JSKN003, a HER2-targeting antibody-drug conjugate, in patients with platinum-resistant ovarian cancer: A pooled analysis of two studies.

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BACKGROUND

- Patients with platinum-resistant ovarian cancer (PROC) receiving nonplatinum chemotherapy alone have poor responses, with an objective response rate (ORR) ranging from 4 to 13%.
- JSKN003 is a bispecific HER2-targeting antibody-drug conjugate (ADC) conjugated to a topoisomerase I inhibitor (TOP1i) via a dibenzocyclooctyne tetrapeptide linker on the glycan of a humanized bispecific antibody.
- Pre-clinical studies demonstrate strong anti-tumor activity of JSKN003 with superior tolerance and serum stability.

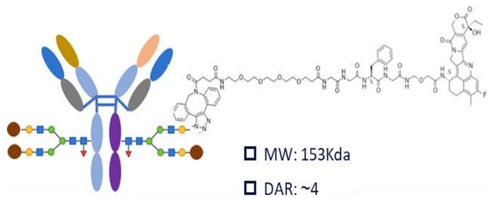

Figure 1 JSKN003 Structure Diagram

METHODS

- JSKN003-101 (NCT05494918) is a first-in-human, dose-escalation and dose-expansion study in Australian patients (pts) with advanced/metastatic solid tumors.
- JSKN003-102 (NCT05744427) is a phase I (dose escalation and dose expansion) and phase II (cohort expansion) study in Chinese pts with advanced solid tumors.
- A pooled analysis of the two studies was conducted for the efficacy and safety of JSKN003 in pts with PROC patients (pts).

RESULTS

- As of 15th July 2024, 50 pts with PROC had received JSKN003 at 4.2 mg/kg (n = 2), 5.2 mg/kg (n = 2), 6.3 mg/kg (n = 44), 7.3 mg/kg (n = 1) and 8.4 mg/kg (n = 1). In total, 50 pts were enrolled on the basis of local HER2 testing, and 10 (20%) were HER2 IHC 0, 20 (40.0%) were IHC 1+, 18 (36.0%) were IHC 2+, and 2 (4.0%) were IHC 3+. On the basis of central testing, there were 17 (34.0%) pts with IHC 0, 10 (20.0%) pts with IHC 1+ expression, 5 (10.0%) pts with IHC 2+ expression, 2 (4.0%) pts with IHC 3+ expression and 16 (32.0%) pts had no HER2 results because they had not been tested by 15th July. 28 (56.0%) pts received ≥ 3 prior lines of therapy, 37 (74.0%) pts had received prior bevacizumab, and 28 (56.0%) pts had received prior PARP inhibitors. Baseline characteristics of patients are shown in Table 1.
- The median duration of treatment was 12.4 (range, 0.7 - 51.0) weeks, and 32 pts (64.0%) remained on treatment.Treatment-related adverse events (TRAEs) occurred in 47 pts (94.0%), the most common TRAEs were nausea (32.0%), AST increased (26.0%), diarrhea (24.0%), anemia (24.0%), asthenia (20.0%), vomiting (18.0%), which were mostly grade 1-2 (see Table2). Grade 3 or higher drug related adverse events occurred in 5 (10%) pts, with the most common being diarrhea (2.0%) and anemia (2.0%). Serious drug-related events occurred in 2 (4.0%) pts. Drug-related adverse events led to dose reduction in 2 (4.0%) pts and discontinueation in 1 (2.0%) pts. 3 pt experienced drug-related events of ILD / pneumonitis, and only 1 was ≥3 grade event. No TRAE led to death.
- Among the 44 efficacy evaluable patients, the ORR was 56.8% (95%CI: 41.0, 71.7) and 88.6% (39/44) pts had tumor shrinkage. The ORR in pts with locally confirmed HER2 IHC 0 and HER2 expression(IHC 1+, 2+ and 3+) were 75% (95% CI: 34.9, 96.8) and 52.8 % (95% CI: 35.5, 69.6), respectively. The ORR in pts with centrally confirmed HER2 IHC 0 and HER2 expression was 52.9% (95% CI: 27.8, 77.0) and 68.8% (95% CI: 41.3, 89.0), respectively. For 33 pts who received prior bevacizumab the ORR was 54.5% (95% CI: 36.4, 71.9), for 26 pts who received prior PARPi the ORR was 46.2% (95% CI: 26.6, 66.6). Efficacy data are shown in Table 3.
- The median follow up time was 2.8 months, so the median PFS were unmature, and 6-month PFS rate was 44.7%.

