Evaluation of the safety, pharmacokinetics, and efficacy of JSKN003 in patients with advanced solid tumors: a Phase I/II clinical study

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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 a good serum stability, that may lead to a broader therapeutic window.
- Here we reported results from the phase I part of JSKN003-102 study.

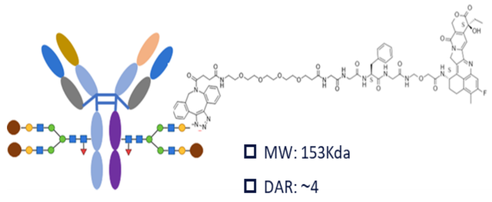

Figure 1 JSKN003 Structure Diagram

METHODS

- **Study design:**JSKN003-102 (NCT05744427) is a phase I (dose escalation and dose expansion) and phase II (cohort expansion) study in Chinese patients (pts) with advanced solid tumors. Dose-escalation part adopts BOIN design across 7 dose levels (1.0, 2.1, 4.2, 5.2, 6.3, 7.3, and 8.4 mg/kg, Q3W). (Figure 2).
- **Study objectives:** The objectives of phase I were safety, maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D), preliminary antitumor activity, pharmacokinetics (PK) parameters and immunogenicity.
- **Key eligibility**: Patients with confirmed pathological records of unresectable locally advanced or metastatic solid tumors with HER2 expression (IHC ≥ 1+) or gene mutation (HER2 exon 19 or 20 mutation) who failed standard therapy, cannot tolerate standard therapy, or lack of effective treatment were enrolled.

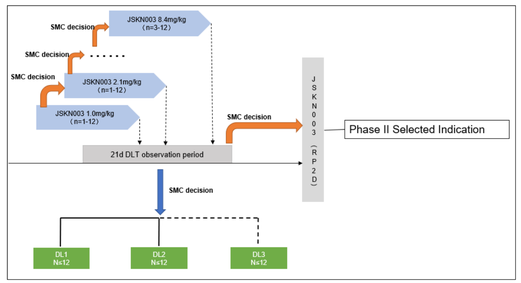

Figure 2 Design of JSKN003-102

RESULTS

- As of April 5, 2024, 46 patients (25 breast cancers, 11 gastric cancers, 8 colorectal cancers, 1 lung cancer, and 1 ovarian cancer) were enrolled and received JSKN003 across 6 dose levels, including 2.1 (n=1), 4.2 (n=10), 5.2 (n=14), 6.3 (n=15), 7.3 (n=3), and 8.4 mg/kg (n=3), Q3W, in phase I part. 34 pts (73.9%) had received ≥ 3 lines prior treatment, 60.9% and 45.7% pts had received anti-HER2 and anti-HER ADC treatment, respectively. Baseline characteristics of patients are shown in Table 1.
- The median duration of treatment was 19.2 (range, 3.0 – 52.0) weeks, and 26 pts (56.5%) remained on treatment. Treatment-related adverse events (TRAEs) occurred in 46 pts (100%, see Table 2), Only 9 pts (19.6%) experienced grade 3 TRAEs and no > grade 3 TRAE occurred. 3 pts (6.5%) had treatment related SAEs (1 pt G3 nausea, 2 pts G2 ILD). No DLT event and no TRAE led to discontinuation.
- Following a single dose, exposures (C_{max} and AUC) of JSKN003 increased with dose escalation and the mean half-life of JSKN003 is approximately 5 days for 6.3 mg/kg. No significant accumulation was observed after 4 cycles treatment. The systemic exposure of free payload was significantly lower than JSKN003, demonstrating the stability of JSKN003 in circulation.
- Among the 45 efficacy evaluable patients, the ORR and DCR were 51.1% (95%CI: 35.8, 66.3) and 93.3% (95%CI: 81.7, 98.6), respectively. The ORR in pts with IHC 1+, 2+ and 3+ was 14.3% (95% CI: 0.4, 57.9), 35.0% (95% CI: 15.4, 59.2), and 83.3% (95% CI: 58.6, 96.4), respectively. For 28 pts who received prior anti-HER2 the ORR was 57.1% (95% CI: 37.2, 75.5),for 21 pts who received prior anti-HER2 ADC the ORR was 57.1% (95% CI: 34.0, 78.2). For HER2 positive (HER2 IHC 3+, or IHC 2+ & FISH +) breast cancer and gastric cancer, the ORR was 73.3% (95% CI: 44.9, 92.2) in 15 pts and 80% (95% CI: 28.4, 99.5) in 5 pts, respectively. For HER2-low (HER2 IHC 1+, or IHC 2+ &FISH -) breast cancer and gastric cancer, the ORR was 33.3% (95% CI: 7.5, 70.1) in 9 pts and 20% (95% CI: 0.5, 71.6) in 5 pts, respectively. Efficacy data are shown in Table 3.

