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Final results and biomarker analysis from a phase 1 dose-expansion (Part II) study of ISU104 (barecetamab; a novel anti-ErbB3) monotherapy or in combination with cetuximab (CET), in patients (pts) with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)

Sung-Bae Kim[1], Bhumsuk Keam[2], SeongHoon Shin[3], Yee Soo Chae[4], Seyoung Seo[1], Keunchil Park[5], Tae Min Kim[6], Lee Chun Park[3], Seung-Beom Hong[7], Myung-Ju Ahn[8];

[1]Oncology Dept. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2] Internal Medicine Dept. Seoul National University Hospital, Seoul, Republic of Korea; [3] Medicine, Kosin University Gospel Hospital, Busan, Republic of Korea; [4] Dept. of Oncology/Hematology, Kyungpook National University Medical Center Biobank, Daegu, Republic of Korea; [5] Hematology/Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6] Dept. of Hematol Oncology, Seoul National University Hospital, Seoul, Republic of Korea; [7] Research Center, ISU ABXIS Co., Ltd., Seongnam, Republic of Korea; [8] Division of Hematology-Oncology, Samsung Medical Center, Seoul, Republic of Korea

Background

Following a dose-escalation study, a dose-expansion study for ISU104 (monotherapy and combination therapy with CET) has been conducted in R/M HNSCC (Ann Oncol, abst #928P, 2020). Here we report updated final safety, clinical efficacy and biomarker analysis results from the dose-expansion study.

Table 1. Part 1: Safety summary (Dose-escalation: 0.3 ~ 20 mg/kg, Q1W)

	total, n=15
Dose-limiting toxicity	0.0%
TEAEs regardless of causality	93.3%
IP related	40.0%
Treatment-emergent SAEs regardless of causality	13.3%
IP related	0.0%
ADRs leading to permanent dose discontinuation	0.0%
ADRs leading to temporary dose discontinuation	13.3%
ADRs leading to dose reduction	0.0%
TEAEs leading to death	0.0%

Table 2. Part 1: Efficacy summary

Evaluated Pts total, n	14
Objective Response Rate (ORR)	7.1%
Disease Control Rate (DCR)	57.1%
Maximum tumor size changes, median % (min, max)	3.6% (-60.5, 73.8)
Median PFS, days	107.5

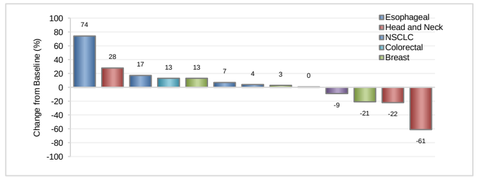

Figure 1. Part 1: Maximum tumor size changes

Methods

Eighteen R/M HNSCC pts excluding nasopharyngeal cancer, were enrolled and allocated to Mono (ISU104, 20 mg/kg/day, Q3W; N=6) or Combo groups (ISU104 20 mg/kg, Q3W and CET, initially 400 mg/m^2 followed by 250 mg/m^2, Q1W; N=12). Tumor response assessments (RECIST 1.1), safety and occurrence of anti-drug antibodies (ADA) were determined. Immunohistochemistry, RNAscope® Assay-based in situ hybridization (ISH) and next generation sequencing were performed on sections of biopsy samples.

Table 3. Part 2: Groups and patient demographics

Part II	Treatment	Gender, male%; female %	Age, median (min, max)	Primary tumors, n
Group 1 (n=6); Mono	ISU104 20 mg/kg, Q3W	100; 0	63 (30, 76)	Larynx, 1
				Oropharynx, 1
				Hypopharynx,3
				Tonsil, 1
Group 2 (n=12); Combo	ISU104, Q3W, 20 mg/kg; Cetuximab Q1W, initially 400 mg/m^2 followed by 250 mg/m^2	75; 25	62 (44, 72)	Larynx, 2
				Oral cavity, 2
				Nasal cavity, 1
				Paranasal cavity, 2
				Oropharynx, 2
				Pyriform Sinus, 1
				Lacrimal Sac, 1
				Tongue, 1
Total (n=18)	-	83; 17	62 (30, 76)	-

Results

Safety:

No DLT was observed in either groups for ISU104 (20 mg/kg IV on day 1, Q3W) alone or in combination with approved dose of cetuximab. Most common treatment emergent adverse events (TEAEs) included decreased appetite (66.7%) and stomatitis (50%) in Mono, and diarrhea (75.0%) and dermatitis acneiform (50%) in Combo. Serious AEs were reported 16.7% in Mono and 58.33% in Combo, but no AEs led to treatment discontinuation. One patient (1/18, 5.56%) developed ADA, which did not have neutralizing activity.

Table 4. Part 2: Safety summary

	Group 1 (n=6) %	Group 2 (n=12) %
DLT	0.0	0.0
TEAEs regardless of causality	83.3	100.0
ISU104-related	50.0	58.3
CET-related	NA	91.7
Treatment-emergent SAEs regardless of causality	16.7	58.3
ISU104-related	0.0	16.7
CET-related	0.0	25.0
ADRs leading to permanent ISU104 or cetuximab dose discontinuation	0.0	0.0
TEAEs leading to death	0.0	0.0

1. ADR, adverse drug reaction

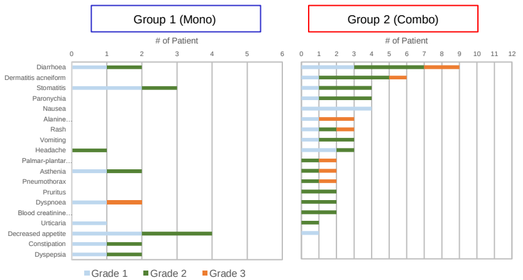

Figure 2. TEAEs in the patients treated by mono- and combination-therapy by term and grade (> n=2 in either groups).

