Poster 172P

Trastuzumab deruxtecan in Chinese patients with previously treated HER2-positive locally advanced/metastatic gastric cancer or gastroesophageal junction adenocarcinoma: primary efficacy and safety from the Phase 2 single-arm DESTINY-Gastric06 trial

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Objective

- The objective of the DESTINY-Gastric06 (DG-06) trial was to evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) in Chinese patients with human epidermal growth factor receptor 2-positive (HER2+) advanced gastric cancer or gastroesophageal junction adenocarcinoma (GEJA) who have received two or more prior anticancer regimens
- The primary endpoint was to determine the confirmed objective response rate (ORR) by independent central review (ICR) in Chinese patients with HER2+ advanced gastric cancer or GEJA
- Secondary endpoints included investigator-assessed (INV) confirmed ORR; progression-free survival (PFS) and duration of response (DOR) by ICR; overall survival (OS); and safety and tolerability

Conclusions

- In this Phase 2 multicenter trial, T-DXd demonstrated clinically meaningful and durable responses, with a manageable safety profile, in Chinese patients with HER2+ advanced gastric cancer or GEJA who had received two or more prior anticancer regimens
- The survival outcomes of DG-06 were consistent with the findings from DESTINY-Gastric01

Plain language summary

Why did we perform this research?

Human epidermal growth factor receptor 2 (HER2) is a protein that promotes tumor growth,[1] and is found at high levels in some people with gastric or gastroesophageal junction cancers.[2,3] Trastuzumab deruxtecan (T-DXd) is a type of drug called an antibody-drug conjugate, which is a chemotherapy (deruxtecan) joined to an antibody (trastuzumab). By binding to the cancer cell before releasing the chemotherapy, T-DXd reduces the level of chemotherapy exposed to the body, so fewer side effects are seen.[4,5] T-DXd is already approved in more than 30 countries for people with gastric cancers whose cells have higher than normal levels of HER2 (HER2-positive[+]), and tumors have spread to nearby tissues or elsewhere in the body (advanced cancer).[6–10] In China, treatment options are limited for people with HER2+ advanced gastric or gastroesophageal junction cancers.

How did we perform this research?

In DESTINY-Gastric06 (DG-06), we evaluated the safety of T-DXd and how well it works as a treatment for Chinese participants with HER2+ advanced gastric and gastroesophageal junction cancers who had received two or more prior anticancer treatments.

What were the findings of this research?

The results of this clinical study showed that ~29% of participants who had already received at least two prior anticancer treatments had a response to T-DXd, and side effects were manageable. Limitations of the clinical study included the small number of participants, and that T-DXd was the only treatment studied.

What are the implications of this research?

These results support the use of T-DXd in Chinese patients with HER2+ gastric or gastroesophageal junction cancers.

Where can I access more information?

For more information about DG-06, please visit https://clinicaltrials.gov/study/NCT04989816, or please reach out to Professor Lin Shen at linshenpku@163.com.

This clinical study was sponsored by AstraZeneca and Daiichi Sankyo. Poster presented at ESMO Asia 2023 by Professor Lin Shen.
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Poster

Infographic plain language summary

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Introduction

- Among patients from East Asia with advanced gastric cancer or GEJA, ~10–18% have tumors that are HER2+[1,2]
- For these HER2+ tumors, effective therapies are needed particularly for patients with disease refractory to standard-of-care therapy[3]
- T-DXd is an antibody-drug conjugate, composed of an anti-HER2 antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload[4,5]
- T-DXd 6.4 mg/kg is approved in the US, EU, Japan, South Korea, and Singapore for the treatment of locally advanced or metastatic HER2+ gastric cancer or GEJA in adults who have received a prior trastuzumab-based regimen[6–10]
- In the DESTINY-Gastric01 trial, T-DXd demonstrated significant improvements in response rates and OS versus standard-of-care in patients from Japan or South Korea with HER2+ locally advanced or metastatic gastric cancer or GEJA[11]

