Safety and efficacy of JSKN003 in Patients with advanced/metastatic solid tumors: A first-in-human, dose-escalation and expansion, multicenter, open-label, phase I study

Claire Beecroft[1], Bo Gao[2], Andrew Parsonson[2], John Park[3], Kate Wilkinson[4], Karl Zhang[5], Xiangyun Yan[5], Yuan Lv[5]

1.Hollywood Private Hospital, Perth, Australia; 2.Blacktown and Westmead Hospital, Sydney, Australia; 3.Macquarie University Hospital, Sydney, Australia; 4.Liverpool Hospital, Liverpool, Australia; 5.Alphamab Oncology, Suzhou, China

Abstract ID: CT179

BACKGROUND

- JSKN003 is a bispecific HER2-directed antibody-drug conjugate (ADC) conjugated to a TOP1i via a dibenzocyclooctyne tetrapeptide linker on the glycan of a humanized bispecific antibody.
- Pre-clinical studies showed that JSKN003 had a good serum stability and strong anti-tumor activity.
- Here we reported the dose-escalation results from JSKN003-101, a first-in-human phase I study to evaluate the efficacy and safety of JSKN003 in patients with advanced/metastatic solid tumors.

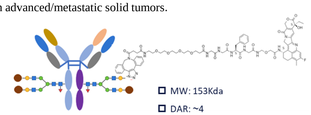


Figure 1 Structure of JSKN003

METHODS

- JSKN003-101 is a first-in-human, dose-escalation and -expansion study in pts with advanced/metastatic solid tumors (Figure 2).
- 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).
- The objectives were safety, tolerability, maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D), pharmacokinetics (PK), and preliminary antitumor activity.
- The cut-off date was Mar 15, 2024.

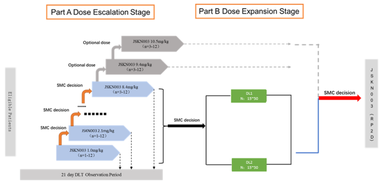


Figure 2 Study Design

RESULTS

Patients

- As of Mar 15, 2024, 32 pts were enrolled and received JSKN003 during the dose-escalation part. 62.5% of patients had ≥ 3 prior lines of systemic treatment.
- The median duration of treatment was 20.4 (range, 6-56) weeks, and 8 pts (25.0%) remain on treatment.

Safety

- All the patients had experienced treatment-emerged adverse events. Treatment-related adverse events (TRAEs) occurred in 27 pts (84.4%) and 4 pts (12.5%) experienced grade 3 TRAE, which was 1 pt in 4.2mg/kg (anemia, diarrhea), 1 pt in 7.3mg/kg (fatigue), and 2 pts in 8.4mg/kg (diarrhea, fatigue) .
- The incidence of ILD was 3.1% (1/32, occurred in 7.3 mg/kg).
- All the subjects had finished DLT observation, and no DLT events were identified yet, and no TRAE led to death or treatment discontinuation.
- MTD has not been reached in 8.4 mg/kg.

Table 1 Demographics & Baseline Characteristics

Dose	1.0 mg/kg	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	1	6	4	4	4	12	32
Median age (years)	60	54	70	60	70	58	65	65
Range	--	--	57 – 73	51 – 67	42 – 73	47 – 77	30 – 79	30 – 79
Gender, male/female	0/1	0/1	2/4	1/3	0/4	1/3	1/11	5/27
Race								
Asian	0	0	1 (16.7)	1 (25.0)	1 (25.0)	1 (25.0)	2 (16.7)	6 (18.8)
White	1 (100)	1 (100)	5 (83.3)	3 (75.0)	3 (75.0)	3 (75.0)	10 (83.3)	26 (81.3)
ECOG PS, n (%)								
0	1 (100)	1 (100)	3 (50.0)	4 (100)	2 (50.0)	0	4 (33.3)	15 (46.9)
1	0	0	2 (33.3)	0	2 (50.0)	3 (75.0)	8 (66.7)	15 (46.9)
2	0	0	1 (16.7)	0	0	1 (25.0)	0	2 (6.3)
HER2 (IHC), n (%)								
1+	0	1 (100)	0	2 (50.0)	1 (25.0)	2 (50.0)	3 (25.0)	9 (28.1)
2+	0	0	4 (66.7)	2 (50.0)	2 (50.0)	2 (50.0)	6 (50.0)	16 (50.0)
3+	1 (100)	0	2 (33.3)	0	1 (25.0)	0	3 (25.0)	7 (21.9)
Site of Primary Cancer, n(%)								
Breast	1 (100)	1 (100)	2 (33.3)	1 (25.0)	2 (50.0)	2 (50.0)	6 (50.0)	15 (46.9)
Ovary	0	0	1 (16.7)	2 (50.0)	1 (25.0)	1 (25.0)	0	5 (15.6)
Bladder	0	0	2 (33.3)	0	0	0	1 (8.3)	3 (9.4)
Lung	0	0	0	0	0	0	2 (16.7)	2 (6.3)
Esophagus	0	0	0	0	0	1 (25.0)	0	1 (3.1)
Stomach	0	0	0	0	0	0	1 (8.3)	1 (3.1)
Head and Neck	0	0	0	1 (25.0)	0	0	0	1 (3.1)
Other	0	0	1 (16.7)	0	1 (25.0)	0	2 (16.7)	4 (12.5)
Prior Lines of Therapy, n (%)								
1 Line	0	0	0	1 (25.0)	1 (25.0)	1 (25.0)	2 (16.7)	5 (15.6)
2 Line	0	0	3 (50.0)	0	0	1 (25.0)	3 (25.0)	7 (21.9)
≥3 Line	1 (100)	1 (100)	3 (50.0)	3 (75.0)	3 (75.0)	2 (50.0)	7 (58.3)	20 (62.5)

