First in Human, a Phase I Study of ISU104, a Novel ErbB3 Monoclonal Antibody, in Advanced Solid Tumors

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Background

- ErbB3, a heterodimeric partner of EGFR or ErbB2, is activated by heregulin binding in various cancers.
- ISU104, a monoclonal human antibody, blocking ErbB3 activation by heregulin and subsequent dimerization, showed anti-tumor effects in various preclinical models as mono- or combination therapy.
- ErbB3 activation is one of the key mechanism how cancer cells acquire resistance to the currently used therapies.
- Accordingly, ISU104 would likely give clinical benefits to patients with no available therapeutic options. Here, for the first time, the safety, efficacy and pharmacokinetic profiles of ISU104 were investigated in patients with advanced solid tumors.

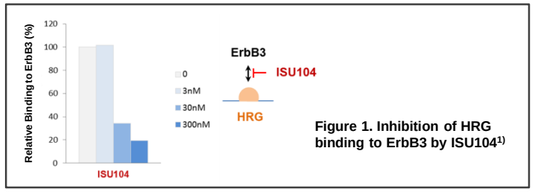

Figure 1. Inhibition of HRG binding to ErbB3 by ISU104[1)]

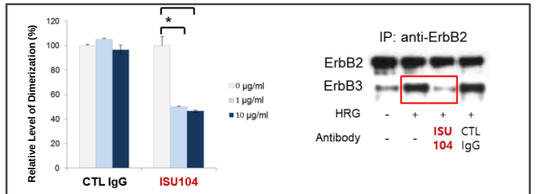

Figure 2. Inhibition of ErbB2/ErbB3 Dimerization: ISU104 can inhibit HRG induced ErbB3-ErbB2 dimer formation in ZR-75-30 breast cancer cells[2)]

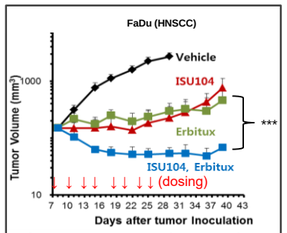

Figure 3. Tumor Growth Regression (TGR) Effect by combination of ISU104 and Erbitux®[1)]

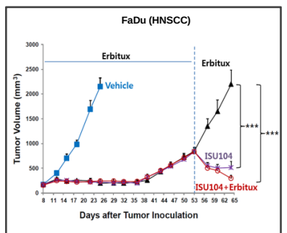

Figure 4. TGR in Erbitux®-Resistant Head and Neck Cancer Model[2)]

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

Methods

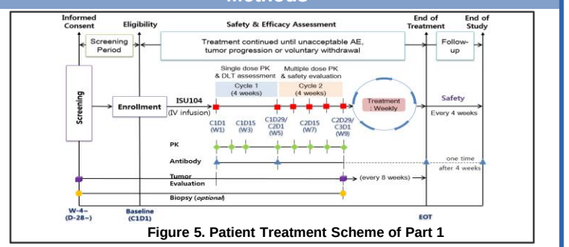

Figure 5. Patient Treatment Scheme of Part 1

- This Phase 1 study consists of two parts, a part 1 of dose-escalation cohort and a part 2 of dose-expansion cohort.
- In the part 1, we enrolled the patients with advanced solid tumor who were refractory to standard treatments.
- Study was conducted with a standard 3+3 dose escalation scheme at 5 different doses (1, 3, 5, 10, 20 mg/kg/day, weekly).
- Dose-limiting toxicities (DLTs) were evaluated during the 1st cycle of treatment (28 days after single IV injection) based on hematologic & non-hematologic toxicities. After the first cycle, ISU104 was dosed weekly, and tumor responses were assessed every 8 weeks. Blood samples for pharmacokinetics (PK) and immunogenicity studies were collected.

Results

Subject demographics

In the part 1, 15 patients (13 males, 2 females) were enrolled and median age was 54 (range 36–96).

