(661) Initial Results from a Phase 1a/b Study of IK-175, an Oral AHR Inhibitor, as Single Agent and in Combination with Nivolumab in Patients with Advanced Solid Tumors and Urothelial Cancer

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Background

- Aryl Hydrocarbon Receptor (AHR) is a ligand-activated transcription factor that regulates activity of multiple innate and adaptive immune cells
- AHR can bind to a number of immunosuppressive ligands, one of them being kynurenine generated from the precursor tryptophan by IDO1 and TDO2
- AHR upregulates PD-1 on CD8+ T cells as well as inducing Treg cells and suppressing IFN leading to immunosuppression and tumorigenesis

Figure 1: IK-175 Inhibits AHR Activation

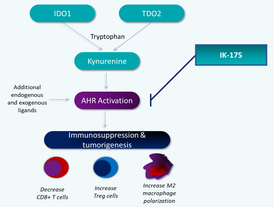
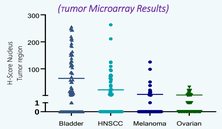


Figure 2: AHR Signaling Activation in Solid Tumors
(rumor Microarray Results)



- Urothelial carcinoma has been shown to have high levels of AHR signaling activation [1]
- **IK-175 is a selective, small molecule AHR inhibitor; 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**

Methods

- Study is enrolling patients with locally advanced or metastatic solid tumors (dose escalation) or unresectable locally recurrent or metastatic urothelial carcinoma (dose expansion) who have exhausted prior standard of care therapies
- Expansion cohorts (urothelial carcinoma only) is enriched to include patients expressing high levels of AHR by IHC[2]
- Dose escalation ranged from 200-1200 mg QD and 800 mg BID (monotherapy) and 800 mg and 1200 mg QD (combination with nivolumab 480 mg q4w) using mTPI2 design
- Expansion cohorts used Simon 2-stage design requiring at least 1 responder in stage 1 UC patients to proceed to the second stage
- **Primary endpoints**: Safety, tolerability, MTD, RP2D
- Secondary endpoints: PK (t1/2, AUC, C_{max}), ORR, PFS, DoR, DCR, DOT, immune pharmacodynamic endpoints
- Exploratory endpoints: additional PK and AHR target gene changes

Results

Table 1: Patient Demographics

	Monotherapy (n=26)	Combination w/Nivolumab (n=17)	All Treated Patients (N=43)
Age, years median (range)	71 (28-83)	70 (45-82)	70 (28-83)
Sex, n(%)			
Female	10 (38.5)	8 (47.1)	22 (41.9)
Prior Lines of Anticancer Therapy, n(%)			
0-2	9 (34.6)	6 (35.3)	15 (34.9)
3-10	17 (65.4)	11 (64.7)	28 (65.1)
Prior ADC Therapy (% of UC patients only)	9/11 (81.8)	6/11 (54.5)	15/22 (68.2)

- Analysis of 26 patients in monotherapy and 17 in combination arm (Data cutoff 22Sept2022)(**Safety analysis**)
- A total of 20 response-evaluable urothelial carcinoma patients from both expansion cohorts are evaluated(**RECIST 1.1 response analysis)**
- 4 monotherapy and 5 combination patients expressed high levels of AHR
- **All patients had progressed within 12 weeks of the last dose of any CPI including patients who were either primary refractory or resistant to nivolumab**

1. Sanchez-Martin, et al, STIC 2021 Computational Biology and Tissue-based Approaches to Inform Indication Selection for a Novel AHR Inhibitor
2. McKean et al, ASCO 2022 TIP: A Phase 1a/b Open Label Study of IK-175, an Oral AHR Inhibitor, Alone and in Combination with Nivolumab in Patients with Locally Advanced or Metastatic Solid Tumors and Urothelial Carcinoma

