JSKN003, a Biparatopic HER2-Targeting ADC, in Heavily Pretreated HER2-Positive Breast Cancer: A Pooled Analysis of Early-Phase Studies

Abstract #1028

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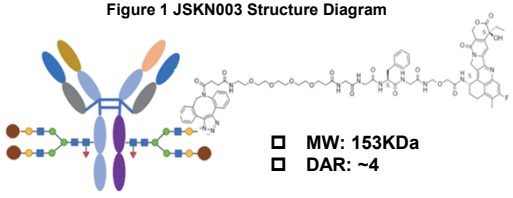
Background

- JSKN003 is a **biparatopic** HER2-targeting antibody-drug conjugate (ADC) conjugated to a **topoisomerase I inhibitor** (TOP1i) via a tetrapeptide linker, designed to enhance serum stability and anti-tumor activity.
- The efficacy and safety of JSKN003 in advanced ovarian cancer[1] and other solid tumors[2-4] have been highlighted in previous reports, and this analysis provides updated insights into its performance in HER2-positive breast cancer.

Figure 1 JSKN003 Structure Diagram



- MW: 153KDa
- DAR: ~4

Methods

- JSKN003-101 (NCT05494918) is a first-in-human, dose-escalation and expansion study in Australia, and JSKN003-102 (NCT05744427) is a Phase I/II study in China, both involving patients with advanced solid tumors.
- A pooled analysis was performed to evaluate the efficacy and safety of JSKN003 in **HER2-positive (IHC 3+ or 2+/ISH+) advanced breast cancer**.

Results

- As of February 28, 2025, the median follow-up duration was **6.08 months** (range: 5.45-6.31). A total of 88 patients with HER2-positive breast cancer were enrolled, with the majority receiving **6.3 mg/kg** or **8.4 mg/kg** doses.
- The median age was 55 years (range: 32-79), with **77.3% ECOG PS 1**. All patients had stage IV disease, with 76.1% having visceral metastases **(Table 1).**
- All patients had **prior anti-HER2 therapy**, including **85.2%** with prior ADCs or TKIs, and **55.7% having ≥ 3 prior lines**.

Table 1 Demographics and Baseline Characteristics

	Total (N=88)
Age, median(range), years	55.0 (32, 79)
Female/Male, n(%)	86 (97.7) / 2 (2.3)
Asian race, n (%)	83 (94.3)
ECOG performance status 0/1, n(%)	20 (22.7) / 68 (77.3)
HER2 status by IHC 2+/3+ (Local), n (%)	25 (28.4) / 63 (71.6)
Hormone receptor positive/negative, n (%)	43 (48.9) / 40 (45.5)
Stage IV at screening, n (%)	88 (100)
Visceral metastases, n (%)	67 (76.1)
Brain metastases，n (%)	13 (14.8)
Prior anti-tumor surgery, n (%)	77 (87.5)
Prior anti-tumor radiotherapy, n (%)	88 (100)
Prior therapy lines 1L/2L/≥3L, n (%)	19 (21.6) / 20 (22.7) / 49 (55.7)
Prior HER2-targeted therapy, n (%)	88 (100)
Prior anti-HER2 monoclonal antibody, n (%)	86 (97.7)
Prior HER2-targeted ADC (including T-DXd), n (%)	54 (61.4)
Prior HER2-targeted TKI, n (%)	57 (64.8)
Prior endocrine therapy, n (%)	35 (39.8)

ECOG, Eastern Cooperative Oncology Group; HER2, Human Epidermal Growth Factor Receptor 2; IHC, Immunohistochemistry; ISH, in situ hybridization; ADC, Antibody-Drug Conjugate; TKI, Tyrosine Kinase Inhibitor; T-DXd, trastuzumab deruxtecan.

Efficacy

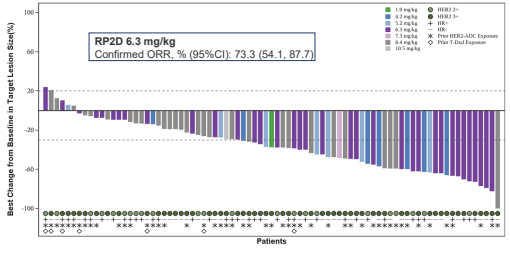
- A total of 80 T-DXd-naïve patients were enrolled, of whom 75 were evaluable for efficacy. In this population(N=75), JSKN003 demonstrated a confirmed objective response rate (ORR) of **54.7%** (95% CI: 42.7-66.2). The disease control rate (DCR) and clinical benefit rate (CBR) were **94.7%** and **66.7%**, respectively **(Table 2)**.
  - ✓ Among patients treated at the **RP2D of 6.3 mg/kg** (n=30), the confirmed ORR was **73.3%**, and CBR reached **83.3%**.
  - ✓ Subgroup analyses by line of therapy showed ORRs of **66.7% in the 1L** group (n=15) and 63.2% in the 2L group (n=19), respectively.
- In addition, 8 patients who had **previously received T-DXd** were enrolled, among whom 7 had evaluable efficacy data.
  - ✓ One patient achieved a partial response (PR), four had stable disease (SD), and **tumor shrinkage was observed in four patients (Figure 2).**
  - ✓ These patients were analyzed separately for exploratory purposes.

