JSKN033, an Innovative Subcutaneous-Injected Fixed-Dose Combination (FDC) of Biparatopic anti-HER2 Antibody Drug Conjugate (ADC) and PD-L1 inhibitor in Advanced Solid Tumor

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BACKGROUND

- Antibody Drug Conjugates (ADCs) combined with immunotherapy (IO) represent a promising anti-cancer approach. However, such combinations often result in increased toxicity.
- Subcutaneous (SC) delivery offers a safer alternative, with comparable efficacy to intravenous delivery, as demonstrated by treatments like amivantamab and daratumumab.
- JSKN033 is a Fixed-Dose Combination (FDC) for SC injection, utilizing innovative technology. It comprises JSKN003, a biparatopic HER2-directed ADC, and Envafolimab (KN035), a PD-L1 inhibitor approved by the National Medical Products Administration (NMPA) of China (Figure 1).
- JSKN033 is the first SC co-formulation of an ADC and PD-L1 inhibitor in clinical trials. Its high-concentration formulation enables injection in seconds and greater convenience compared to hyaluronidase-based SC infusions, which can take 5-15 minutes.
- Preclinical studies have demonstrated good bioavailability and safety with JSKN033.

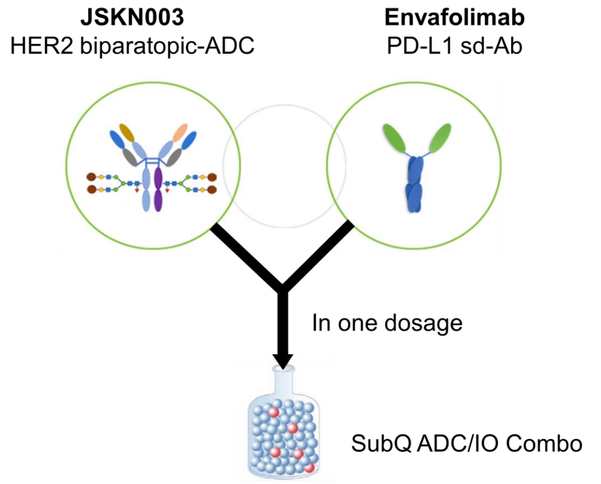

Figure 1. JSKN033 Structure Diagram

METHODS

- The JSKN033-101 study is an open-label, multicenter, first-in-human Phase Ⅰ/Ⅱ trial designed to evaluate the safety, tolerability, and preliminary anti-cancer efficacy of JSKN033 in patients (pts) with advanced HER2-expressing solid tumor (IHC ≥ 1+) or HER2-mutant non-Small Cell Lung Cancer (NSCLC) (NCT06226766).
- The dose-escalation phase follows an accelerated titration and 3+3 design across five JSKN033 dose levels (1.1, 2.3, 4.5, 5.6, and 6.7 mg/kg, QW). The design of dose-escalation is shown in Figure 2.
- One or two doses will be selected for the expansion phase to enroll additional pts for further exploration.

Key Eligibility Criteria

- Advanced/unresectable or metastatic solid tumor
- HER2 expression (IHC ≥1+) or HER2 mutation NSCLC
- Refractory to or intolerable with SOC
- Baseline measurable disease according to RECIST v1.1
- Adequate organ function

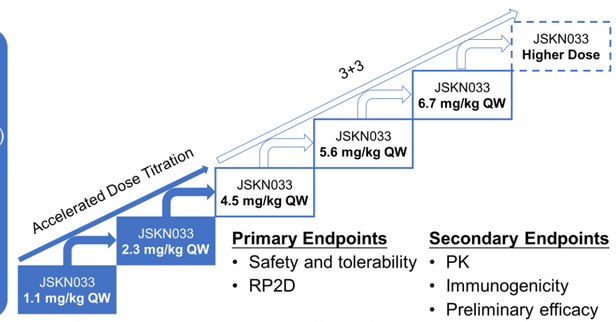

Figure 2. Trial Design (Dose-escalation phase)

RESULTS

Baseline Characteristics

- As of October 14, 2024, 11 pts were enrolled in the dose escalation phase. Pts received JSKN033 at doses of 1.1 mg/kg (n=1), 2.3 mg/kg (n=1), 4.5 mg/kg (n=3), 5.6 mg/kg (n=3), and 6.7 mg/kg (n=3). Demographics and baseline characteristics of pts are summarized in Table 1.

