(680) A Phase 1b open-label, single-arm study of IK-175, an oral AHR inhibitor, in combination with nivolumab in patients with PD-1 inhibitor resistant metastatic or recurrent head and neck cancer

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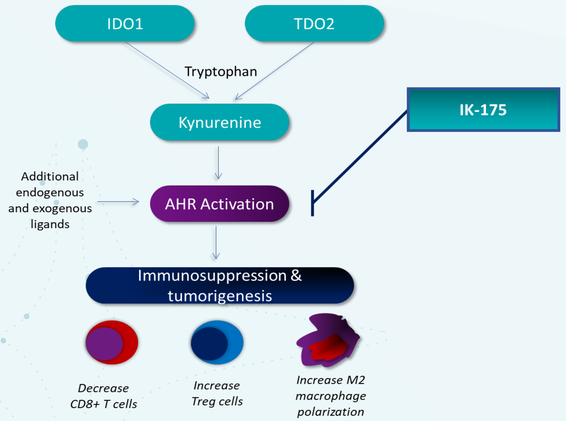
Background

- Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide
- PD-1 inhibitors targeting immune checkpoint proteins are the current standard of care in HNSCC in advanced disease, however despite the clear clinical benefit associated with their use, only a subset of patients with R/R HNSCC gain long term benefit from these therapies
- Resistance to checkpoint inhibitors (CPI) still represents an area of significant unmet medical need
- Aryl Hydrocarbon Receptor (AHR) is a ligand-activated transcription factor that regulates the activity of multiple innate and adaptive immune cells
- AHR plays a dominant role in mediating immunosuppression by modifying immune cell gene expression and the pathway is highly activated in HNSCC
- IK-175 is an oral, selective, potential first-in-class inhibitor of AHR and is currently being studied in solid tumors and urothelial carcinoma showing initial antitumor activity in patients who have progressed on prior CPI
- IK-175 may help overcome the immunosuppressive effects driving resistance to PD-1 inhibitors in HNSCC and may improve the clinical activity of nivolumab in this setting

Figure 1: IK-175 Inhibits AHR Activation

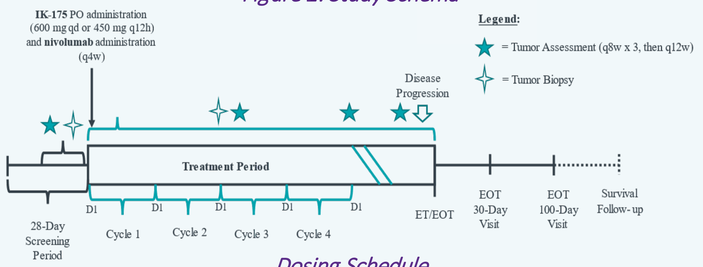


Methods

Study Design

- This is a phase 1b, open-label, multicenter, dose optimization study assessing the safety and preliminary antitumor activity of IK-175 in combination with nivolumab in R/R HNSCC patients
- Approximately 54 patients with primary or secondary PD-1 inhibitor resistant metastatic or locally incurable, recurrent HNSCC will be enrolled and randomized in two dose level cohorts to determine the optimal dose of IK-175 in combination with nivolumab in this population
- Enrichment by assessment of AHR nuclear localization by IHC in patients with HNSCC in both treatment arms

Figure 2: Study Schema



Dosing Schedule

	IK-175	Nivolumab
Cohort 1	600mg QD PO	480mg q4w IV
Cohort 2	450mg q12h PO	480mg q4w IV

Key Objectives and Endpoints

Objectives	Endpoints
Primary	• Safety and tolerability of IK-175 in combination with nivolumab • ORR, DCR, DoR (RECIST1.1)
Secondary	• PK of IK-175 and metabolites including $t_{1/2}$, AUC, C_{max}, and C_{min} • PFS (RECIST1.1)
Exploratory	• Pharmacodynamic immune effects • PFS and OS at 12 months (RECIST1.1)

Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Subject has a histologically confirmed metastatic or locally incurable, recurrent HNSCC with primary or secondary resistance to PD-1 inhibitors, whether administered alone or in combination with chemotherapy	Subject who are unable to swallow or have an impaired GI function that could significantly interfere with the absorption of IK-175. Subjects who are dependent on a gastrostomy tube for feeding and medication administration are permitted to enroll.
Tumors must express PD-L1 with a minimum CPS ≥ 1	Subject has received prior treatment with an AHR inhibitor
Subjects can be enrolled regardless of their tumor's expression of human papillomavirus (HPV)	Subject has untreated or symptomatic CNS tumors or metastases
Subjects are required to have received prior treatment with a platinum-based chemotherapy in the recurrent or metastatic disease setting, unless medically contraindicated	Subject has any condition requiring continuous systemic treatment with either corticosteroids (> 11 mg daily prednisone or equivalent) or other immunosuppressive medications within 2 weeks prior to first dose of study treatment

Translational Research

- Correlative analyses of tumor AHR nuclear localization with clinical outcomes
- Evaluation of pharmacodynamic effects of IK-175 in combination with nivolumab in paired tumor biopsies and peripheral immune cells

Statistical Considerations

- Patients will be randomized 1:1 across 2 dose cohorts
- A Simon 2-stage design will be used to evaluate preliminary antitumor activity of IK-175 in combination with nivolumab
- Enrichment strategy to include patients with elevated nuclear AHR

Study Status

- The study was approved in July 2022 and will be open for enrollment in November 2022
- Region: USA
- Clinical trial information: NCT05472506

Learn more about the study at clinicaltrials.gov

Download this poster and visit the Ikena website