First in Human, a Phase I Study of ISU104, a Novel ErbB3 Monoclonal Antibody, in R/M HNSCC

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Background

- ISU104, a monoclonal human anti-ErbB3, inhibits heregulin binding to ErbB3 and subsequent dimerization between ErbB2 and ErbB3.
- Combination of ISU104 and cetuximab demonstrated enhanced anti-tumor activity compared to the respective mono therapies in a preclinical model of head and neck cancer, FaDu (Figure 1). In addition, FaDu tumors acquired resistance to cetuximab through activation of ErbB3, which then became sensitive to ISU104 monotherapy (Mono), and ISU104 and cetuximab combination therapy (Combo) (Figure 2).
- Phase 1 dose-escalation (Part 1) study investigated the safety, MTD and pharmacokinetic profiles of ISU104 in patients with advanced solid tumors. IV administrations of ISU104 were well tolerated up to 20 mg/kg/day without dose-limiting toxicity (DLT), Disease control rates were 60% (9/15) for all the patients and 86% (6/7) for the HNSCC patients. Based on the safety and PK profiles of ISU104, the dosing regimen for Part 2 was set as 20 mg/kg Q3W.
- Based on the preclinical and clinical data, ISU104 alone or in combination with cetuximab would likely give clinical benefits to HNSCC patients with no available therapeutic options. Here, the safety, efficacy and pharmacokinetic profiles for ISU104 monotherapy and ISU104/cetuximab combination therapy were investigated in patients with advanced HNSCC. In addition, potential biomarkers for treatment were explored through mandatory tumor biopsies from the participants prior and post treatment.

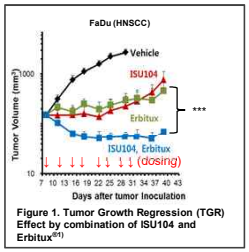

Figure 1. Tumor Growth Regression (TGR) Effect by combination of ISU104 and Erbitux[R1]

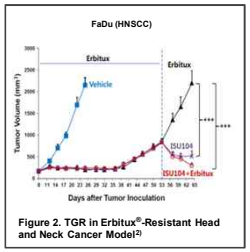

Figure 2. TGR in Erbitux®-Resistant Head and Neck Cancer Model[2]

Ref.: 1) Kim M (#5937), AACR 2018; 2) Kim M (#5695), AACR2018

Methods

Key Eligibility Criteria

- Recurrent/Metastatic HNSCC patients, excluding nasopharyngeal cancer
- Prior treatment including platinum-based chemotherapy
- ECOG ≤ 2
- RECIST 1.1 measurable disease
- No other active primary cancer
- No active brain metastases

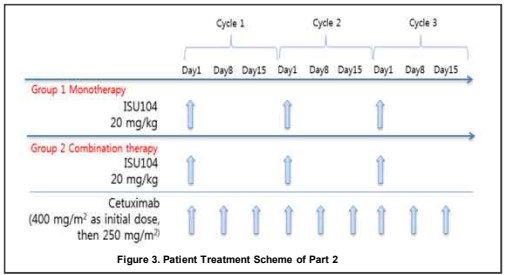

Figure 3. Patient Treatment Scheme of Part 2

- In Part 2, R/M HNSCC patients, excluding nasopharyngeal cancer, were enrolled and allocated to Group 1 (N=6) or in Group 2 (N=12).
- Primary Endpoints: Tolerability (DLT for MTD/RP2D) and Safety (AE, anti-ISU104 antibody)
- Secondary Endpoints: PK, Efficacy (ORR, DCR, PFS)
- Exploratory Endpoints: Biomarker (EGFR, ERBB2, ERBB3, pERBB3, NRG1, HPV and other genetic alterations)

Results

Subject Demographics in Part 2

Table 1. Baseline Patient and Disease Characteristics (N=18)