Table 2 Summary of Efficacy in T-DXd Naïve HER2-Positive Advanced Breast Cancer Patients

	Total (N=75)	RP2D 6.3mg/kg (n=30)	LoT 1 (n=15)	LoT 2 (n=19)
Confirmed ORR, n (%) 95% CI	41 (54.7) 42.7, 66.2	22 (73.3) 54.1, 87.7	10 (66.7) 38.4, 88.2	12 (63.2) 38.4, 83.7
CR	0	0	0	0
PR	41 (54.7)	22 (73.3)	10 (66.7)	12 (63.2)
SD	27 (36.0)	6 (20.0)	5 (33.3)	5 (26.3)
PD	4 (5.3)	2 (6.7)	0	1 (5.3)
NE	0	0	0	0
DCR, n (%) 95% CI	71 (94.7) 86.9, 98.5	28 (93.3) 77.9, 99.2	15 (100) 78.2, 100	18 (94.7) 74.0, 99.9
CBR, n (%) 95% CI	50 (66.7) 54.8, 77.1	25 (83.3) 65.3, 94.4	11 (73.3) 44.9, 92.2	14 (73.7) 48.8, 90.9
PFS at 3 months, % 95% CI	91.10 81.1, 95.9	93.33 75.8, 98.2	100 100, 100	94.44 66.6, 99.2
PFS at 6 months, % 95% CI	80.13 66.2, 88.7	79.41 56.2, 91.1	100 100, 100	78.70 31.7, 95.1

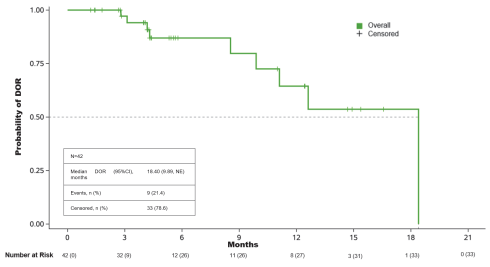
T-DXd, trastuzumab deruxtecan; RP2D, Recommended Phase II Dose; LoT, line of therapy; ORR, Objective Response Rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DCR, Disease Control Rate; CBR, Clinical Benefit Rate; PFS, progression-free survival.
ORR = CR + PR; CBR = CR + PR + uCR + uPR + SD ≥ 24 weeks.

Figure 2 Best Percent Change from Baseline in Target Lesions



- The median duration of response (DoR) in the overall population was **18.4 months** (95% CI: 9.9-NE) **(Figure 3)**.
- Median progression-free survival (PFS) was not mature at the time of data cutoff. The 3-month and 6-month PFS rates were 88.4% (95% CI: 78.8–93.8) and 75.4% (95% CI: 62.3–84.4), respectively.

Figure 3 Kaplan-Meier Analysis of Duration of Response



Safety

- TEAEs occurred in 94.3% of patients, with 93.2% considered treatment-related. Grade ≥ 3 TEAEs were reported in 21.6% of patients, including 15.9% TRAEs. SAEs occurred in 11.4%, and 5.7% were treatment-related **(Table 3).**
- Dose reductions due to TRAEs occurred in 12.5%, and one patient discontinued due to a TRAE.
- No TRAEs led to death.

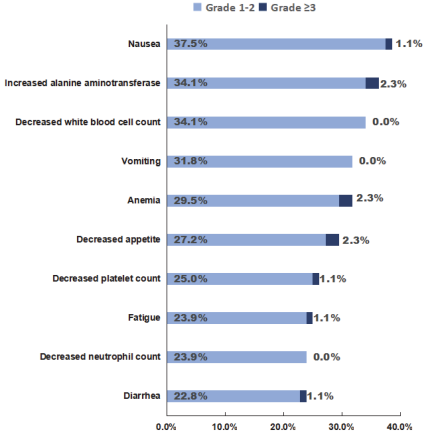
Table 3 Overall Safety Summary

AEs, n (%)	Total(n=88)
TEAEs	83 (94.3)
TRAEs	82 (93.2)
Grade ≥3 TEAEs	19 (21.6)
Grade ≥3 TRAEs	14 (15.9)
SAEs	10 (11.4)
TRSAEs	5 (5.7)
TEAEs Leading to Dose Reduction	12 (13.6)
TRAEs Leading to Dose Reduction	11 (12.5)
TEAEs Leading to Discontinuation	1 (1.1)
TRAEs Leading to Discontinuation	1 (1.1)
TEAEs Leading to Death	1 (1.1)
TRAEs Leading to Death	0

AE, Adverse Event; TEAE, Treatment-Emergent Adverse Event; TRAE, Treatment-Related Adverse Event; SAE, Serious Adverse Event; TRSAE, Treatment-Related Serious Adverse Event; CTCAE: Common Terminology Criteria for Adverse Events. Grading of AEs was based on CTCAE v5.0.

- The most common TRAEs (≥20%) were nausea, increased alanine aminotransferase, decreased white blood cell count, vomiting, anemia, decreased appetite, thrombocytopenia, fatigue, neutropenia, and diarrhea **(Figure 4).**
- Interstitial lung disease (ILD) was reported in 4 patients (4.5%), mostly Grade 1-2; one case was Grade 3.

Figure 4 TRAEs Observed in ≥ 20% of Patients



Conclusions

- JSKN003 demonstrated promising antitumor activity and manageable safety in heavily pretreated HER2-positive breast cancer, including patients previously treated with T-DXd.
- Its biparatopic HER2 antibody design may enhance target binding and contribute to the observed clinical benefit.
- A pivotal Phase 3 trial (NCT06846437) is ongoing to compare JSKN003 with T-DM1 in patients with HER2-positive advanced breast cancer who previously treated with trastuzumab.

[1] Q. Rao, Y. Chen, B. Gao, et al. ESMO 2024; Poster 759P. [2] L. Shen, D. Liu, J.J.W. Park, et al. ESMO 2024; Poster 675P. [3] Xiaojun Liu, Jian Zhang, Lin Shen, et al. ASCO 2024; Poster 176. [4] Claire Beecroft, Bo Gao, John Park, et al. AACR 2024; Poster CT179.

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