Table 2 Safety Overview

	1.0 mg/kg N=1	2.1 mg/kg N=1	4.2 mg/kg N=6	5.2 mg/kg N=4	6.3 mg/kg N=4	7.3 mg/kg N=4	8.4 mg/kg N=12	Total N=32
TEAE	1 (100)	1 (100)	6 (100)	4 (100)	4 (100)	4 (100)	12 (100)	32 (100)
TRAE	1 (100)	1 (100)	5 (83.3)	3 (75.0)	3 (75.0)	4 (100)	10 (83.3)	27 (84.4)
Grade ≥ 3 TEAE	0	1 (100)	4 (66.7)	1 (25.0)	2 (50.0)	1 (25.0)	5 (41.7)	14 (43.8)
Grade ≥3 TRAE	0	0	1 (16.7)	0	0	1 (25.0)	2 (16.7)	4 (12.5)
SAE	0	0	2 (33.3)	0	2 (50.0)	1 (25.0)	3 (25.0)	8 (25.0)
Treatment-related SAE	0	0	0	0	0	0	1 (8.3)	1 (3.1)
TEAE Leading to Discontinuation	0	0	1 (16.7)	0	1 (25.0)	1 (25.0)	0	3 (9.4)

Table 3 Most Commonly Reported TRAEs (≥10%)

PT	1.0 mg/kg N=1	2.1 mg/kg N=1	4.2 mg/kg N=6	5.2 mg/kg N=4	6.3 mg/kg N=4	7.3 mg/kg N=4	8.4 mg/kg N=12	Total N=32
Diarrhea	1 (100)	1 (100)	3 (50.0)	3 (75.0)	3 (75.0)	2 (50.0)	7 (58.3)	20 (62.5)
Nausea	0	1 (100)	2 (33.3)	2 (50.0)	2 (50.0)	3 (75.0)	7 (58.3)	17 (53.1)
Fatigue	0	0	1 (16.7)	0	0	2 (50.0)	4 (33.3)	7 (21.9)
Vomiting	0	0	0	1 (25.0)	2 (50.0)	2 (50.0)	2 (16.7)	7 (21.9)
Decreased appetite	0	0	0	1 (25.0)	2 (50.0)	0	3 (25.0)	6 (18.8)
Abdominal pain	0	0	1 (16.7)	0	1 (25.0)	0	2 (16.7)	4 (12.5)
Lethargy	0	0	0	0	0	0	4 (33.3)	4 (12.5)
Alopecia	0	1 (100)	1 (16.7)	0	0	0	2 (16.7)	4 (12.5)

Efficacy

- The objective response rate (ORR) and disease control rate (DCR) was 56.3% (95%CI: 37.7%, 73.6%) and 90.6% (95%CI: 75.0%, 98.0%), respectively.
- The ORR in pts with IHC 1+, 2+ and 3+ was 66.7% (6/9), 37.5% (6/16), and 85.7% (6/7), respectively.
- As for the efficacy of the HER2+ BC and HER2-low BC, the ORR was 100% (5/5) and 50.0% (5/10), respectively.

Figure 3 Best change in target lesion from baseline by RECIST 1.1

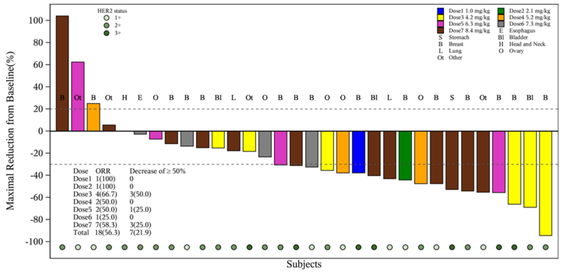


Figure 4 Individual response by duration of treatment

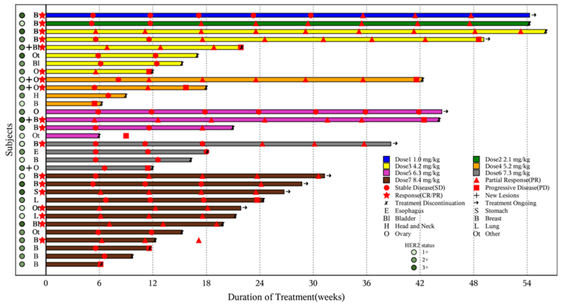
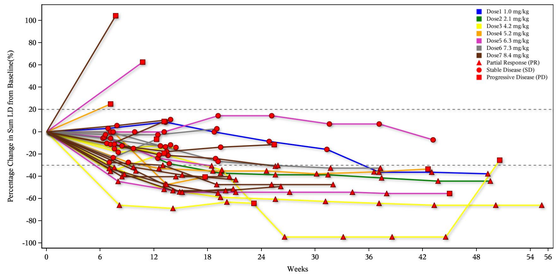


