# JSKN003, a Biparatopic anti-HER2 Antibody Drug Conjugate (ADC), in patients with Advanced HER2-overexpressing (IHC 3+) Gastrointestinal Tumors

**Abstract #3022**

*Dan Liu[1], Bo Liu[2], Zhen Li[3], Bo Gao[4], Xiaochen Zhang[5], Jian Ruan[5], Jia Wei[6], John J. Park[7], Wenfeng Li[8], Hong Zong[9], Jing Dai[10], Qun Li[11], Jiong Wu[12], Jian Zhang[12], Guixiang Weng[13], Zhongmin Zhang[13], Ting Xu[14], Zhenjiu Wang[14], Ruyi Xu[14], Lin Shen[1]**

1. Beijing Cancer Hospital, Beijing, China; 2.Shandong Cancer Hospital and Institute, Shandong First Medical University, Jinan, China; 3. Linyi Cancer Hospital, Linyi, China; 4. Westmead Hospital, Sydney, Australia; 5. The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 6. Affiliated Drum Tower Hospital to Medical School of Nanjing University, Nanjing, China; 7. Macquarie University Department of Clinical Medicine, NSW, Australia; 8. The Affiliated Hospital of Qingdao University, Qingdao, China; 9. The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; 10. Gastrointestinal Oncology (Chemoradiotherapy) Department, Zhongnan Hospital of Wuhan University, Wuhan, China; 11.Department of Medical Oncology, Shanghai East Hospital, Shanghai, China; 12. Fudan University Shanghai Cancer Center; 13. Linyi People's Hospital, Linyi, China; 14. Alphamab Oncology Ltd, Suzhou, China.

## 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 (**Figure 1**).
- The efficacy and safety of JSKN003 in advanced ovarian cancer[1] and other solid tumors[2-4] have been highlighted in previous reports.
- This pooled analysis provides updated insights into its performance in HER2-overexpressing gastrointestinal tumors.

## Methods

- JSKN003-101 (NCT05494918) is a first-in-human, dose-escalation and expansion study conducted in Australia.
- JSKN003-102 (NCT05744427) is a Phase I/II study conducted in China, enrolled pts with advanced solid tumors.
- A pooled analysis was performed to evaluate the efficacy and safety of JSKN003 in **HER2-overexpressing (IHC 3+)** metastatic **gastric or gastroesophageal cancer (G/GEJC) and colorectal cancer (CRC) patients.**

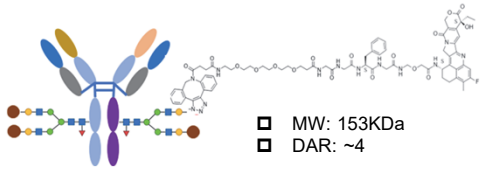



**Figure 1 JSKN003 Structure Diagram**

## Results

- As of February 28, 2025, a total of 50 patients with HER2-overexpressing gastrointestinal tumors (27 in G/GEJC and 23 in CRC) were enrolled across 7 dose levels: 2.1 mg/kg (n=1), 4.2 mg/kg (n=1), 5.2 mg/kg (n=1), 6.3 mg/kg (n=43), 7.3 mg/kg (n=1), 8.4 mg/kg (n=2), 10.5 mg/kg (n=1), treated with JSKN003 monotherapy.
- The median age was 60 years (range: 52-66), with **86.0% ECOG PS 1**. Most patients were heavily pretreated: 38.0% had ≥ 3 lines of prior therapies, 68.0% received anti-HER2 therapy, 48.0% received Irinotecan **(Table 1).**

**Table 1 Demographics & Baseline Characteristics**

| | Total (N=50) |
|---|---|
| Age, median(range), years | 60 (52, 66) |
| Female/Male, n (%) | 15 (30.0) / 35 (70.0) |
| Asian race , n (%) | 49 (98.0) |
| ECOG PS 0/1, n(%) | 6 (12.0) / 43 (86.0) |
| HER2 IHC 3+ (by Local Lab), n (%) | 50 (100) |
| RAF/RAS-mut, n (%) | 4 (8.0) |
| Brain mets, n (%) | 3 (6.0) |
| Liver mets, n (%) | 30 (60.0) |
| Prior anti-cancer therapy lines ≥3L, n (%) | 19 (38.0) |
| Prior anti-HER2 therapy, n (%) | 34 (68.0) |
| Prior IO therapy, n (%) | 23 (46.0) |
| Prior Irinotecan, n (%) | 24 (48.0) |

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

### Efficacy

- Fourty-eight pts had at least one tumor assessment after baseline, JSKN003 demonstrated the objective response rate (ORR) of **62.5%**. The disease control rate (DCR) was **93.8%.**
  - ✓ Among 27 **G/GEJC** pts, the ORR was **63.0%** and DCR reached **92.6%** (**Figure 2**).
  - ✓ Among 21 **CRC** pts, the ORR was 61.9% and DCR reached 95.2%. Among twenty BRAF V600E-wild type pts the ORR was **65.0%** (**Figure 3**).
- Additionally, among 24 (G/GEJC n=4, CRC n=20) pts who were **pretreated with irinotecan**, the ORR achieved **58.3%**.

