661 INITIAL RESULTS FROM A PHASE 1A/B STUDY OF IK-175, AN ORAL AHR INHIBITOR, AS A SINGLE AGENT AND IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS AND UROTHELIAL CARCINOMA

[1]David Aggen*, [2]Meredith McKean, [3]Nehal Lakhani, [4]Babar Bashir, [5]Jean Hoffman-Censits, [6]Omar Alhalabi, [7]Elizabeth Guancial, [8]Isaac Bowman, [9]Alan Tan, [10]Trupti Lingaraj, [10]Marissa Timothy, [10]Nerymar Ortiz-Otero, [10]Wilmin Bartolini, [10]Katherine Kacena, [10]Karim Malek, [10]Sergio Santillana, [11]Jason Luke. *[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Tennessee Oncology, Nashville, TN, USA; [3]START Midwest, Grand Rapids, MI, USA; [4]Thomas Jefferson University, Philadelphia, PA, USA; [5]Johns Hopkins, Baltimore, MA, USA; [6]MD Anderson Cancer Center, Houston, TX, USA; [7]Florida Cancer Specialists, Sarasota, FL, USA; [8]Banner Health, Gilbert, AZ, USA; [9]Rush University, Chicago, IL, USA; [10]Ikena Oncology, Boston, MA, USA; [11]University of Pittsburgh, Pittsburgh, PA, USA*

Background Aryl Hydrocarbon receptor (AHR) is a transcription factor activated by binding to ligands, including kynurenine, causing expression of immune modulating genes leading to immunosuppression. IK-175 is an oral, selective, small molecule being developed as a potential first-in-class AHR inhibitor to overcome the immunosuppressive effects driving resistance to PD-1/L1 inhibitors. Computational and tissue-based analyses revealed urothelial cancer as having high levels of AHR signaling and nuclear protein localization.

Methods Dose escalation patients with advanced solid tumors received escalating daily doses of IK-175 as monotherapy or in combination with nivolumab 480 mg IV every 4 weeks (mTPI-2 design). Expansion cohorts of both treatment arms enrolled heavily pretreated urothelial carcinoma patients, who have progressed within 12 weeks of last dose of PD-1/L1 inhibitors (Simon 2-stage design). Expansion cohorts were enriched to include AHR+ patients determined by immunohistochemistry using a cutoff of 65% cells with 2+/3+ staining. Study objectives included evaluation of safety, pharmacokinetics, pharmacodynamics, MTD, RP2D and antitumor activity (RECIST 1.1) of IK-175 in both arms.

Results As of June 24, 2022, 43 patients were evaluated: 26 monotherapy (from 200 to 1600mg PO daily) and 17 combination (800 and 1200mg PO daily). Median age was 70 years (range 28-82), 28/43 (65%) patients received ≥3 lines of prior therapy including CPIs. 4/11 monotherapy and 3/11 combination urothelial cancer patients had AHR+ tumors. In both treatment arms, MTD was not reached and 1200mg PO QD was the selected IK-175 expansion dose based on the totality of the data. Most common treatment-related adverse events (TRAEs) in monotherapy were nausea and rash with 3 patients (12%) reporting ≥Grade3 TRAEs (nausea, proteinuria, and adrenal insufficiency). Most frequent TRAEs in combination arm were fatigue and dysgeusia with 1 patient (6%) reporting ≥Grade3 TRAEs (immune-related arthritis). Other suspected immune-related AEs included adrenal insufficiency, proteinuria, rash, and myopathy. In dose escalation, 3/13 response-evaluable patients in monotherapy and 2/5 in combination had prolonged stable disease (range 16-74 weeks). Preliminary assessment of antitumor activity in 20 response-evaluable urothelial carcinoma patients in both treatment arms showed 3 confirmed partial responses, having DoR up to 11.7 months and ongoing. Updated results, immune monitoring, and biomarker analysis will be presented.

Conclusions In this initial analysis, IK-175 was well tolerated and showed encouraging antitumor activity in eligible urothelial cancer patients in both monotherapy and combination arms. Based on the objective responses observed in stage 1 of both cohorts, investigation of AHR inhibition with IK-175 in urothelial carcinoma is ongoing.

Trial Registration NCT04200963

Ethics Approval This trial was approved by all participating IRBs.

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