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	Total
N		1	10	14	15	3	3	46
Gender, n (%)	Male	0	1 (10.0)	4 (28.6)	9 (60.0)	0	1 (33.3)	15 (32.6)
	Female	1 (100)	9 (90.0)	10 (71.4)	6 (40.0)	3 (100)	2 (66.7)	31 (67.4)
Age, years	Median (min, max)	65 (65, 65)	52 (32, 71)	57 (47, 65)	54 (30, 65)	36 (30, 50)	66 (51, 73)	55 (30, 73)
ECOG, n (%)	0	0	0	1 (7.1)	0	1 (33.3)	0	2 (4.3)
	1	1 (100)	10 (100)	13 (92.9)	15 (100)	2 (66.7)	3 (100)	44 (95.7)
HER2 (IHC), n (%)	IHC 1+	0	1 (10.0)	3 (21.4)	3 (20.0)	0	0	7 (15.2)
	IHC 2+	0	5 (50.0)	4 (28.6)	9 (60.0)	1 (33.3)	2 (66.7)	21 (45.7)
	IHC 3+	1 (100)	4 (40.0)	7 (50.0)	3 (20.0)	2 (66.7)	1 (33.3)	18 (39.1)
History of Metastasis	Yes	1 (100)	10 (100)	14 (100)	15 (100)	3 (100)	3 (100)	46 (100)
	No	0	0	0	0	0	0	0
Prior treatment line(s), n (%)	1 line	0	1 (10.0)	1 (7.1)	0	2 (66.7)	0	4 (8.7)
	2 lines	0	1 (10.0)	3 (21.4)	4 (26.7)	0	0	8 (17.4)
	≥ 3 lines	1 (100)	8 (80.0)	10 (71.4)	11 (73.3)	1 (33.3)	3 (100)	34 (73.9)
Prior anti-HER2 treatment, n (%)	Anti-HER2	1 (100)	7 (70.0)	11 (78.6)	6 (40.0)	2 (66.7)	1 (33.3)	28 (60.9)
	Anti-HER2 ADC	1 (100)	5 (50.0)	9 (64.3)	5 (33.3)	0	1 (33.3)	21 (45.7)

Table 3 Efficacy Outcomes (tumor response by RECIST 1.1)

Efficacy evaluable patients	Total	HER2 IHC			Prior anti-HER2	Prior anti-HER2 ADC	Breast cancer		Gastric cancer	
		1+	2+	3+			HER2 low	HER2 positive	HER2 low	HER2 positive
N	45	7	20	18	28	21	9	15	5	5
Best Overall Response (BOR),n (%)										
Complete Response (CR)	0	0	0	0	0	0	0	0	0	0
Partial Response (PR)	23 (51.1)	1(14.3)	7 (35.0)	15 (83.3)	16 (57.1)	12 (57.1)	3 (33.3)	11 (73.3)	1 (20.0)	4 (80.0)
Stable Disease (SD)	19 (42.2)	5(71.4)	12(60.0)	2 (11.1)	10 (35.7)	8 (38.1)	5(55.6)	3 (20.0)	3 (60.0)	1 (20.0)
Progression Disease (PD)	3 (6.7)	1 (14.3)	1 (5.0)	1 (5.6)	2 (7.1)	1(4.8)	1 (11.1)	1 (6.7)	1 (20.0)	0
ORR*, n (%) (95% CI)	23 (51.1) (35.8, 66.3)	1(14.3) (0.4,57.9)	7 (35.0) (15.4, 59.2)	15 (83.3) (58.6, 96.4)	16 (57.1) (37.2, 75.5)	12 (57.1) (34.0, 78.2)	3 (33.3) (7.5, 70.1)	11 (73.3) (44.9, 92.2)	1 (20.0) (0.5, 71.6)	4 (80.0) (28.4, 99.5)
DCR, n (%) (95% CI)	42 (93.3) (81.7, 98.6)	6(85.7) (42.1,99.6)	19(95.0) (75.1,99.9)	17(94.4) (72.7,99.9)	26(92.9) (76.5, 99.1)	20(95.2) (76.2,99.9)	8 (88.9) (51.8, 99.7)	14(93.3) (68.1,99.8)	4 (80.0) (28.4, 99.5)	5(100) (47.8,100)

