Poster 297P

First-line trastuzumab deruxtecan 5.4 mg/kg and fluoropyrimidine with pembrolizumab in advanced HER2+ gastric cancer, gastroesophageal junction adenocarcinoma, or esophageal adenocarcinoma: updated results from DESTINY-Gastric03 Part 2F

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Objective

- To report updated results for DESTINY-Gastric03 Part 2 arm F, evaluating first-line (1L) trastuzumab deruxtecan (T-DXd) 5.4 mg/kg with fluoropyrimidine (FP) and pembrolizumab in advanced or metastatic human epidermal growth factor receptor 2 (HER2)–positive (+) gastric cancer (GC), gastroesophageal junction adenocarcinoma (GEJA), or esophageal adenocarcinoma (EA)

Conclusions

- These results provide further evidence of antitumor activity with 1L T-DXd 5.4 mg/kg and FP and pembrolizumab in advanced HER2+ GC, GEJA, or EA[1,2]
  - Clinical activity was observed regardless of programmed cell death ligand 1 (PD-L1) expression level
- The safety profile of 1L T-DXd 5.4 mg/kg with FP and pembrolizumab was generally consistent with the known profiles of each agent as monotherapy,[3–5] with no new safety signals observed
- Overall, data support ongoing Phase 3 studies evaluating 1L T-DXd combinations in advanced HER2+ GCs[6,7]

Plain language summary

Why did we perform this research?

Human epidermal growth factor receptor 2 (HER2) is a protein found at high levels in some cancers (known as HER2-positive or HER2+), including those in the stomach (gastric cancer [GC]), where the stomach meets the food pipe (gastroesophageal junction adenocarcinoma [GEJA]), and in the food pipe (esophageal adenocarcinoma [EA]).[1,2] Trastuzumab deruxtecan (T-DXd; a HER2-directed antibody-drug conjugate that kills HER2-altered cancer cells[3,4]) is approved in multiple countries for people with previously treated HER2+ GC or GEJA that has spread from its original site to other parts of the body (known as advanced or metastatic cancer).[5–7] Initial results from Part 2 arm D of the DESTINY-Gastric03 study showed that T-DXd 6.4 mg/kg with chemotherapy and pembrolizumab (a cancer drug that targets a protein called programmed cell death protein 1) decreased the size or number of selected tumors (known as an objective response) in people with HER2+ GC, GEJA, or EA who had not received any prior treatment for advanced or metastatic disease; however, the incidence of side effects was high.[8] Early data from Part 2 arm F showed that reducing the doses of T-DXd and chemotherapy improved the safety of the treatment without reducing the clinical benefit.[9] Here, we report updated results for DESTINY-Gastric03 Part 2 arm F.

How did we perform this research?

In DESTINY-Gastric03 Part 2 arm F, we evaluated the benefit and safety of T-DXd 5.4 mg/kg every 3 weeks (Q3W) with chemotherapy (5-fluorouracil 600 mg/m^2/day for 5 days Q3W or capecitabine 750 mg/m^2 twice daily for 14 days Q3W) and pembrolizumab 200 mg Q3W in people with advanced or metastatic HER2+ GC, GEJA, or EA who had not received any prior treatment for advanced or metastatic disease.

What were the findings of this research?

Overall, 24 out of 32 people (75.0%) had an objective response to T-DXd 5.4 mg/kg with chemotherapy and pembrolizumab. Among people with high or low levels of programmed cell death ligand 1 expression in their tumors, response rates were 70.6% and 72.7%, respectively. The side effects were consistent with those reported in previous T-DXd studies,[10,11] and no new safety concerns were observed.

What are the implications of this research?

These results provided further evidence of the benefit of T-DXd 5.4 mg/kg with chemotherapy and pembrolizumab for people with advanced or metastatic HER2+ GC, GEJA, or EA who had not received any prior treatment for advanced or metastatic disease.

Where can I access more information?