Table 1 Demographics & Baseline Characteristics

Characteristics		Cohort 1 1.1 mg/kg (N=1)	Cohort 2 2.3 mg/kg (N=1)	Cohort 3 4.5 mg/kg (N=3)	Cohort 4 5.6 mg/kg (N=3)	Cohort 5 6.7 mg/kg (N=3)	Overall (N=11)
Age (years)	Median (Q1, Q3)	63.0 (63.0, 63.0)	53.0 (53.0, 53.0)	60.0 (48.0, 70.0)	62.0 (60.0, 72.0)	61.0 (34.0, 66.0)	61.0 (53.0, 66.0)
Gender n (%)	Female	0	0	3 (100)	1 (33.3)	3 (100)	7 (63.6)
	Male	1 (100)	1 (100)	0	2 (66.7)	0	4 (36.4)
Race n (%)	Asian	0	1 (100)	0	1 (33.3)	2 (66.7)	4 (36.4)
	White	1 (100)	0	3 (100)	2 (66.7)	1 (33.3)	7 (63.6)
ECOG, n (%)	PS 0	1 (100)	1 (100)	3 (100)	3 (100)	1 (33.3)	9 (81.8)
Type of Cancer n (%)	Breast Cancer	0	0	1 (33.3)	1 (33.3)	2 (66.7)	4 (36.4)
	NSCLC	0	1 (100)	0	1 (33.3)	0	2 (18.2)
	Colorectal Cancer	0	0	1 (33.3)	0	0	1 (9.1)
	Biliary tract Cancer	0	0	0	1 (33.3)	0	2 (18.2)
	Ovarian Cancer	0	0	0	0	1 (33.3)	1 (9.1)
	Salivary gland Cancer	1 (100)	0	0	0	0	1 (9.1)
HER2 status[1] n (%)	IHC 0	0	0	0	0	0	0
	IHC 1+	0	0	1 (33.3)	0	1 (33.3)	2 (18.2)
	IHC 2+	0	0	2 (66.7)	1 (33.3)	2 (66.7)	5 (45.5)
	IHC 3+	1 (100)	0	0	1 (33.3)	0	2 (18.2)
	mutant	0	1 (100)	0	1 (33.3)	0	2 (20.0)
Prior anti-cancer therapy n (%)	≥3 Lines	0	0	2 (66.7)	1 (33.3)	1 (33.3)	4 (36.4)
	Anti-HER2	0	0	0	1 (33.3)	0	1 (9.1)
	IO	0	1 (100)	2 (66.7)	2 (66.7)	0	5 (45.5)

[1] HER2 status was tested by the local lab.

Safety

Most frequent Treatment-Related Adverse Events (TRAEs) are summarized in Table 2.

- The most common TRAE was injection site reaction:
  - All were grade 1
  - Usually resolved within 2 weeks without any treatment or with antihistamines
- No dose-limited toxicity (DLT), serious AEs, AE leading to dose reduction or death were observed.
- There were no significant differences in the incidence of TRAEs across dose levels.