Figure 5 Change in tumor size of target lesion overtime



Pharmacokinetics

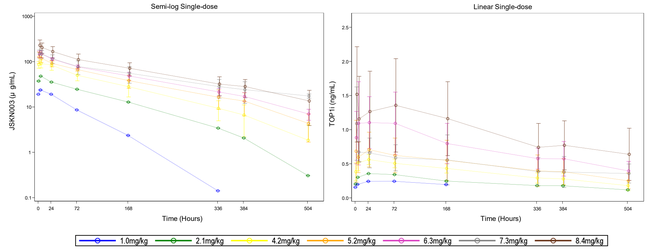
- Following a single dose, exposures (C_{max} and AUC) of JSKN003 and released TOP1i increased proportionally over a dose range of 1 to 8.4 mg/kg. The mean half-life of JSKN003 is approximately 5 days for 6.3 mg/kg.
- Following multiple doses, the PK profile of JSKN003 and released TOP1i were similar with single dose, and the mean accumulation ratio following 6.3 mg/kg was approximately 1.3-fold for JSKN003.
- The exposure of released payload was significantly lower than JSKN003 ADC, demonstrating the stability of JSKN003 in circulation.

Table 4 PK Parameters after single dose

	PK Parameters	1.0 mg/kg N=1	2.1 mg/kg N=1	4.2 mg/kg N=6	5.2 mg/kg N=4	6.3 mg/kg N=4	7.3 mg/kg N=3	8.4 mg/kg N=12
JSKN003	T_{max} (day)	0.23 (0.23,0.23)	0.22 (0.22,0.22)	0.23 (0.23,1.07)	0.16 (0.08,0.23)	0.15 (0.06,0.29)	0.09 (0.07,0.22)	0.18 (0.06,0.23)
	$t_{1/2}$ (day)	1.67	1.95	3.37±1.12	4.63±0.91	5.32±0.53	7.03±0.73	5.94±1.18
	C_{max} (μg/mL)	23.69	47.77	91.88±18.23	124.14±28.61	155.00±26.86	151.03±29.00	223.84±71.19
	AUC_{0-t} (μg*day/mL)	84.90	233.24	534.75±158.57	705.48±199.67	896.46±129.46	1011.14±362.49	1342.71±406.50
	CL (mL/day/kg)	11.68	8.95	8.33±2.64	7.38±2.28	6.75±0.96	7.12±3.45	6.38±2.59
	V_{ss} (mL/kg)	28.16	25.16	37.27±5.52	47.20±5.45	51.66±6.57	70.41±28.45	51.16±10.76
TOP1i	T_{max} (day)	4.04 (4.04,4.04)	1.06 (1.06,1.06)	1.07 (0.22,7.03)	0.56 (0.08,1.10)	0.26 (0.08,1.09)	0.07 (0.06,0.10)	0.19 (0.06,3.01)
	$t_{1/2}$ (day)	-	12.59	12.92±8.64	13.83±4.53	11.59±2.39	16.48±3.09	15.80±2.81
	C_{max} (ng/ml)	0.24	0.36	0.58±0.075	0.76±0.31	1.21±0.53	1.09±0.54	1.64±0.71
	AUC_{0-t} (ng*day/mL)	1.82	4.73	7.95±1.21	10.16±5.08	15.47±5.88	9.71±5.23	22.43±10.20
	CL (L/day/kg)	-	305.68	394.92±122.87	370.75±99.53	317.14±113.64	517.92±258.17	364.95±244.57
	V_{ss} (L/kg)	-	5553.99	6342.69±1665.20	7665.27±3616.39	5095.34±1437.95	12616.80±6953.79	7847.68±4176.92

T_{max} is presented as median(min,max); other parameters are presented as mean±SD; - means not calculated

Figure 6 JSKN003 and TOP1i mean concentration-time curves



CONCLUSIONS

- JSKN003 was well tolerated with encouraging preliminary antitumor activity in heavily pretreated pts with advanced/metastatic solid tumors.
- As of the cut-off date, all the subject had finished DLT observation period, and no DLT was observed, MTD has not been reached yet.
- JSKN003 exhibited a favorable tolerability and safety profile, with very low occurrence of hemotoxicity and ILD (1/32, grade 2).

CONFLICT OF INTEREST

- The authors have no conflicts of interest.