Safety

- **No DLTs observed and MTD was not reached at doses explored in either treatment arm**
- Dose of 1200 mg QD was selected for expansion cohorts in urothelial carcinoma patients
- 2 related SAEs (Gr3 generalized weakness and Gr3 immune-mediated arthritis) were reported in combination arm
- TEAEs were primarily Gr1 and Gr2 (Table 2) with the most frequently occurring treatment-related AEs being rash and nausea (monotherapy) and fatigue and dysgeusia (combination)
- **Immune-related AEs were reported in both monotherapy and combination arms** (Table 3)

Table 2: Treatment Emergent Adverse Event (TEAE) Summary

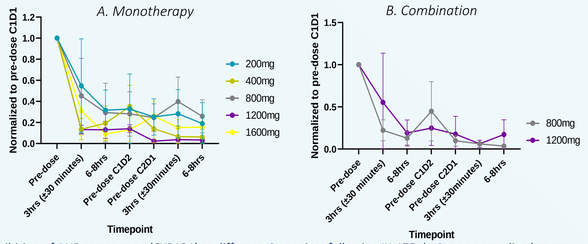
	Monotherapy (n=26)	Combination with Nivolumab (n=17)	All Treated Patients (N=43)
Any TEAE n(%)	26 (100.0)	17 (100.0)	43 (100.0)
Any ≥Gr 3 TEAE	14 (53.8)	11 (64.7)	25 (58.1)
Any treatment-related TEAE	11 (42.3)	15 (88.2)	26 (60.5)
Any ≥Gr 3 treatment-related TEAE	3 (11.5)	4 (23.5)	7 (16.3)
Any SAE	10 (38.4)	9 (52.9)	19 (44.2)
Any treatment-related SAE	0 (0)	2 (11.8)	2 (4.7)
Dose Modification and Interruption n(%)			
TEAE leading to dose modification	5 (19.2)	2 (11.8)	7 (16.3)
TEAE leading to drug interruption	2 (7.7)	1 (5.9)	3 (7.0)
TEAE leading to drug discontinuation	3 (11.5)	1 (5.9)	4 (9.3)

Table 3: Suspected Immune-related Adverse Events

Immune-related AE (PT)	Monotherapy (n=26)	Combination with Nivolumab (n=17)	All treated patients (n=43)
Rash maculopapular n (%)	3 (11.5)	2 (11.8)	5 (11.6)
Proteinuria n(%)	1 (3.8)	1 (5.9)	2 (4.7)
Generalized weakness n(%)	0 (0.0)	2 (11.8)	2 (4.7)
Immune-mediated arthritis n(%)	0 (0.0)	1 (5.9)	1 (2.3)
Adrenal insufficiency n (%)	1 (3.8)	0 (0.0)	1 (2.3)

Pharmacodynamics

Figure 3: Pharmacodynamic Modulation of AHR in Peripheral Blood (Dose Escalation)



Inhibition of AHR target gene (CYP1B1) at different timepoints following IK-175 dosing as normalized to pre-dose C1D1 gene expression in dose escalation patients for single agent (A) and the nivolumab combination (B). Cycle 1 Day 1 (C1D1), Cycle 2 Day 1 (C2D1). N=3 for each dose groups analyzed.

IK-175 Antitumor Activity

Total patient: 43
Evaluable dose escalation: 20 (15 mono, 5 combo)
Evaluable urothelial carcinoma dose expansion: 20 (10 mono, 10 combo)

- In dose escalation 3/15 (monotherapy) and 2/5 (combination) patients had prolonged stable disease (16-74 weeks)
- In dose expansion cohorts **3 confirmed partial responses (cPR)** were observed in urothelial carcinoma patients (Table 4) with **duration of response ranging from 4.5-14.9 months**

Table 4: Clinical Outcomes in Response-Evaluable Urothelial Carcinoma Patients (Dose Expansion)*

	Monotherapy (n=10)	Combination (n=10)
Best overall response		
Confirmed partial response	1 (10%)	2 (20%)
Stable Disease	1** (10%)	2 (20%)
Progressive disease	6 (60%)	6 (60%)
ORR, n(%)	1 (10%)	2 (20%)
DCR, n(%)	2 (20%)	4 (40%)