For more information about DESTINY-Gastric03, please visit https://clinicaltrials.gov/study/NCT04379596. You can also speak to your doctor about this and other clinical studies.

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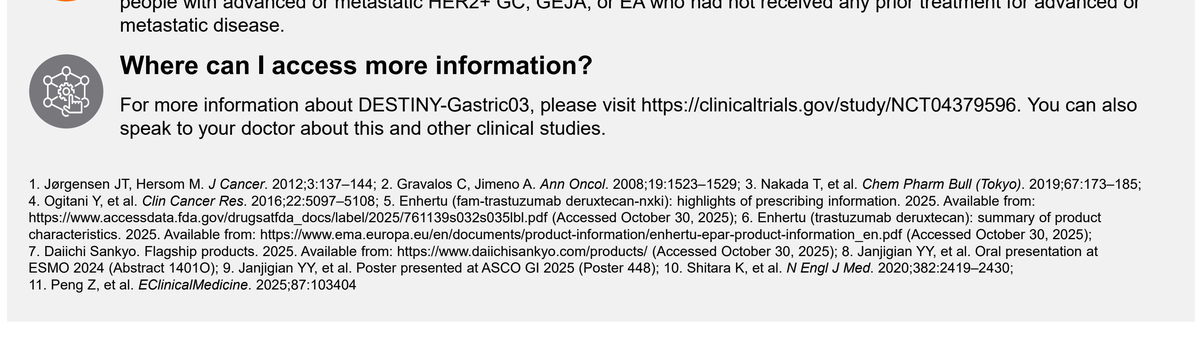
Introduction

- T-DXd (a HER2-directed antibody-drug conjugate) 6.4 mg/kg monotherapy is approved in multiple countries for advanced or metastatic HER2+ GC or GEJA after an indicated HER2-directed regimen[8–10]
- Trastuzumab (a HER2-directed antibody) plus pembrolizumab (an anti-programmed cell death protein 1 antibody) and chemotherapy is an approved 1L treatment for advanced HER2+ GC or GEJA with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1[11]
- Preliminary results from DESTINY-Gastric03 Part 2 arm D showed that 1L T-DXd 6.4 mg/kg with FP and pembrolizumab demonstrated antitumor activity in advanced HER2+ GC, GEJA, or EA; however, it was associated with higher-than-expected toxicity[1]
  - Early data from arm F showed that reducing the doses of T-DXd and FP improved tolerability of the triplet regimen while maintaining the promising antitumor activity observed in this population[2]
- Here, we report updated efficacy and safety data for DESTINY-Gastric03 Part 2 arm F

Methods

- DESTINY-Gastric03 (NCT04379596) is a Phase 1b/2 multicenter, open-label, dose-escalation (Part 1) and -expansion (Parts 2, 3, 4, and 5) study[12]
- In Part 2 arm F, patients with previously untreated advanced or metastatic HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+ / in situ hybridization–positive by local testing) GC, GEJA, or EA, irrespective of PD-L1 status, were enrolled (**Figure 1**)

Figure 1. DESTINY-Gastric03 Part 2 arm F trial design



DESTINY-Gastric03 Part 2 consists of six arms (A–F);[12] only arm F is presented in this poster. *Treatment with 5-fluorouracil or capecitabine was decided by the investigator; †per RECIST 1.1; ‡confirmed ORR, defined as the best objective response of complete or partial response, required confirmation after at least 4 weeks; §protocol-defined AEs of special interest, including ILD/pneumonitis and left ventricular ejection fraction decrease events, were reported; ILD/pneumonitis was assessed by an ILD adjudication committee
AE, adverse event; BID, twice daily; EA, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2+, human epidermal growth factor receptor 2–positive; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; IV, intravenous; PO, orally; ORR, objective response rate; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Results

Patient characteristics

- At data cutoff (February 28, 2025), 32 patients were enrolled and received T-DXd 5.4 mg/kg with FP and pembrolizumab in Part 2 arm F
- Patient demographics and clinical characteristics are summarized in **Table 1**

