Evaluation of the safety and efficacy of JSKN003 in patients with advanced HER2-positive (IHC 3+) solid tumors (excluding breast cancer)

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BACKGROUND

- JSKN003 is a bispecific HER2-directed antibody-drug conjugate (ADC) conjugated to a topoisomerase I inhibitor via a dibenzocyclooctyne tetrapeptide linker on the glycan of a humanized bispecific antibody (KN026).
- Clinical studies demonstrated that KN026 has good efficacy and safety for HER2 positive solid tumors.
- Pre-clinical studies showed that JSKN003 had good serum stability, which may lead to a broader therapeutic window.
- JSKN003-101 and JSKN003-102 are dose escalation and expansion studies involving Australian and Chinese patients (pts) with metastatic solid tumors.
- Here we reported results from the phase I part of JSKN003-101 and JSKN003-102 study.

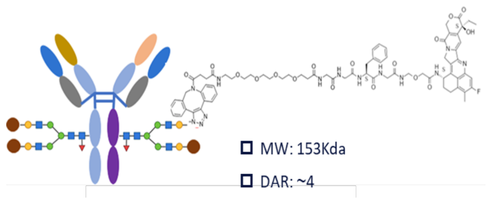

Figure 1 JSKN003 Structure Diagram

METHODS

- **Study design:** This is a pooled analysis of patients enrolled in JSKN003-101 (NCT05494918) and JSKN003-102 (NCT05744427) with histologically documented HER2-positive (IHC 3+) solid tumors who had failed prior systemic therapies, received JSKN003 monotherapy intravenously Q3W.
- **Study objectives:** The objectives were safety and efficacy of JSKN003.
- **Key eligibility**:
  - Patients with confirmed pathological records of unresectable locally advanced or metastatic solid tumors (excluding breast cancer) with HER2-positive(ICH 3+) who have failed standard therapy, cannot tolerate standard therapy, or lack effective treatment were enrolled;
  - ECOG:0 or 1 points;
  - Age: ≥ 18 years old;
  - At least one measurable lesion, or a measurable lesion with clear progression after local treatment (based on RECIST V1.1 criteria).

RESULTS

- As of July 15, 2024, 29 patients (9 colorectal cancer, 6 gastric cancer, 4 biliary tract carcinoma, 3 esophageal carcinoma, 2 ovarian cancer, 1 head and neck cancer and 4 others) were enrolled and received JSKN003 across 7 dose levels, including 2.1 mg/kg (n=1), 4.2 mg/kg (n=1), 5.2 mg/kg (n=1), 6.3 mg/kg (n=17), 7.3 mg/kg (n=5), 8.4 mg/kg (n=3) and 10.5 mg/kg (n=1), Q3W. 12 pts (41.4%) had received ≥ 3 lines prior treatment, 48.3% and 24.1% of the patients had received anti-HER2 and anti-HER ADC treatment, respectively. Baseline characteristics of patients are shown in Table 1.
- Among the 28 efficacy evaluable patients, the ORR and DCR were 75.0% and 89.3%, respectively. 7 pts who received prior anti-HER2 ADC, the ORR was 71.4%. The ORR of gastric cancer and colorectal cancer were 83.3% (5/6) and 66.7% (6/9). Efficacy data are shown in Table 2.
- The median duration of treatment was 23.6 (range: 4.7~52.0) weeks, and 14 pts remained on treatment. Treatment-related adverse events (TRAEs) occurred in all the patients, and the mostly common grade 1 and 2 TRAEs were diarrhea (60.9%) and nausea (65.5%), infusion related reaction (24.1%), fatigue (24.1%), appetite decreased (24.1%) and rash (20.7%) (see Table 3). 6 pts (20.7%) experienced grade ≥3 TRAEs, were neutrophil count decreased (6.9%), vomiting (3.4%), fatigue (3.4%), white blood cell decreased (3.4%) and appetite decreased (3.4%). 3 pts had interstitial lung disease, grade 2 (2 pts in 6.3 mg/kg and 1 pt in 8.4 mg/kg), all recovered thereafter. No TRAE led to death and only 1 patient experienced TRAE led to treatment discontinuation.

