Trastuzumab deruxtecan in Chinese patients with previously treated HER2-positive locally advanced/metastatic gastric or gastroesophageal junction adenocarcinoma: DESTINY-Gastric06 final analysis

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Declaration of interests

- Lin Shen reports consulting for AstraZeneca, Boehringer Ingelheim, MSD, Servier, and Transcenta Holding Limited; and research funding from BeiGene, Innovent, NovaRock Biotherapeutics Limited, Roche, and Rongchang Pharmaceuticals

- Zhi Peng reports consulting for AstraZeneca and BeiGene

Background and study design

- T-DXd is a HER2-directed antibody-drug conjugate;[1,2] in DESTINY-Gastric01, T-DXd showed significant clinical benefit versus chemotherapy in pretreated patients from Japan or the Republic of Korea with HER2+ advanced GC[3]
- In China, patients with HER2+ advanced GC/GEJA have limited treatment options[4]
- DESTINY-Gastric06 (NCT04989816) was a Phase 2, multicenter, open-label study in China; results from the primary analysis demonstrated a clinically meaningful ORR of 28.8% in Chinese patients with HER2+ advanced GC/GEJA[5]
- In August 2024, T-DXd 6.4 mg/kg monotherapy received conditional approval in China for the treatment of adult patients with locally advanced or metastatic HER2+ GC/GEJA who have received two or more prior treatment regimens[6]
- Here, we report the final analysis from the DESTINY-Gastric06 study

Patient population

- Adults aged ≥18 years
- Pathologically confirmed advanced or metastatic GC/GEJA
- Progression on or after ≥2 prior regimens for advanced or metastatic disease*
- HER2 (IHC 3+/IHC 2+; locally documented)
- ECOG PS 0–1

T-DXd
6.4 mg/kg
IV Q3W

N=95†

Primary endpoint

- Confirmed ORR by ICR‡

Secondary endpoints

- Confirmed ORR by INV‡
- DOR by ICR‡
- PFS by ICR‡
- OS
- Safety and tolerability
- Pharmacokinetics and immunogenicity

*Prior systemic therapy must have included a fluoropyrimidine agent and a platinum agent; †intent-to-treat population included all patients enrolled in the study; ‡per RECIST 1.1
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancers; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

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Patient demographics and disease characteristics

	N=73*
Median age, years (range)	60 (28–77)
Female, n (%)	18 (24.7)
ECOG PS, n (%)	
0 / 1	27 (37.0) / 46 (63.0)
HER2 status,† n (%)	
IHC 3+ / IHC 2+/ISH+	53 (72.6) / 20 (27.4)
Primary tumor site, n (%)	
Gastric	51 (69.9)
GEJ	22 (30.1)
Sum of diameters of measurable tumors, n (%)	
<5 cm	29 (39.7)
≥5 cm	44 (60.3)
Number of metastatic sites, n (%)	
<2	15 (20.5)
≥2	58 (79.5)
Median prior lines of therapy, n (range)	2 (2–6)
Previous anti-HER2 therapy,‡ n (%)	
Trastuzumab-containing regimen	67 (91.8)
RC48-containing regimen	11 (15.1)
KN026-containing regimen	6 (8.2)
ARX788-containing regimen	3 (4.1)
Pyrotinib-containing regimen	2 (2.7)