**Table 2 Summary of Efficacy in HER2-overexpressing Metastatic G/GEJC and CRC Patients**

| | GC/GEJC N=27 | CRC N=21 |
|---|---|---|
| ORR, n (%)<br>95% CI | 17 (63.0)<br>42.4, 80.6 | 13 (61.9)<br>38.4, 81.9 |
| CR | 0 | 0 |
| PR | 17 (63.0) | 13 (61.9) |
| SD | 8 (29.6) | 7 (33.3) |
| PD | 2 (7.4) | 1 (4.8)[1] |
| NE | 0 | 0 |
| DCR, n (%)<br>95% CI | 25 (92.6)<br>86.9, 98.5 | 20 (95.2)<br>76.2, 99.9 |
| mPFS, months<br>95% CI | 9.59<br>4.34,11.60 | 13.77<br>6.77, NE |
| mDoR, months<br>95% CI | 9.59<br>2.99, NE | 12.06<br>5.78, NE |
| PFS at 3 months, %<br>95% CI | 77.45<br>53.88, 89.98 | 95.24<br>70.72, 99.32 |
| PFS at 6 months, %<br>95% CI | 70.40<br>44.53, 85.88 | 88.89<br>61.84, 97.16 |

[1] One pt with PD as BoR was BRAF V600E-mutant

**Figure 2 Best Percentage Change from Baseline in Target Lesions in G/GEJC**

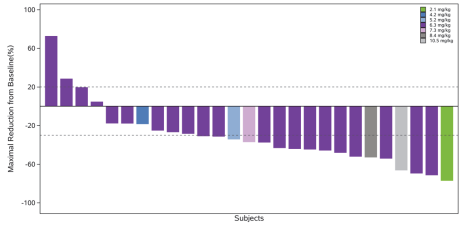
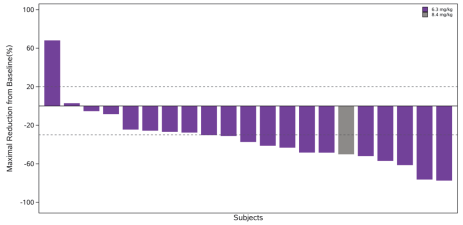



**Figure 3 Best Percentage Change from Baseline in Target Lesions in CRC**




- The median duration of response (DoR) in **G/GEJC** pts was **9.6 months** (95% CI: 3.0-NE), the DoR in **CRC** pts was **12.1 months** (95% CI: 5.8-NE) (**Table 2**).
- Median progression-free survival (PFS) was **9.6 months** (95%CI : 4.3, 11.6) with 70.4% PFS rate at 6 months in G/GEJC patients.
- The PFS was **13.8 months** (95%CI : 6.8, NE) with 88.9% PFS rate at 6 months in CRC patients.

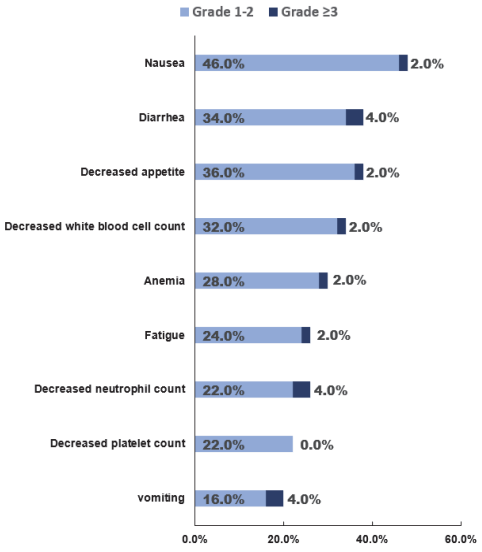
**Table 3 Overall Safety Summary**

| AEs, n (%) | RP2D (n=43) | Total (n=50) |
|---|---|---|
| TEAEs | 41 (95.3) | 48 (96.0) |
| TRAEs | 39 (90.7) | 46 (92.0) |
| Grade ≥ 3 TEAEs | 6 (14.0) | 11 (22.0) |
| Grade ≥ 3 TRAEs | 6 (14.0) | 9 (18.0) |
| SAEs | 5 (11.6) | 7 (14.0) |
| TRSAEs | 3 (7.0) | 3 (6.0) |
| TEAEs Leading to Dose Reduction | 9 (20.9) | 12 (24.0) |
| TRAEs Leading to Dose Reduction | 7 (16.3) | 10 (20.0) |
| TEAEs Leading to Discontinuation | 0 | 0 |
| TEAEs Leading to Death | 0 | 0 |

### Safety

- TEAEs occurred in 96.0% of pts, with 92.0% considered treatment-related. Grade ≥3 TEAEs were reported in 22.0% of pts, including 18.0% TRAEs. SAEs occurred in 14.0%, and 6.0% were treatment-related (**Table 3**).
- Dose reduction due to TRAEs occurred in 20.0% of pts and 16.3% at RP2D.
- No TEAEs led to discontinuation or death.
- The most common TRAEs (≥ 20%) were nausea, diarrhea, decreased appetite, decreased white blood cell count, anemia, fatigue, decreased neutrophil count, decreased platelet count and vomiting (**Figure 4**).
- Interstitial lung disease (ILD) was reported in 3 (6.0%; n=2 G1, n=1 G2) pts.

**Figure 4 Most common TRAEs (≥ 20%) / Preferred Term**




## Conclusions

- JSKN003 demonstrated promising efficacy in heavily pretreated HER2-overexpressing (IHC3+) gastrointestinal tumors including pts previously treated with irinotecan, with a manageable and predictable safety profile.
- The biparatopic HER2 antibody design may enhance target binding and contribute to the observed clinical benefit.

[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.



*Corresponding author email address: doctorshenlin@sina.cn