Table 5. Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (nAb)

	Group 1 n=6	Group 2 n=12
ADA (Positive)	0%	8.3%
nAb (Positive, if ADA positive)	NA	0.0%

Efficacy:

Four pts in Combo were responsive to treatment (1 CR and 3 PR out of 11 analyzed pts; 36.36%); one patient remained CR up to now. Duration of responses were 46, 62, 163+ and 449+ days in Combo, and median progression-free survival was 54 and 99 days in Mono and Combo groups, respectively, in median follow-up period of 480 days (as of 30th April 2021).

Table 6. Part 2: efficacy summary

	Group 1 n=6	Group 2 n=11*
Objective Response Rate (ORR)	0.0%	36.4%
Disease Control Rate (DCR)	50.0	81.8%
Median tumor size changes	21.9%	-17.7%
Median PFS	54 days	99 days

*, 1 pt was excluded due to lack of tumor measurement.

Results

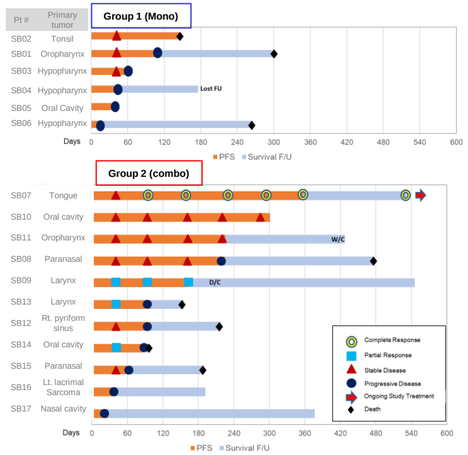

Figure 3. Tumor responses and treatment Durations

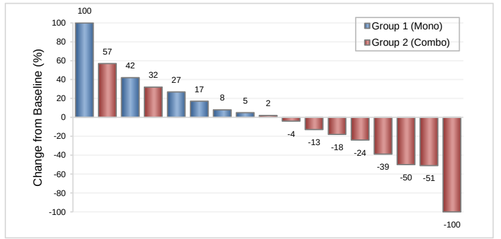

Figure 4. Part 2: Maximum tumor size changes

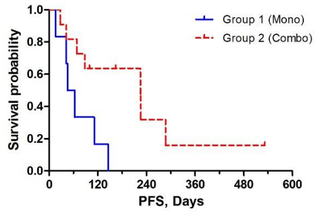

Figure 5. Kaplan-Meier curve for progression-free survival

Table 7. Progression-free survival analysis

	Subjects	Event	Censored	Median Survival, days	95% CL	
Group 1	6	6	0	54	16	145
Group 2	11	7	4	99	42	

Results

Biomarker Analysis

H-scores of potential biomarkers including EGFR-ISH at pre-treatment were correlated with tumor size changes following combination therapy. Potential implication of TP53 mutations and EGFR amplification in patient selection was also noted.

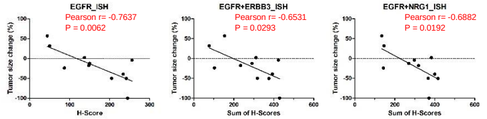

Figure 6. Correlation: biomarker (H-Score or sum of H-scores) vs maximum tumor size change (%) in Group 2 (Combo). P<0.05, colored red.

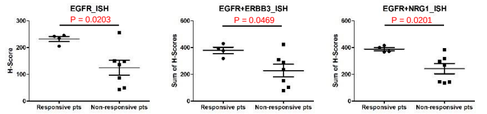

Figure 7. Potential biomarkers to predict efficacy: Responsive pts to combination therapy (Group 2) expressed higher levels of EGFR_ISH, EGFR+ERBB3_ISH or EGFR+NGR1_ISH (H-Score or sum of H-scores) compared with non-responsive pts. P<0.05, colored red.

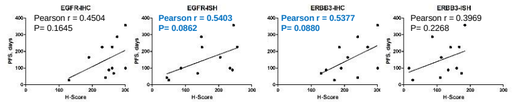

Figure 8. Correlation: biomarker (H-Score) vs PFS in Group 2 (Combo). P<0.1, colored blue

Table 8. Genetic alterations (pathogenic mutations and copy number variations) in pts.

Type	Gene	Best Clinical Responses and Patient number												
		PD			SD							PR		CR
		SB04	SB05	SB06	SB02	SB03	SB15	SB08	SB10	SB11	SB12	SB14	SB13	SB09	SB07
Mutation	TP53	O						O			O	O	O	O	O
	PIK3CA												O	O	
	FGFR4	O	O	O		O	O	O	O	O	O	O	O	O	O
	PTEN							O			O		O		
Duplication /deletion	EGFR														O
	MYC	O											O		O
	ERCC1							O			O		O		O
	CCNE1														O

Pts in Group 1 (SB02~SB06) colored blue; Pts in Group 2 (SB07~SB15) colored red.

Conclusion in Part 2

ISU104 alone or in combination with CET was safe and tolerable in R/M HNSCC pts. Encouraging clinical efficacy and potential biomarkers to predict efficacy were demonstrated from combination therapy. A phase 2 study of ISU104 (Q3W, 20 mg/kg/day) in combination with CET (Q1W) is planned to further strengthen the clinical utility of ISU104.

Acknowledgement

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- Presenting Author: Sung-Bae Kim (sbkim3@amc.seoul.kr)
- Representing Author of ISU Abxis: Seung-Beom Hong (hongsb@isu.co.kr)
- Business Development of ISU Abxis: Soohyun Jeong (shjeong@isu.co.kr), Junho Lim (junho.lim@isu.co.kr)