*Response-Evaluable: Patients with at least 2 imaging assessments. **2 additional patients reached SD at first post-baseline scan ; **1 patient treated beyond progression

IK-175 + Nivolumab Combo Antitumor Activity

Encouraging, durable, anti-tumor activity including 40% disease control rate seen on stage 1 combination dose expansion cohort (urothelial carcinoma)

Figure 4: Percent Δ in Sum of Diameters Over Time (Urothelial Carcinoma; Combination Dose Expansion)

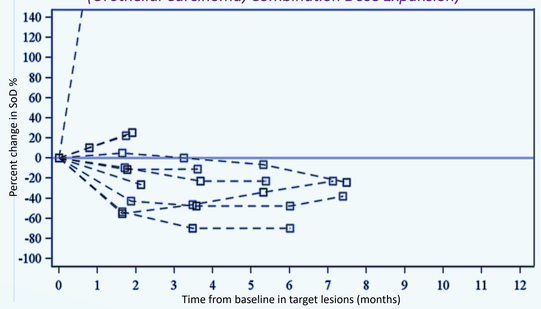
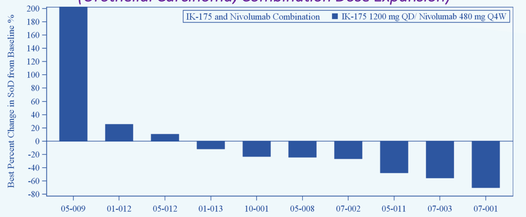


Figure 5: Percent Δ in Sum of Diameters (Urothelial Carcinoma; Combination Dose Expansion)



IK-175 Monotherapy Antitumor Activity

Figure 6: Percent Δ in Sum of Diameters Over Time (Urothelial Carcinoma; Monotherapy Dose Expansion)

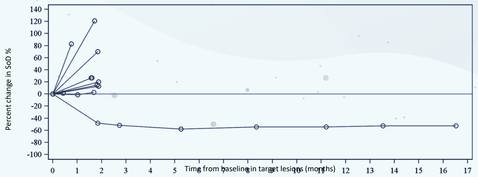
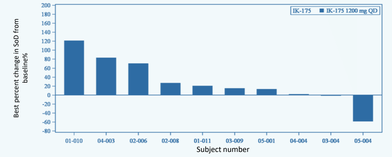


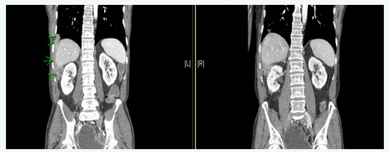
Figure 7: Percent Δ in Sum of Diameters (Urothelial Carcinoma; Monotherapy Dose Expansion)



Monotherapy Urothelial Carcinoma Patient - Case Study

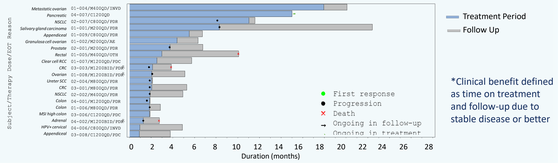
Figure 8: Radiographic Scan

- 66 yo male with urothelial carcinoma and peritoneal metastases
- **5 prior lines of therapy including** chemotherapy/atezolizumab, enfortumab, nivolumab with clear progression
- Significant AEs include Gr3 proteinuria
- **53% Reduction in tumor and DoR is 14.9 months and ongoing**



3/25/2021 6/22/2021

Figure 9: Clinical Benefit in other Solid Tumor Patients Excluding Urothelial Carcinoma (Dose Escalation)*



*Clinical benefit defined as time on treatment and follow-up due to stable disease or better

Conclusions

- **To our knowledge , IK-175-001 is the first clinical program to report data for a small molecule AHR antagonist in urothelial carcinoma patients who have progressed on prior CPI**
- **Initial data shows that IK-175 is well tolerated with a predictable safety profile**
- **Initial results demonstrate encouraging, durable, anti-tumor activity seen in stage 1 both in monotherapy and combination arms in urothelial carcinoma patients**
- **Stage 2 of dose expansion in both treatment arms continue to enroll**