Gender, n (%)	
Male	15 (83.3)
Female	3 (16.7)
Median age, years (range)	62 (30-76)
ECOG PS, n (%)	
0	1 (5.6)
1	14 (77.8)
2	3 (16.7)
Primary tumor type, n (%)	
Oral Cavity Cancer	4 (22.2)
Oropharyngeal Cancer	4 (22.2)
Hypopharyngeal Cancer	4 (22.2)
Paranasal Sinus and Nasal Cavity Cancer	3 (16.7)
Laryngeal Cancer	2 (11.1)
Others	1 (5.6)

Safety: No DLT was observed in both groups for ISU104 (20 mg/kg IV on day 1, Q3W) alone or in combination with approved dose of cetuximab

Table 2. Safety Summary of Patients in Group 1 (Mono-therapy, N=6)

	n (%)
TEAEs regardless of causality	5 (83.3)
IP related	5 (83.3)
Treatment-emergent SAEs regardless of causality	1 (16.7)
IP related	0 (0.0)
TEAEs leading to dose reduction or drug discontinuation	0 (0.0)
IP related	0 (0.0)
TEAEs leading to death	0 (0.0)

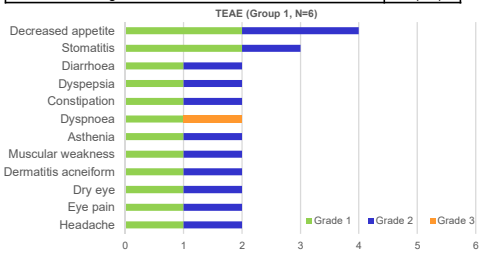

Figure 4. TEAEs in Patients treated with ISU104 (Mono) by Term and Grade (> n=2)

Table 3. Safety Summary of Patients in Group 2 (Combination Therapy, N=12)

	n (%)
TEAEs regardless of causality	12 (100.0)
IP related	9 (75.0)
Treatment-emergent SAEs regardless of causality	7 (58.3)
IP related	3 (25.0)
TEAEs leading to dose reduction or drug discontinuation	2 (16.7)
IP related	0 (0.0)
TEAEs leading to death	0 (0.0)

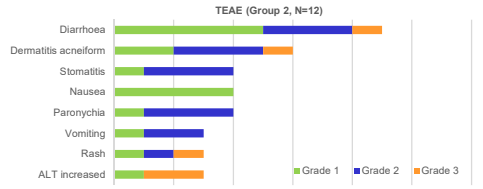

Figure 5. TEAEs in Patients treated with ISU104 and Cetuximab (Combo) by Term and Grade (> n=3)

Efficacy

Table 4. Summary of Tumor Response

Best Response, n (%)	Group 1 Mono-Therapy (N=6)	Group 2 Combination Therapy (N=11)
Complete Response	0 (0)	1 (9.1)
Partial Response	0 (0)	3 (27.3)
Stable Disease	3 (50)	5 (45.5)
Progressive Disease	3 (50)	2 (18.2)
Objective Response Rate	0 (0)	4 (36.4)
Disease Control Rate	3 (50)	9 (81.8)

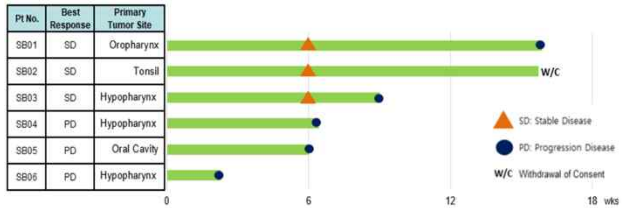

Figure 6. Tumor Response and Treatment Duration in Group 1 (Mono)