Methods

- DG-06 was an open-label, single-arm, multicenter trial in China that evaluated the efficacy and safety of T-DXd (6.4 mg/kg) in patients with HER2+ gastric cancer or GEJA that had progressed on or after ≥2 prior anticancer regimens including a fluoropyrimidine agent and a platinum agent (**Figure 1**)
- Patients with centrally confirmed HER2+ tumors (defined as immunohistochemical [IHC] 3+ or IHC 2+/in situ hybridization [ISH]+) were evaluated for the primary endpoint

Definitions

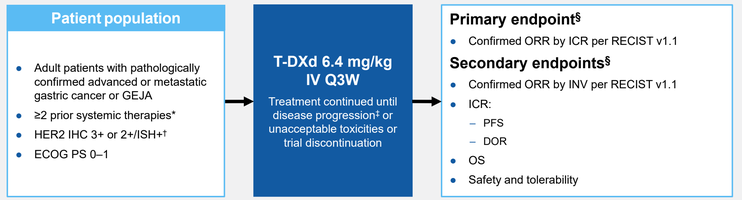
Primary endpoint

- **ORR:** proportion of patients who had a confirmed complete or partial response determined by ICR per RECIST v1.1

Secondary endpoints

- **ORR:** proportion of patients who had a confirmed complete or partial response determined by INV per RECIST v1.1
- **PFS:** time from the date of enrolment until RECIST v1.1-defined disease progression assessed by ICR or death due to any cause
- **DOR:** time from the first documented response until documented progression or death in the absence of disease progression
- **OS:** time from the date of enrolment until the date of death from any cause

Figure 1. DG-06 trial design



*Prior systemic therapy included a fluoropyrimidine agent and a platinum agent
†Confirmed by investigator based on a documented pathology result from a local laboratory or from a pathology report, and confirmed by central laboratory testing
‡Defined by RECIST v1.1
§Efficacy analysis was based on tumor assessments performed at screening and every 6 weeks from the first dose of trial intervention until RECIST v1.1 defined disease progression
DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; GEJA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; INV, investigator-assessed; ISH, in situ hybridization; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance score; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan

Results and interpretation

Population characteristics

- As of the data cutoff (June 16, 2023), 95 patients with advanced gastric cancer or GEJA were enrolled into the intent-to-treat population
- 73 patients with confirmed HER2+ (IHC 3+ or IHC 2+/ISH+) tumors by central laboratory were included in the full analysis set (FAS) (**Table 1**)

Table 1. Patient demographics and disease characteristics (FAS)

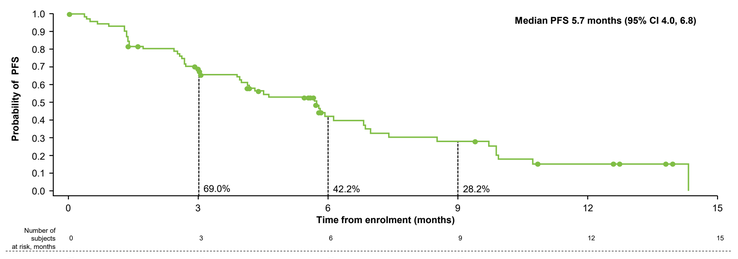
	N=73*
Median age, years (range)	60 (28–77)
Female, n (%)	18 (24.7)
ECOG PS, n (%)	
0	27 (37.0)
1	46 (63.0)
HER2 status, n (%)	
IHC 3+	53 (72.6)
IHC 2+/ISH+	20 (27.4)
Primary site, n (%)	
Gastric†	51 (69.9)
Gastroesophageal junction	22 (30.1)
Sum of diameters of measurable tumors, n (%)	
<5 cm	29 (39.7)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

*FAS defined as patients with centrally confirmed HER2+ status (IHC 3+ or 2+/ISH+) †Included tumors of gastric cardia (n=2), fundus of the stomach (n=5), body of the stomach (n=35), antrum pylori (n=8), and other location (n=1). ‡Only 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, Eastern Cooperative Oncology Group; FAS, full analysis set; IHC, immunohistochemistry; ISH, in situ hybridization; PS, performance score

