(#2599) IK-175, an Oral AHR Inhibitor, as Monotherapy and in Combination with Nivolumab in Patients with Urothelial Carcinoma Resistant/Refractory to PD-1/L1 Inhibitors: Final Phase 1b Results

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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 upregulates PD-1 on CD8+ T-cells and induces Treg cells, suppressing IFN and leading to immunosuppression and tumorigenesis
- Urothelial Carcinoma (UC) demonstrates increased AHR signaling and nuclear protein localization shown by gene expression analysis and tissue-based IHC[1]

Figure 1: IK-175 Inhibits AHR Activation

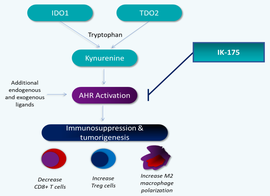
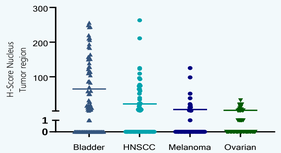


Figure 2: AHR Signaling Activation in Solid Tumors
(Tumor Microarray Results)



IK-175 is an oral, 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

- Phase 1a/b study enrolled 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
- UC patients must have shown progression within 12 weeks of last dose of CPI and included patients who were primary refractory or resistant to nivolumab
- Dose expansion UC patients in monotherapy and combination arms received 1200mg QD of IK-175; combination patients received 480 mg q4w of nivolumab
- UC Expansion cohorts used Simon 2-stage design and the combination arm was enriched for nuclear AHR+ tumors[1]
- **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

- Results shown here are from the 1200mg UC expansion cohorts (Data cutoff July 31, 2023); dose escalation results were previously presented[3]

Table 1: Demographics and Baseline Characteristics (Safety Population)

	Monotherapy (n=14)	Combination w/Nivolumab (n=43)	All Treated Patients (N=57)
Age, years median (range)	69 (26-81)	69 (44-79)	69 (26-79)
Sex, n(%)			
Female	12 (41.4)	13 (26.5)	25 (32.1)
Prior Lines of Anticancer Therapy, n(%)			
0-1	1 (7.1)	4 (9.3)	5 (10.3)
2-4	7 (50.0)	26 (60.5)	33 (57.9)
≥5	6 (42.9)	13 (30.2)	19 (33.3)
Prior ADC, n(%)	10 (71.4)	29 (67.4)	39 (68.4)
AHR+ nuclear localization	5 (35.7)	14 (32.6)	19 (33.3)

Safety

- 3 related SAEs (Gr2 atrial fibrillation, 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 4)
- No treatment-related deaths were reported

Table 2: Treatment Emergent Adverse Event (TEAE) Summary

	Monotherapy (n=14)	Combination with Nivolumab (n=43)	All Treated Patients (N=57)
Any TEAE n(%)	14 (100.0)	43 (100.0)	57 (100.0)
related	10 (71.4)	37 (86.0)	47 (82.4)
Any ≥Gr 3 TEAE	9 (64.3)	23 (22.5)	32 (56.1)
related	3 (21.4)	8 (18.6)	11 (19.3)
Any SAE	8 (57.1)	23 (53.4)	31 (54.4)
related	0 (0)	3 (7.0)	3 (5.3)
TEAE leading to drug discontinuation n(%)	3 (21.4)	1 (2.3)	4 (7.0)

Table 3: Most Frequent Treatment-related Adverse Events (≥10% of patients)

Preferred Term n(%)	Monotherapy (n =14)	Combination with Nivolumab (n=43)	All treated patients (n=57)
Nausea	4 (28.6)	12 (27.9)	16 (28.1)
Diarrhoea	2 (14.3)	13 (30.2)	15 (26.3)
Fatigue	3 (21.4)	10 (23.3)	13 (22.8)
Decreased appetite	1 (3.8)	6 (14.0)	7 (12.3)
Vomiting	0 (0.0)	5 (11.6)	5 (8.7)

Table 4: Suspected Immune-related Adverse Events

Immune-related AE (PT)	Monotherapy (n =14)	Combination with Nivolumab (n=43)	All treated patients (n=57)
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)