Table 1. Baseline Patient and Disease Characteristics (N=15)

Gender, n (%)	
Male	13 (86.7)
Female	2 (13.3)
Median age, years (range)	54 (36-96)
ECOG PS, n (%)	
0	2 (13.3)
1	12 (80.0)
2	1 (6.7)
Primary tumor type, n (%)	
Head and Neck cancer	7 (46.7)
Colorectal cancer	4 (26.7)
Esophageal cancer	2 (13.3)
Breast cancer	1 (6.7)
NSCLC	1 (6.7)
Prior treatment, n (%)	
Radiotherapy	11 (73.3)
Chemotherapy	14 (93.3)
Other	4 (26.6)
Lines of chemotherapy, median (range)	
Head and Neck cancer	1 (0-4)
Colorectal cancer	4 (3-5)
Esophageal cancer	2 (1-3)
Breast cancer	4
NSCLC	4

Safety

- No DLT reported in all cohorts (1-20 mg/kg/day, weekly)
- No infusion reaction reported

Table 2. Safety Summary of Patients treated with ISU104 (N=15)

	n (%)
TEAEs regardless of causality	14 (93.3)
IP related	9 (60.0)
Treatment-emergent SAEs regardless of causality	2 (13.3)
IP related	0 (0.0)
TEAEs leading to dose interruption	3 (20.0)
IP related	2 (13.3)
TEAEs leading to dose reduction	1 (6.7)
IP related	0 (0.0)
TEAEs leading to drug withdrawal/discontinuation	0 (0.0)
TEAEs leading to death	0 (0.0)

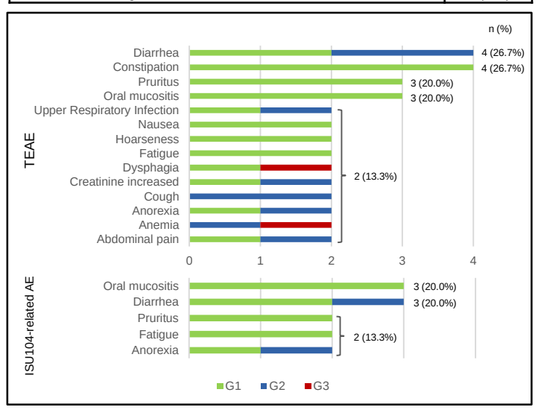

Figure 6. AEs in Patients treated with ISU104 by Term and Grade (>10%)

Efficacy

- From the data of patients who have at least 1 tumor assessment result with measurable target lesions, disease control rate was 61.5% (8/13):
  - 1 patient (1/13, 7.7%) showed partial response
  - 7 patients (7/13, 53.8%) showed stable disease
- In case of Head and Neck cancer, DCR was 83.3%

Table 3. Summary of Tumor Response

Best response, n (%)	All patients		Head and Neck	
	ITT (n=15)	PP (n=13)	ITT (n=7)	PP (n=6)
Complete response	0 (0)	0 (0)	0 (0)	0 (0)
Partial response	1 (6.7)	1 (7.7)	1 (14.3)	1 (16.7)
Stable disease	8 (53.3)	7 (53.8)	5 (71.4)	4 (66.7)
Progressive disease	5 (33.3)	5 (38.5)	1 (14.3)	1 (16.7)
DCR (Disease control rate)	60.0%	61.5%	85.7%	83.3%
ORR (Objective response rate)	6.7%	7.7%	14.3	16.7%

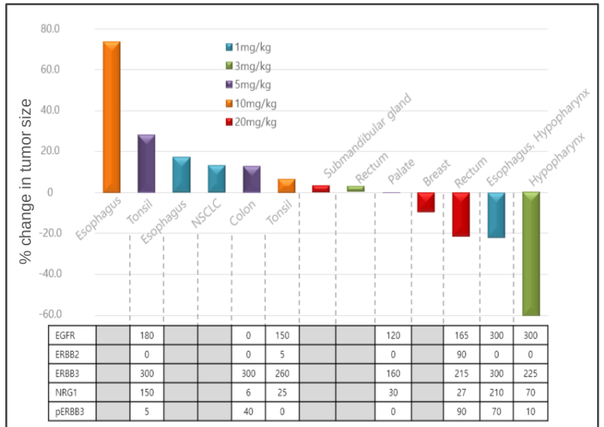

Figure 7. Upper: Percent (%) Change from Baseline to Nadir in Sums of Diameters of Target Lesions. Lower: Exploratory Biomarker Analysis using Archival Paraffin-Embedded Patient Tumor Tissues (H-score, 0-300)

- In part 1 study, an exploratory biomarker study was conducted only for the patients who agreed to provide archival tumor tissue (7 of 15 subjects).
- Potential biomarkers will be further explored in head and neck, colorectal and breast cancers in part 2 study.