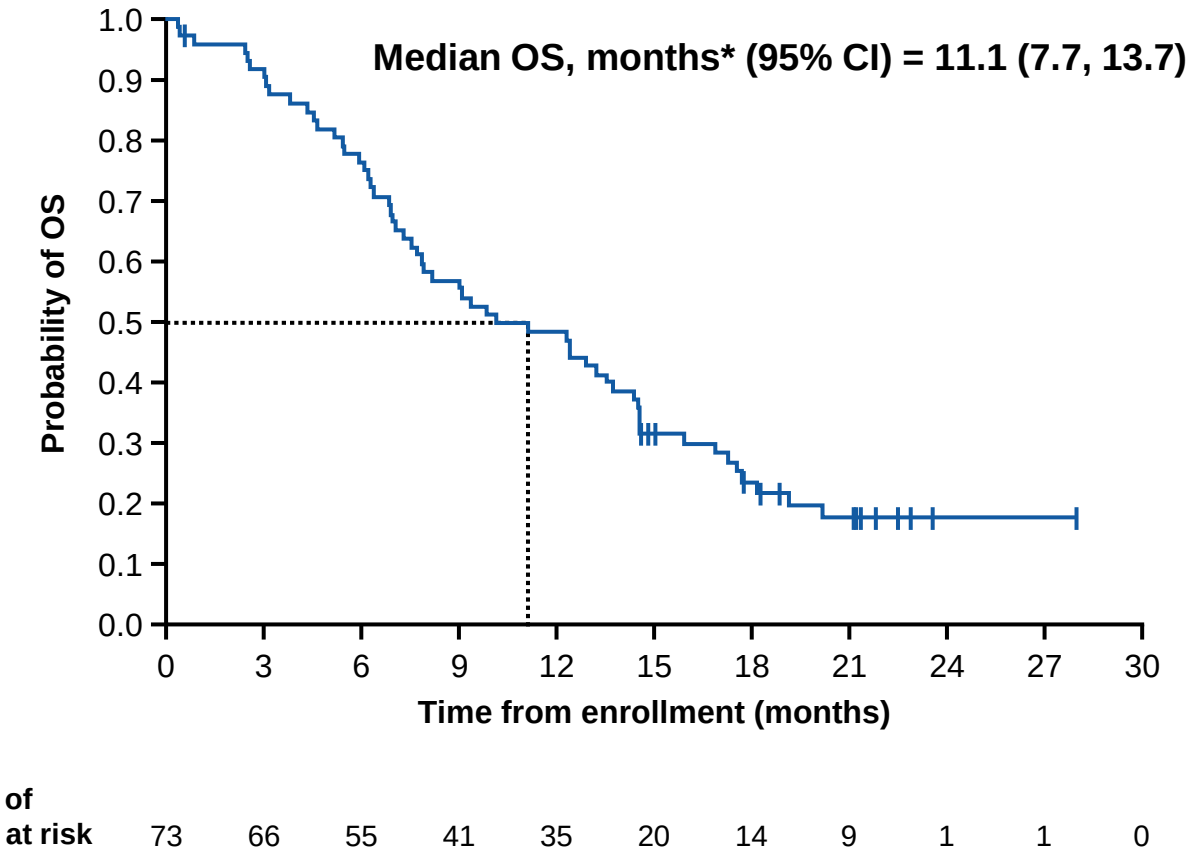
Data cutoff: February 28, 2024
*Full analysis set: 73 patients with centrally confirmed HER2+ status (IHC 3+ or IHC 2+/ISH+) and 22 patients had HER2 status not centrally confirmed as IHC 3+ or IHC 2+/ISH+; †by central laboratory; ‡only anti-HER2 therapies received by ≥2 patients are listed; therapies included anti-HER2 monoclonal and bispecific antibodies, anti-HER2 antibody-drug conjugates, and tyrosine kinase inhibitors
ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; IHC, immunohistochemistry; ISH+, in situ hybridization–positive

Response and survival outcomes

	N=73*
Median duration of follow up, months (Q1, Q3)	10.2 (6.1, 16.9)
Confirmed ORR by ICR, % (n)	**28.8 (21)**
Complete response	1.4 (1)
Partial response	27.4 (20)
Confirmed ORR by ICR and HER2 IHC status, % (n)	
IHC 3+	32.1 (17)
IHC 2+/ISH+	20.0 (4)
Confirmed ORR by INV, % (n)	**37.0 (27)**
Median DOR by ICR, months (95% CI)	**6.7 (4.6, 8.8)**
Median PFS by ICR, months (95% CI)	**5.7 (4.0, 6.8)**

Efficacy analyses per RECIST 1.1
*Full analysis set: 73 patients with centrally confirmed HER2+ status (IHC 3+ or IHC 2+/ISH+) and 22 patients had HER2 status not centrally confirmed as IHC 3+ or IHC 2+/ISH+
CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; ISH+, in situ hybridization–positive; ORR, objective response rate; PFS, progression-free survival; Q, quartile; RECIST, Response Evaluation Criteria in Solid Tumours