Table 1. Patient demographics and clinical characteristics

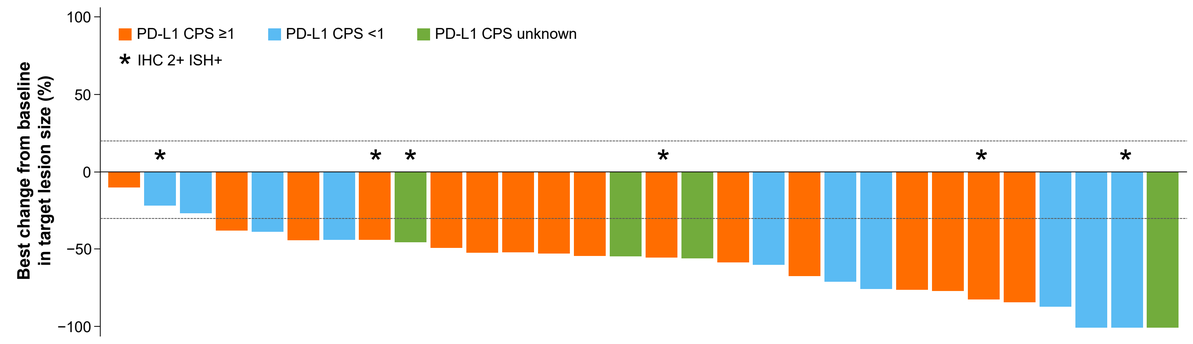
	Arm F: T-DXd 5.4 mg/kg + FP + pembrolizumab (n=32)
Age, median (range), years	61.0 (20–78)
Sex, n (%)	
Female	3 (9.4)
Race, n (%)	
Asian / Non-Asian	15 (46.9) / 17 (53.1)
ECOG PS, n (%)	
0 / 1	17 (53.1) / 15 (46.9)
Primary tumor site, n (%)	
Gastric	21 (65.6)
GEJ	7 (21.9)
Esophageal	4 (12.5)
Local HER2 status, n (%)	
IHC 3+	26 (81.3)
IHC 2+/ISH+	6 (18.8)
Central HER2 status,* n (%)	
IHC 3+	17 (53.1)
IHC 2+/ISH+	3 (9.4)
Missing	5 (15.6)
Central PD-L1 status, n (%)	
CPS ≥1 / CPS <1	17 (53.1) / 11 (34.4)
Not reported	4 (12.5)

*One patient had a HER2 IHC 0 tumor, six patients had HER2 IHC 2+/ISH− tumors
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FP, fluoropyrimidine; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH(+/−), in situ hybridization(–positive/–negative); PD-L1, programmed cell death ligand 1; T-DXd, trastuzumab deruxtecan