Table 1 Demographics & Baseline Characteristics

Dose		2.1 mg/kg	4.2 mg/kg	5.2 mg/kg	6.3 mg/kg	7.3 mg/kg	8.4 mg/kg	10.5 mg/kg	Total
N		1	1	1	17	5	3	1	29
Gender, n (%)	Male	0	0	1 (100)	11 (64.7)	3(60.0)	1 (33.3)	1 (100)	17 (58.6)
	Female	1 (100)	1 (100)	0	6 (35.3)	2 (40.0)	2 (66.7)	0	12 (41.4)
Age, years	Median (min, max)	65 (65, 65)	68 (68, 68)	59 (59, 59)	57 (30, 70)	54 (51, 57)	58 (51, 60)	61 (61, 61)	58 (30, 72)
ECOG, n (%)	0	0	1 (100)	0	5 (29.4)	2 (40.0)	1 (33.3)	0	2 (4.3)
	1	1 (100)	0	1 (100)	12 (70.6)	3 (60.0)	2 (66.7)	1 (100)	44 (95.7)
HER2 (IHC), n (%)	IHC 3+	1 (100)	1 (100)	1 (100)	17 (100)	5 (100)	3 (100)	1 (100)	29 (100)
History of Metastasis	Yes	1 (100)	1 (100)	1 (100)	16 (94.1)	5 (100)	3 (100)	1 (100)	28 (96.6)
	No	0	0	0	1 (5.9)	0	0	0	1 (3.4)
Prior treatment line(s), n (%)	1 line	0	1 (100)	0	4 (23.5)	1 (20.0)	0	0	6 (20.7)
	2 lines	0	0	0	6 (35.3)	3 (60.0)	1 (33.3)	1 (100)	11 (37.9)
	≥ 3 lines	1 (100)	0	1 (100)	7 (41.2)	1 (20.0)	2 (66.7)	0	12 (41.4)
Prior anti-HER2 treatment, n (%)	Anti-HER2	1 (100)	1 (100)	1 (100)	6 (35.3)	2 (40.0)	1 (33.3)	1 (100)	14 (48.3)
	Anti-HER2 ADC	1 (100)	0	1 (100)	5 (29.4)	0	0	0	7 (24.1)

Table 2 Efficacy Outcomes (tumor response by RECIST 1.1)

Efficacy evaluable patients	Total	2.1 mg/kg	4.2 mg/kg	5.2 mg/kg	6.3 mg/kg	7.3 mg/kg	8.4 mg/kg
N	28	1	1	1	17	5	3
Best Overall Response (BOR),n (%)							
Complete Response (CR)	0	0	0	0	0	0	0
Partial Response (PR)	21 (75.0)	1 (100)	0	1 (100)	11 (64.7)	5 (100)	3 (100)
Stable Disease (SD)	4 (14.3)	0	1 (100)	0	3 (17.6)	0	0
Progression Disease (PD)	3 (10.7)	0	0	0	3 (17.6)	0	0
ORR*, n (%) (95% CI)	21 (75.0)	1 (100)	0	1 (100)	11 (64.7)	5 (100)	3 (100)
DCR, n (%) (95% CI)	25 (89.3)	1 (100)	1 (100)	1 (100)	14 (82.4)	5 (100)	3 (100)

* Including unconfirmed response(PR or CR)

Table 3 Safety (TRAEs Occurred in ≥ 10% of patients)

Preferred Term	Any grade N = 29 (n, %)	≥Gr3 N=29 (n, %)
TRAEs	20 (100)	6 (20.7)
Diarrhea	20 (60.9)	0
Nausea	19 (65.5)	0
Infusion related reaction	7 (24.1)	0
Fatigue	7 (24.1)	1 (3.4)
Appetite decreased	7 (24.1)	0
Rash	6 (20.7)	0
White blood cell decreased	5 (17.2)	1 (3.4)
Neutrophil count decreased	5 (17.2)	0
ALT increased	5 (17.2)	0
Vomiting	5 (17.2)	0
Oral ulcer	4 (13.8)	0
drowsiness	3 (10.3)	0
Blood bilirubin increased	3 (10.3)	0
Platelet count decreased	3 (10.3)	0

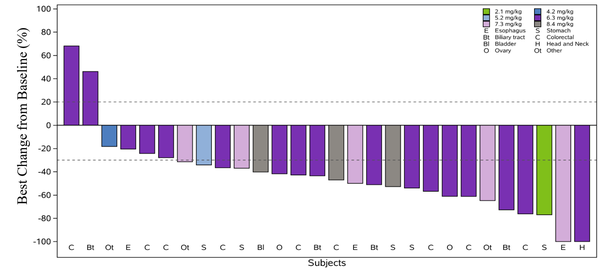

Figure 2 Waterfall Plot (Evaluable patients)

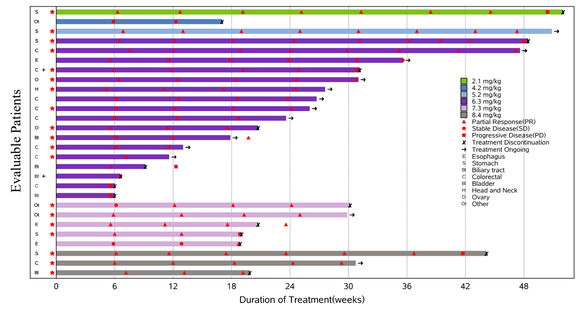

Figure 3 Swimlane Plot (Duration of treatment, weeks)

CONCLUSIONS

- **JSKN003 was well tolerated from 2.1 to 10.5 mg/kg IV every 21 days.**
- **Encouraging antitumor activity observed in heavily pretreated pts with advanced HER2-positive solid tumors.**
- **JSKN003 exhibited a favorable tolerability and safety profile, with a lower incidence of hematological toxicity, compared with the safety profiles of other DXd ADCs[1, 2].**

1. Guo Z, et al. J Clin Pharm Ther. 2022;47:1837-1844; 2. Jänne PA, et al. Cancer Discov. 2022;12:74-89.

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