Efficacy

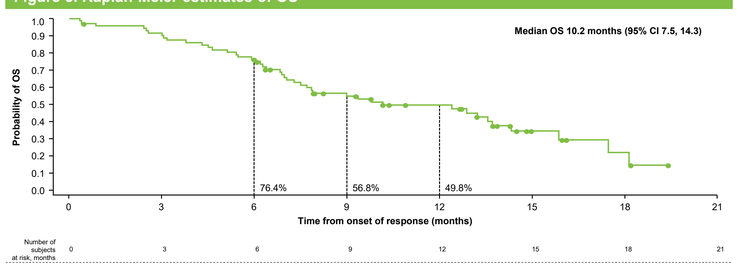
- The median duration of follow up was 8.0 months (interquartile range 6.0–13.2) in the FAS
- Of the 73 patients, 28.8% (21/73) had a confirmed response to T-DXd by ICR; best response by ICR and INV are shown in **Table 2**
  - ORR by ICR was 32.1% (17/53) and 20.0% (4/20) in patients with IHC 3+ and IHC 2+/ISH+, respectively
- Confirmed ORR by INV was 35.6% (26/73) in all patients
- PFS and OS of patients with HER2+ gastric cancer or GEJA following T-DXd treatment are shown in **Figure 2** and **3**, respectively
- The median DOR was 7.9 months (95% CI 4.6, 8.8)

Figure 2. Kaplan-Meier estimates of PFS*



*Assessed by ICR as per RECIST v1.1. Circle indicates a censored observation. Progression events that do not occur within 2 missed visits of the last evaluable assessment or first dose are censored
CI, confidence interval; ICR, independent central review; PFS, progression-free survival; RECIST v1.1; Response Evaluation Criteria in Solid Tumors version 1.1

Figure 3. Kaplan-Meier estimates of OS



Circle indicates a censored observation. Patients not known to have died at the time of analysis are censored at the last recorded date on which the subject was last known to be alive
CI, confidence interval; OS overall survival

Table 2. Best objective response

Best response, n (%)*	ICR	INV
Complete response	1 (1.4)	0 (0)
Partial response	20 (27.4)	26 (35.6)
Stable disease	37 (50.7)	31 (42.5)
Progressive disease†	14 (19.2)	15 (20.5)
Not evaluated	1 (1.4)	1 (1.4)

*Full analysis set population, defined as patients with centrally confirmed HER2+ status (IHC 3+ or 2+/ISH+). †Included RECIST v1.1 progression and death ≤13 weeks without RECIST v1.1 progression
HER2, human epidermal growth factor receptor 2; ICR, independent central review; INV, investigator-assessed; RECIST v1.1; Response Evaluation Criteria in Solid Tumors version 1.1

Safety

- The median duration of T-DXd exposure was 3.4 months (range 0.4, 14.5), and the safety profile was manageable (**Table 3**)
- The most common adverse events among patients were anemia (78.9%, n=75), leukopenia (71.6%, n=68), and neutropenia (61.1%, n=58)
- All cases of interstitial lung disease/pneumonitis were of low grade (grade <3) as adjudicated by an independent committee (**Table 4**)

Table 3. Safety profile of T-DXd

	N=95*
TEAEs, n (%)	95 (100)
Drug-related TEAEs, n (%)	94 (98.9)
Grade ≥3 TEAEs, n (%)	70 (73.7)
Grade ≥3 drug-related TEAEs, n (%)	62 (65.3)
COVID-19-related TEAEs, n (%)	24 (25.3)
COVID-19-related TEAEs associated with discontinuations, n (%)	5 (5.3)
Drug-related TEAEs associated with dose reductions, n (%)	21 (22.1)
Drug-related TEAEs associated with discontinuations, n (%)	3 (3.2)
Drug-related TEAEs associated with deaths,† n (%)	2 (2.1)

Table 4. Interstitial lung disease/pneumonitis adjudicated as T-DXd related

N (%)	Grade 1	Grade 2	Grade 3–5	Any grade
All patients (N=95)*	2 (2.1)	1 (1.1)	0	3 (3.2)

*Analyses were performed in the safety analysis set, defined as all patients who were enrolled in the trial and received at least one dose of T-DXd
†Included deaths caused by pneumonia (n=1) and pulmonary embolism (n=1)
AE, adverse events; T-DXd, trastuzumab deruxtecan; TEAEs; treatment-emergent adverse events

Disclosures

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