Table 1 Demographics & Baseline Characteristics

		4.2 mg/kg	5.2 mg/kg	6.3 mg/kg	7.3 mg/kg	8.4 mg/kg	Total
N		2	2	44	1	1	50
Age, year	median (Q1, Q3)	64.5 (59.0, 70.0)	53.5 (51.0, 56.0)	59.0 (52.5, 62.5)	61.0 (61.0, 61.0)	64.0 (64.0, 64.0)	59.0 (53.0, 63.0)
ECOG performance status, n (%)	0	0	2 (100)	17 (38.6)	0	0	19 (38.0)
	1	2 (100)	0	27 (61.4)	0	1 (100)	30 (60.0)
	2	0	0	0	1 (100)	0	1 (2.0)
Prior therapy lines , n (%)	1 lines	0	0	9 (20.5)	0	0	9 (18.0)
	2 lines	0	0	12 (27.3)	1 (100)	0	13 (26.0)
	≥3 lines	2 (100)	2 (100)	23 (52.3)	0	1 (100)	28 (56.0)
Prior exposure, n (%)	bevacizumab, n (%)	1 (50.0)	2 (100)	33 (75.0)	1 (100)	0	37 (74.0)
	PARP inhibitor, n (%)	2 (100)	1 (50.0)	25 (56.8)	0	0	28 (56.0)
HER2(local), n (%)	0	0	0	10 (22.7)	0	0	10 (20.0)
	1+	0	1 (50.0)	18 (40.9)	0	1 (100)	20 (40.0)
	2+	2 (100)	1 (50.0)	14 (31.8)	1 (100)	0	18 (36.0)
	3+	0	0	2 (4.5)	0	0	2 (4.0)
HER2(central), n (%)	0	0	0	17 (38.6)	0	0	17 (34.0)
	1+	0	0	10 (22.7)	0	0	10 (20.0)
	2+	1 (50.0)	0	4 (9.1)	0	0	5 (10.0)
	3+	0	0	2 (4.5)	0	0	2 (4.0)
	unknown*	1 (50.0)	2 (100)	11 (25.0)	1 (100)	1 (100)	16 (32.0)

* HER2 status had not been tested by the central lab by 15th July 2024.

Table 3 Efficacy Outcomes (tumor response by RECIST 1.1)

