Efficacy and Safety of JSKN003, a Biparatopic anti-HER2 Antibody Drug Conjugate (ADC), in patients with HER2-positive Metastatic Colorectal Cancer (mCRC)

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Dan Liu[1], Bo Liu[2], Xiaochen Zhang[3], Jian Ruan[4], Guixiang Weng[5], Zhongmin Zhang[5], Hong Zong[6], Jing Dai[7], Ting Xu[8], Xiaowen Tang[8], Ruyi Xu[8], Lin Shen[9]*

1. Department of Drug Development Center, Peking University Cancer Hospital and Institute, Beijing, China; 2.Shandong Cancer Hospital and Institute, Jinan, China; 3. The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 4. Linyi People's Hospital, China; 5. Shanghai East Hospital, Shanghai, China; 6. The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; 7. Zhongnan Hospital of Wuhan University, Wuhan, China; 8. Alphamab Oncology Ltd, Suzhou, China; 9. Peking University Cancer Hospital and Institute, Beijing, China*

Background

- HER2-positive (IHC 3+ or 2+/FISH+) accounting for 3~6% in CRC patients[1]. DS-8201, a HER2-ADC, demonstrated robust efficacy. But there are still room to improve efficacy and safety.
- 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 data of JSKN003 in ovarian cancer, breast cancer and gastric cancer have been highlighted in previous reports. This analysis provided updated insights into its performance in HER-2 positive mCRC [2-4].

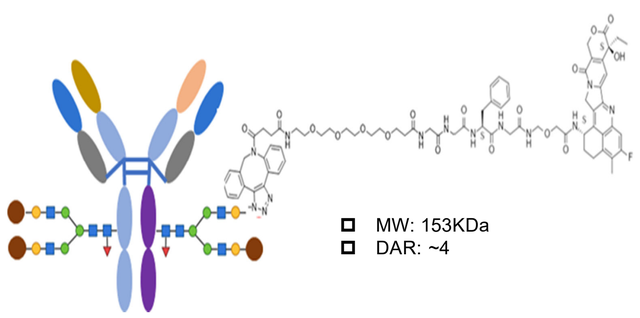


Figure 1. JSKN003 Structure Diagram

Method

- JSKN003-102 (NCT05744427) is a phase I (dose escalation and expansion) and phase II (cohort expansion) study conducted in China, enrolled pts with advanced/metastatic solid tumors.
- Here, we present the efficacy and safety data in HER2-positive mCRC pts.

Results

- As of 30th JUN 2025, a total of 33 pts with HER2-positive (tested by local lab) mCRC were enrolled across 2 dose levels: 6.3 mg/kg Q3W (n=32) and 8.4 mg/kg Q3W (n=1) .
- 69.7% enrolled pts were male with a median age of 59 (range, 30-69; **Table 1**).
- All enrolled pts were stage IV at screening, 54.5% with liver metastases.
- 5 (15.2%) pts with RAS/RAF mutation, including one BRAF V600E-mutant.
- All pts were heavily pre-treated, 42.4% received ≥3L prior anti-tumor treatments.

Table 1. Demographics & Baseline Characteristics

Characteristic	Total (N=33)
Age, median(range), years	59 (30, 69)
Female/Male, n (%)	10 (30.3) / 23 (69.7)
Asian race , n (%)	33 (100)
ECOG PS 0/1, n(%)	4 (12.1) / 29 (87.9)
HER2 IHC 3+ (by Local Lab), n (%)	28 (84.8)
RAF-mut, n (%)	2 (6.3)*
RAS-mut, n (%)	3 (9.4)
Brain mets, n (%)	3 (9.1)
Liver mets, n (%)	18 (54.5)
Prior anti-cancer therapy lines ≥3L, n (%)	14 (42.4)
Prior anti-HER2 therapy, n (%)	11 (33.3)
Prior IO therapy, n (%)	6 (18.2)
Prior Irinotecan, n (%)	27 (81.8)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
* One of the BRAF-mut was BRAF V600E mutant.

Efficacy

- 32 pts had ≥1 post baseline tumor assessment and were included in the efficacy analysis.
- Overall, ORR was 68.8% (22/32), DCR was 96.9% (31/32). **(Table 2)**.
- Additionally, among 31 BRAF V600E wild-type pts, **ORR** was **71.0% (22/31),** DCR was 100%, and median **DoR** was **9.89** months (95%CI, 5.78 to NE). The median **PFS** achieved **11.04** months (95%CI, 6.9 to 14.03), with a 9-month PFS rate of 66.6%.
- Individual patient-level response at the time of data cutoff are shown in **Figures 2 and 3**.