* Including unconfirmed response(PR or CR)

Table 2 Safety (TRAEs Occurred in ≥ 15% of patients)

Preferred Term	Any grade N = 46 (n, %)	≥Gr3 N=46 (n, %)
TRAEs	46 (100)	9 (19.6)
Diarrhea	19 (41.3)	1 (2.2)
ALT increased	15 (32.6)	0
Nausea	15 (32.6)	1 (2.2)
AST increased	15 (32.6)	0
White blood cell decreased	12 (26.1)	1 (2.2)
Vomiting	12 (26.1)	1 (2.2)
Anemia	12 (26.1)	0
Infusion related reaction	11 (23.9)	0
Neutrophil count decreased	10 (21.7)	3 (6.5)
Platelet count decreased	9 (19.6)	0
Hyperglycemia	8 (17.4)	0
Anorexia	8 (17.4)	0
Blood bilirubin increased	7 (15.2)	0

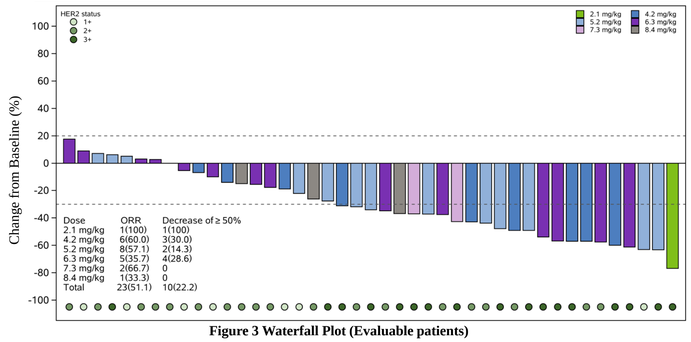

Figure 3 Waterfall Plot (Evaluable patients)

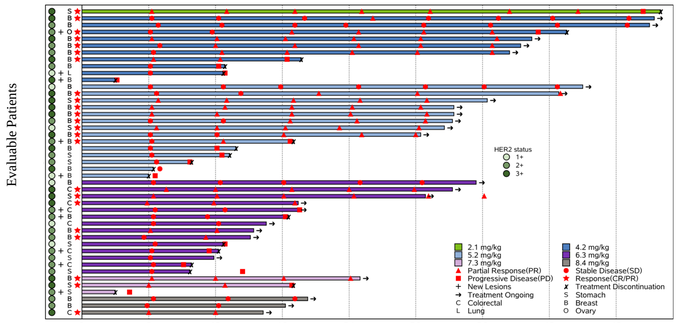

Figure 4 Swimlane Plot (Duration of treatment, weeks)

CONCLUSIONS

- **JSKN003 was well tolerated from 2.1 to 8.4mg/kg IV every 21 days**
  - No DLT was observed, MTD has not been reached yet.
  - Manageable safety profiles with low occurrence of hemotoxicity and ILD (2/46, grade 2).
- **Encouraging antitumor activity observed in heavily pretreated pts during dose escalation below the MTD.**
  - The ORR was 51.1% in all efficacy evaluable pts across HER2 low and HER2 positive populations.
  - For prior anti-HER2 treated pts, the ORR was 57.1%.
  - For breast cancer, the ORR was 73.3% in 15 HER2 positive pts and 33.3% in 9 HER2 low pts, respectively

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