Efficacy evaluable patients		HER2 IHC (local)		HER2 IHC (central)		Prior bevacizumab	Prior PARPi
	Total	HER2 expression†	0	HER2 expression	0		
	(N=44)	(N=36)	(N=8)	(N=16)	(N=17)	(N=33)	(N=26)
Best Overall Response (BOR), n (%)							
Complete Response (CR)	0	0	0	0	0	0	0
Unconfirmed Complete Response (uCR)	1 (2.3)	1 (2.8)	0	1 (6.3)	0	1 (3.0)	1 (3.8)
Partial Response (PR)	15 (34.1)	12 (33.3)	3 (37.5)	7 (43.8)	5 (29.4)	10 (30.3)	5 (19.2)
Unconfirmed Partial Response (uPR)	9 (20.5)	6 (16.7)	3 (37.5)	3 (18.8)	4 (23.5)	7 (21.2)	6 (23.1)
Stable Disease (SD)	17 (38.6)	15 (41.7)	2 (25.0)	4 (25.0)	8 (47.1)	14 (42.4)	13 (50.0)
Progression Disease (PD)	2 (4.5)	2 (5.6)	0	1 (6.3)	0	1 (3.0)	1 (3.8)
ORR$, n (%)	25 (56.8)	19 (52.8)	6 (75.0)	11 (68.8)	9 (52.9)	18 (54.5)	12 (46.2)
95%CI	41.0, 71.7	35.5, 69.6	34.9, 96.8	41.3, 89.0	27.8, 77.0	36.4, 71.9	26.6, 66.6
DCR, n (%)	42 (95.5)	34 (94.4)	8 (100)	15 (93.8)	17 (100)	32 (97.0)	25 (96.2)
95%CI	84.5, 99.4	81.3, 99.3	63.1, 100	69.8, 99.8	80.5, 100	84.2, 99.9	80.4, 99.9

$ Including unconfirmed response(PR or CR); † HER expression included HER2 IHC 3+/2+/1+

Table 2 Incidence of Drug-Related Adverse Events

Adverse Event	Any grade N = 50
Drug-related adverse event, n (%)	47 (94.0)
Grade ≥3	5 (10.0)
Serious adverse events	2 (4.0)
Leading to discontinuation	1 (2.0)
Leading to dose reduction	2 (4.0)
Most common drug-related adverse events (＞15% of total pts), n (%)	
nausea	16 (32.0)
AST increased	13 (26.0)
diarrhea	12 (24.0)
anemia	12 (24.0)
asthenia	10 (20.0)
vomiting	9 (18.0)
decreased appetite	9 (18.0)
WBC decreased	8 (16.0)
ALT increased	8 (16.0)

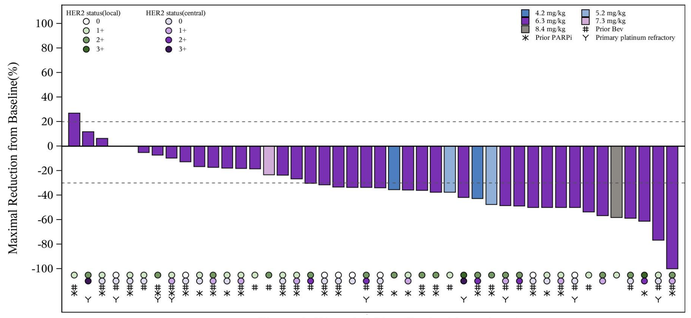

Figure 3 Waterfall Plot (Evaluable patients)

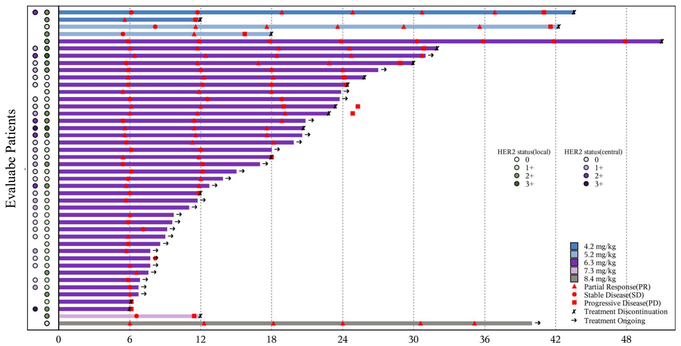

Figure 4 Swimlane Plot (Duration of treatment, weeks)

CONCLUSIONS

- JSKN003 demonstrate promising efficacy in heavily pretreated patients with PROC pts, irrespective of HER2 expression.
- JSKN003 exhibited a favorable tolerability and safety profile, with lower occurrence of gastrointestinal toxicity and hemotoxicity, compared with the safety profiles of other DXd ADCs[1,2].
- These data support further clinical evaluation of JSKN003 in patients with PROC.

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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