Kaplan-Meier survival curve and sensitivity analysis



Sensitivity analysis	N=73*
Censored COVID-19 death,† n (%)	4 (5.5)
Median OS, months (95% CI)	12.4 (7.9, 14.5)

Vertical lines indicate a censored observation. For OS analyses, patients not known to have died at the time of analysis were censored at the last recorded date on which they were last known to be alive
*Full analysis set: 73 patients with centrally confirmed HER2+ status (IHC 3+ or IHC 2+/ISH+) and 22 patients had HER2 status not centrally confirmed as IHC 3+ or IHC 2+/ISH+; †primary cause of death was COVID-19; patients were censored at the date of death −1
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; OS, overall survival

Safety, pharmacokinetics, and immunogenicity

Safety analyses,* n (%)	N=95
All-causality AEs	95 (100)
Drug-related AEs	94 (98.9)
All-causality Grade ≥3 AEs	71 (74.7)
Drug-related Grade ≥3 AEs	64 (67.4)
Most common (≥20%) drug-related Grade ≥3 AEs	
Neutrophil count decreased	24 (25.3)
Anemia	23 (24.2)
Platelet count decreased	19 (20.0)
Drug-related AEs leading to discontinuation	3 (3.2)
SAEs	40 (42.1)
Drug-related SAEs	22 (23.2)
Drug-related SAEs leading to death†	2 (2.1)
COVID-19–associated AEs	24 (25.3)
COVID-19	17 (17.9)
Coronavirus infection	5 (5.3)
COVID-19 pneumonia	4 (4.2)
Adjudicated drug-related ILD/pneumonitis	3 (3.2)
Grade 1	2 (2.1)
Grade 2	1 (1.1)
Grade ≥3	0

PK analyses, arithmetic mean, SD	End of infusion for cycle 1 (n=95)	End of infusion for cycle 4 (n=57)
T-DXd, µg/mL	103.8, 25.8	104.3, 26.0
Total anti-HER2 antibody, µg/mL	119.6, 28.5	109.8, 26.6
MAAA-1181a, ng/mL	4.0, 1.9	1.7, 0.7

Immunogenicity analyses	n=86
ADA positive at baseline and/or post baseline, n (%)	4 (4.7)
Treatment-ADA positive‡	2 (2.3)

Safety analysis set: all patients who received at least one dose of T-DXd. PK analysis set: all patients who received at least one dose of T-DXd and had at least one post-dose measurable serum concentration of T-DXd.
ADA-evaluable set: all patients who received at least one dose of T-DXd with a non-missing baseline assessment and at least one non-missing post-baseline assessment
*Median T-DXd treatment duration was 3.4 months (range 0.4–22.3); †including deaths caused by pneumonia (n=1) and pulmonary embolism (n=1); ‡no neutralizing ADAs were observed
ADA, anti-drug antibody; AE, adverse event; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; PK, pharmacokinetics; SAE, serious adverse event; SD, standard deviation; T-DXd, trastuzumab deruxtecan

Conclusions

- Final analysis results from the DESTINY-Gastric06 study were consistent with the primary analysis. In pretreated patients, T-DXd demonstrated encouraging antitumor activity (**ORR by ICR 28.8%**) and durable responses (**median DOR by ICR 6.7 months**), alongside a clinically meaningful **median OS** (**11.1 months**)
  - Survival data were generally consistent with those from DESTINY-Gastric01;[1] a numerically lower ORR was observed in DESTINY-Gastric06, which may be attributed to differences in patient characteristics, prior use of HER2-directed therapies, disease burden, tumor size, number of prior lines of therapy, and the COVID-19 pandemic
- The safety profile was **manageable and consistent with the established profile of T-DXd**, and no new safety signals were reported
- PK analyses were as expected and generally consistent with previous studies, with **T-DXd stable in circulation**[2]

These results reinforce T-DXd as a therapeutic option in the third- and later-line settings for patients from China with HER2+ advanced GC/GEJA

DOR, duration of response; GC, gastric cancers; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; ICR, independent central review; ORR, objective response rate; OS, overall survival; PK, pharmacokinetics; T-DXd, trastuzumab deruxtecan

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