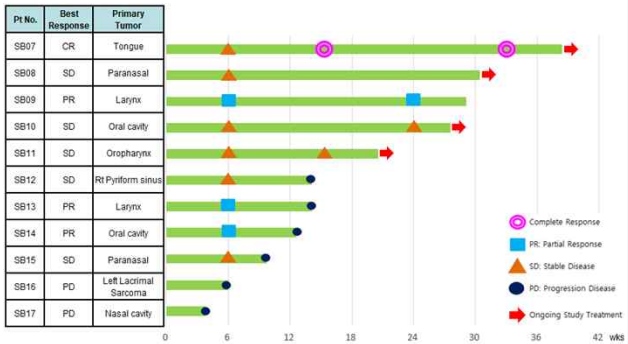

Figure 7. Tumor Response and Treatment Duration in Group 2 (Combo)

Biomarker

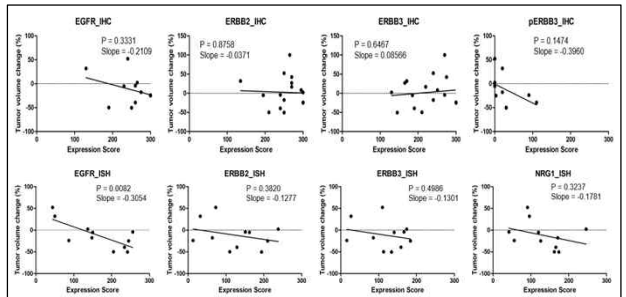

Figure 8. Correlation between tumor volume change at 6 wk and the expression of potential biomarker

- In Group 2 (Combination Therapy), tumor volume reductions at 6 wks were significantly correlated with EGFR mRNA expression (P<0.01 and Slope =-0.31). pERBB3 protein expression tends to be correlated with tumor volume reduction (P=0.15 and Slope = -0.40).

Results

Pharmacokinetics

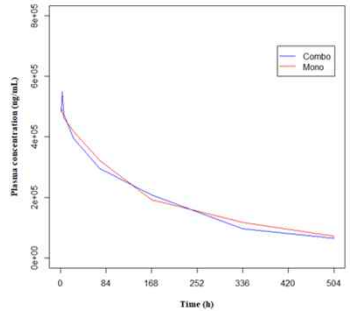

Figure 9. Median Plasma Concentration of ISU104: Mono vs Combo

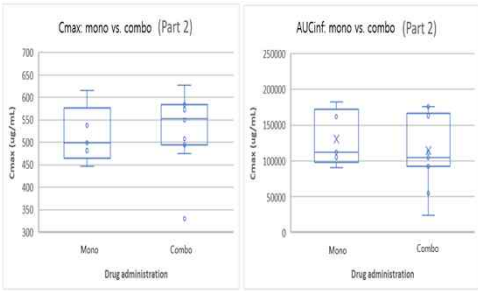

Figure 10. Cmax and AUCinf of ISU104: Mono vs Combo

- Median plasma concentration: Mono (N = 5) vs. Combo (N = 12)
- Drug exposure was compared using t-test
- No statistical difference in Cmax and AUCinf between Mono vs. Combo (p-value > 0.05)
- Cetuximab infusions did not affect the PK profiles of ISU104.

Conclusion in Part 2

- IV administrations of ISU104 20 mg/kg every 3 weeks alone or in combination with approved dose of cetuximab in R/M HNSCC were well tolerated without dose-limiting toxicity (DLT).
- Overall response rate and disease control rate were 0% and 50% in Mono-therapy (n=6, 3 SD) and 36.4% and 81.8% in Combination therapy (n=11, 1 CR, 3 PR and 5 SD), respectively.
- Duration of response were 46, 62, 162+ and 170+ days (4 pts in Combo), and median progression-free survival was 45 days in Mono and 99 days in Combo group, respectively, with median follow-up of 156 days.
- Biomarker analysis suggested EGFR mRNA and pERBB3 protein expression as a potential predictive biomarker for clinical application of ISU104 and Cetuximab combination therapy.
- There was no pharmacokinetic drug-drug interaction between ISU104 and cetuximab.

Acknowledgement

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