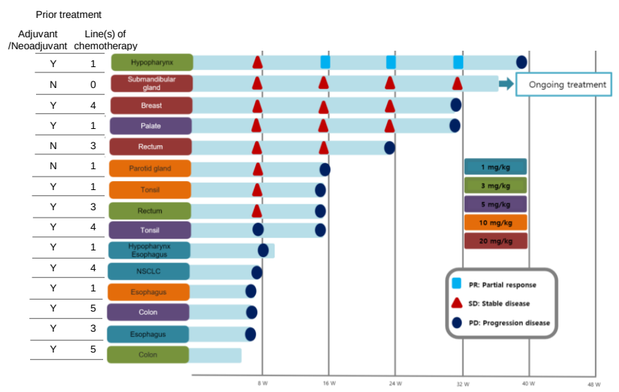

Figure 8. Tumor Response and Treatment Duration in Patients treated with ISU104

Results

Pharmacokinetics

Table 4. Summary of PK Parameters of ISU104 in Patients after a Single IV Administration

PK Parameters	ISU104 (Mean ± SD) Cohort 1 (1 mg/kg/day) N = 3	Cohort 2 (3 mg/kg/day) N = 3	Cohort 3 (5 mg/kg/day) N = 3	Cohort 4 (10 mg/kg/day) N = 3	Cohort 5 (20 mg/kg/day) N = 3
C_{max} (ug/mL)	17.53±4.29	52.49±11.18	81.90±16.69	194.395±33.814	404.40±185.08
AUC_∞ (hr*ug/mL)	1544.19±715.52	8806.55±3691.92	15533.85±7941.47	52031.73±13186.15	104811.95±19684.17
T_{max} (hr)[1]	3.05 (3.00 – 23.15)	24.50 (1.20 – 72.00)	1.68 (1.03 - 3.12)	1.08 (1.02 – 3.00)	1.72 (1.08 – 5.75)
$t_{1/2}$ (hr)	44.50±5.74	84.74±36.87	166.50±131.122	295.05±156.24	269.86±19.08
CL(mL/h/kg)	0.77±0.41	0.39±0.17	0.37±0.15	0.20±0.05	0.20±0.03
Vd(mL/kg)	51.33±32.10	42.21±13.41	70.87±19.33	78.27±29.80	76.33±16.61

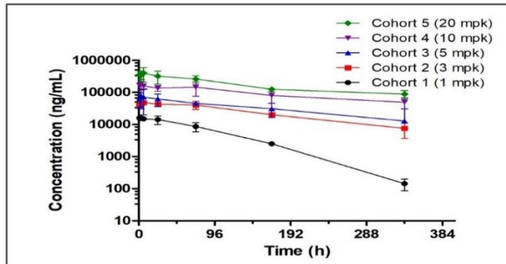

Figure 9. Time vs Concentration Profiles of ISU104 in Patients after a Single IV Administration

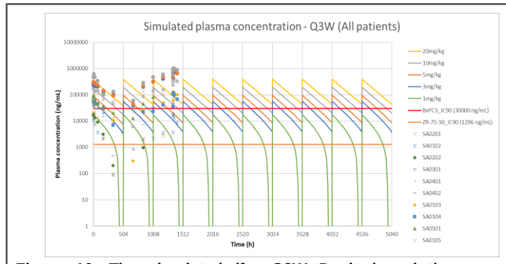

Figure 10. The simulated (for Q3W Dosing) and the measured Plasma Concentrations of ISU104 with respect to the Growth Suppressive Concentrations (IC90) of ISU104 were determined in two Cancer Cell Lines, BxPC3 (Pancreas) and ZR-75-30 (Breast), which are indicated by red and orange lines, respectively.

Conclusion

- IV administrations of ISU104 were well tolerated up to 20 mg/kg/day without dose-limiting toxicity (DLT)
- Overall disease control rate was 60% (9/15):
  1 patient (1/15 or 7%) showed partial response,
  8 patients (8/15 or 53%) showed stable disease.
- PK analysis and simulations for single and repeated dosing were performed to determine the dosages for the upcoming studies.
- Based on the safety and PK profiles of ISU104, from the current Part 1 study, the dosing regimen for Part 2 will be set as 20 mg/kg Q3W. RP2D will be further explored during the upcoming Part 2 study.
- Clinical safety and efficacy of ISU104 as mono- or combination-therapy, and potential biomarkers will be further explored in head and neck, colorectal and breast cancers.

Acknowledgement

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