Table 2. Summary of Efficacy Results

	BRAF V600E wild-type N=31	Total N=32
ORR, % (95% CI)	71.0 (52.0, 85.8)	68.8 (50.0, 83.9)
CR	1 (3.2)	1 (3.1)
PR	21 (67.7)	21 (65.6)
SD	9 (29.0)	9 (28.1)
PD	0	1 (3.1)
DCR, (95% CI)	100.0 (88.8, 100)	96.9 (83.8, 99.9)
mPFS, mths (95% CI)	11.04 (6.9, 14.0)	11.04 (6.9, 14.0)
6-month PFS rate, %	82.02 (61.4,92.3)	79.54 (59.4, 90.4)
9-month PFS rate, %	66.64 (43.1, 82.2)	64.6 (41.9, 80.4)
mDoR, mths (95% CI)	9.89 (5.78, NE)	9.89 (5.78, NE)
6-month DoR rate, %	82.05 (44.4, 95.3)	82.05 (44.4, 95.3)

Figure 2. Best Percentage Change from Baseline in Target Lesions

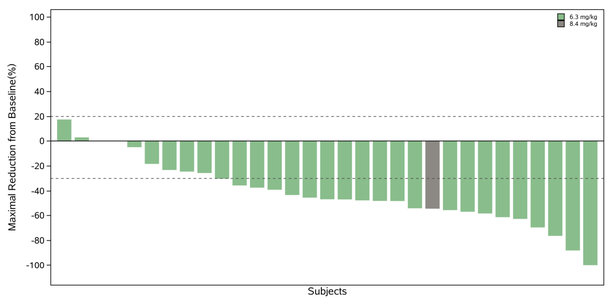


Figure 3. Best Percentage Change from Baseline Over Time

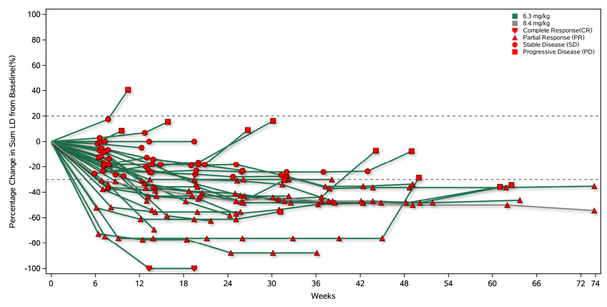


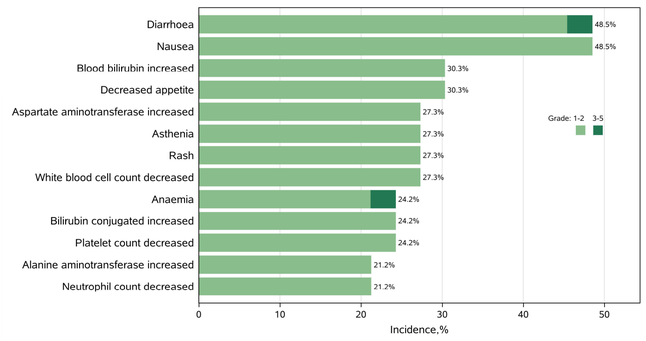
Table 3. Summary of Safety Results

AEs, n (%)	Total (n=33)
TRAEs	33 (100)
Grade ≥ 3 TRAEs	7 (21.2)
TRSAEs	4 (12.1)
TRAEs Leading to Discontinuation	0
TRAEs Leading to Death	0

Safety

- The median follow-up time was 9.26 months (95%CI: 5.82, 12.35).
- Treatment-related adverse events (TRAEs) were reported in 33 pts (100.0%); 7 were grade ≥3 (21.2%, **Table 3**).
- There were **no TRAEs** led to **discontinuation** or **death**.
- Overall, the most common TRAEs were diarrhea and nausea, most of which were grade 1-2. **(Figure 4)**.
- Interstitial lung disease (ILD) was reported in 4 (12.1%) pts, which were grade 1-2 and led no treatment discontinuation.

Figure 4. Most Common TRAEs With an Incidence Rate of ≥ 20%



Conclusions

- **JSKN003 demonstrated promising efficacy in heavily pretreated HER2-positive colorectal cancer with a manageable and predictable safety profile.**
- **The biparatopic HER2 antibody design may enhance target binding and contribute to the observed clinical benefit.**

References

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Disclosures

All authors have no conflicts of interest to disclose.

Contact Information

*Please contact the corresponding author, Dr Lin Shen, at doctorshenlin@sina.cn for questions or comments.

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