020 and is ongoing.

Acknowledgements Ikena Oncology would like to recognize and express gratitude to Dr. Jason Sager for his contributions to the implementation of this trial.

Trial Registration ClinicalTrials.gov registration: NCT04200963

REFERENCE

1. McGovern K, Castro A, Cavanaugh J, Discovery of clinical candidate IK-175, a selective orally active AHR antagonist. *SITC* 2020, poster presentation.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.392>