Table 2 Summary of TRAEs

TRAEs, n (%)	Any grade (N = 11)
Grade ≥3	3 (27.3)
Serious AEs	0
Leading to Dose Delay	3 (27.3)
Leading to Dose Reduction	0
Leading to Drug Discontinuation[1]	2 (18.2)
Leading to Death	0
Most common TRAEs (≥10%) / Preferred Term	
Injection site reaction	10 (90.9)
Diarrhoea	6 (54.5)
Nausea	5 (45.5)
Aspartate aminotransferase increased	3 (27.3)
Decreased appetite	3 (27.3)
Alanine aminotransferase increased	2 (18.2)
Rash maculo-papular	2 (18.2)

[1] One grade 3 AST & ALT increased occurred in 5.6 mg; One grade 3 urticarial rash occurred in 6.7 mg, which resolved to Grade 2 within 3 days and Grade 0 after 8 days with best supportive care.

Efficacy

Ten pts were efficacy evaluable. The Waterfall Plot and the Spider Plot were shown in Figure 3 and Figure 4, respectively.

- Three pts showed partial response (PR), while five pts demonstrated stable disease (SD), resulting in a 80% disease control rate (DCR).
- JSKN033 exhibited anti-tumor activity from the 4.5 mg/kg dose level.
- All three PR pts achieved PR at their first post-baseline scans:
  - Two pts treated at JSKN033 5.6 mg/kg dose level: one had HR-positive/HER2-negative breast cancer (BC) with ≥ four lines of prior therapy, and the other had HER2-mutated NSCLC that had progressed after IO, chemotherapy, and HER2-TKI treatment
  - One pt with triple-negative BC (TNBC) who had previously received Nab-Paclitaxel and radiotherapy was treated at JSKN033 6.7 mg/kg dose level
- Seven pts were still on treatment.

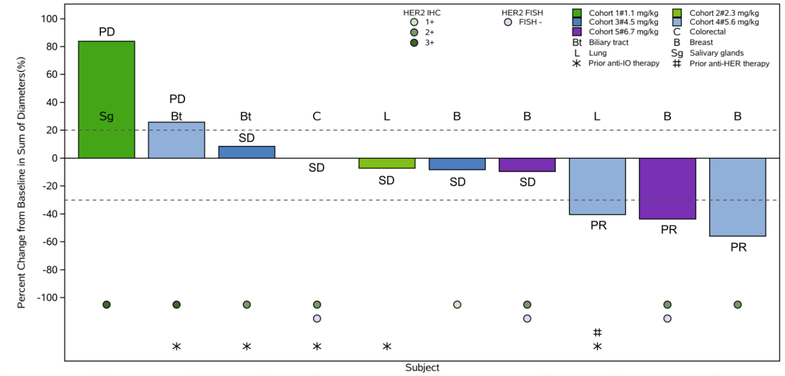

Figure 3. Waterfall Plot of Best Percentage Change in Tumor Size from Baseline

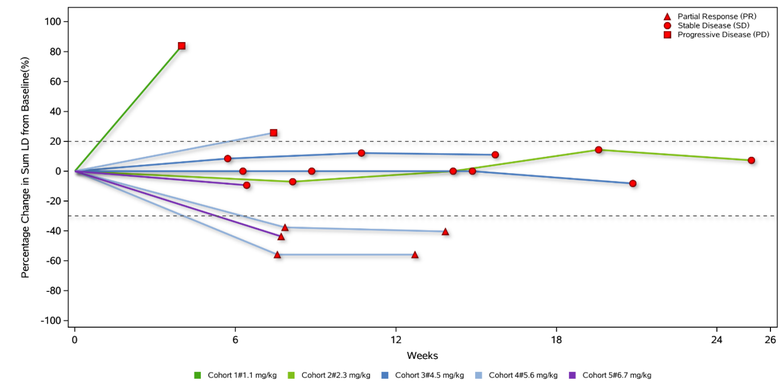

Figure 4. Spider Plot of Percentage Change from Baseline

CONCLUSIONS

- In this first-in-human study, JSKN033 presented a favorable safety profile and encouraging anti-cancer activity in heavily treated patients.
- These data further demonstrated the potential of IO + ADC combination, and support continued exploration of JSKN033.

*The study is sponsored by Alphamab Oncology. Correspondence: Ting Xu; Email: tingxu@alphamabonc.com