IK-175 Antitumor Activity

- **3 confirmed partial responses (1 in mono and 2 in combo arm)** with **duration of response ranging from 4.4-22.6 months**
- Prolonged clinical benefit in 6 patients (1 in monotherapy and 5 in combination) with SD > 6months
- 2 combination patients treated beyond progression (for 4 and 10 additional months) due to clinical benefit and tumor reduction in target lesions
- 1 patient in the combination arm achieved a CR in target and non-target lesions, however new lesions were observed and patient discontinued due to PD
- Small sample size and low number of responders limited the ability to establish a statistically significant association of AHR positivity with clinical outcomes

Table 5: Clinical Outcomes in Response-Evaluable Urothelial Carcinoma Patients (Dose Expansion)*

	Monotherapy (n=13)	Combination (n=33)
Best overall response		
Confirmed partial response	1 (7.7%)	2 (6.1%)
Stable Disease	5 (10%)	14 (20%)
ORR, n(%)	1 (7.7%)	2 (6.1%)
DCR, n(%)	6 (46.2%)	16 (48.5%)
DOR, months	22.6	4.4-7.3

*Response-Evaluable: Patients with at least 1post-baseline imaging assessment.

IK-175 Monotherapy Antitumor Activity

Figure 3: Percent Δ in Sum of Diameters Over Time (Urothelial Carcinoma; Monotherapy Dose Expansion)

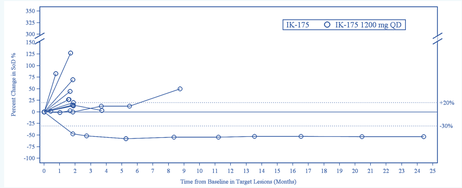
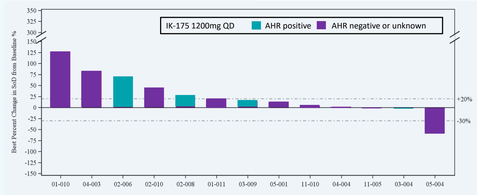


Figure 4: Percent Δ in Sum of Diameters (Urothelial Carcinoma; Monotherapy Dose Expansion)



IK-175 + Nivolumab Combo Antitumor Activity

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

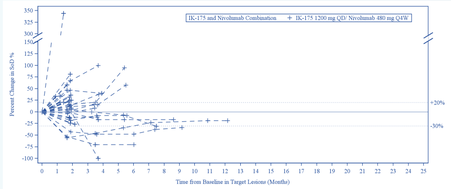


Figure 6: Percent Δ in Sum of Diameters (Urothelial Carcinoma; Combination Dose Expansion)

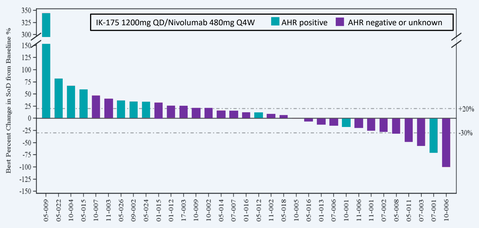
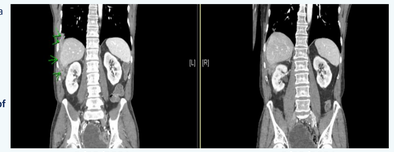


Figure 7: Radiographic Scan of Monotherapy Patient

- 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 of 22.6 months which was ongoing at the time of study closure**



Conclusions

- **IK-175 is well tolerated with a predictable safety profile**
- **IK-175 demonstrated clinical benefit as both a monotherapy and in combination with nivolumab and produced encouraging, durable responses in heavily pre-treated urothelial carcinoma patients who were refractory to prior CPI (DOR up to 22 months)**
- **The favorable safety profile and overall clinical benefit support further investigation of IK-175 to better understand AHR inhibition in cancer therapy**

References

1. Sanchez-Martin, et al, SITC 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
3. Aggen et al, SITC 2022 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