Efficacy

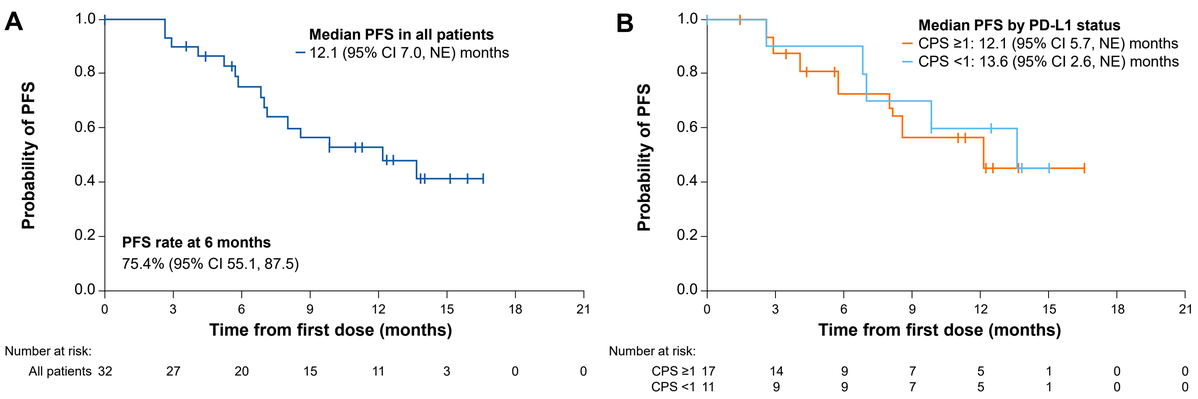
- Median duration of follow up was 12.9 (range 1.0–17.2) months
- In the overall population, the confirmed objective response rate (ORR) was 75.0% (95% confidence interval [CI] 56.6, 88.5; n/N=24/32)
  - The confirmed ORR was 70.6% (95% CI 44.0, 89.7; n/N=12/17) and 72.7% (95% CI 39.0, 94.0; n/N=8/11) for patients with centrally confirmed PD-L1 CPS ≥1 and CPS <1 tumors, respectively
- Median duration of response was 12.3 (95% CI 3.9, not estimable [NE]) months
  - Median duration of response was NE for patients with centrally confirmed PD-L1 CPS ≥1 tumors and 12.3 (95% CI 2.8, NE) months for patients with CPS <1 tumors by central testing
- Best percentage change from baseline in the size of target lesion is shown in **Figure 2**
- Progression-free survival for all patients (total events: n=15; 46.9%) and by PD-L1 status is shown in **Figure 3**; median overall survival was 15.7 (95% CI 12.1, NE) months (total events: n=12; 37.5%)

Figure 2. Best percentage change from baseline in the size of target lesion



Investigator assessed per RECIST 1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively. HER2 status was locally assessed. PD-L1 status was centrally assessed. Patients with no target lesions at baseline (n=1) or no post-baseline scans (n=1) were not included in the analysis
CPS, combined positive score; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours

Figure 3. Kaplan-Meier estimates of PFS in all patients (A) and by PD-L1 status (B)



Symbols indicate a censored observation. For PFS analyses (investigator assessed per RECIST 1.1), patients alive and without disease progression, or who had disease progression or died after two or more missed visits, were censored at the latest evaluable RECIST assessment, or at Day 1 (randomization / treatment assignment) if there were no evaluable visits or no baseline assessment (unless the patient died within 13 weeks of baseline assessment). PD-L1 status was centrally assessed
CI, confidence interval; CPS, combined positive score; NE, not estimable; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Safety

- The median total duration of treatment for T-DXd and pembrolizumab was 7.2 (range 0.7–17.1) months and 8.1 (range 0.7–17.1) months, respectively; a summary of safety data is shown in **Table 2**
- Eight patients (25%) had a Grade ≥3 gastrointestinal disorder event
- There were no adjudicated drug-related interstitial lung disease / pneumonitis events
- One patient (3.1%) had a drug-related Grade ≥3 left ventricular ejection fraction decrease event

Table 2. Summary of AEs

AEs, n (%)	Arm F: T-DXd 5.4 mg/kg + FP + pembrolizumab (n=32)
AEs	31 (96.9)
Drug-related AEs*	27 (84.4)
Grade ≥3 AEs	15 (46.9)
Drug-related Grade ≥3 AEs*	11 (34.4)
Most common (≥8%) Grade ≥3 AEs	
Neutrophil count decreased	5 (15.6)
Platelet count decreased	3 (9.4)
Anemia	3 (9.4)

AEs, n (%)	Arm F: T-DXd 5.4 mg/kg + FP + pembrolizumab (n=32)
SAEs	12 (37.5)
Drug-related SAEs*	4 (12.5)
AEs leading to:	
Dose interruption of T-DXd / pembrolizumab	12 (37.5) / 14 (43.8)
Dose reduction of T-DXd / pembrolizumab	6 (18.8) / 0
Discontinuation of any IP	8 (25.0)
AEs with an outcome of death	0

*Assessed by the investigator as possibly related to any of the IPs
AE, adverse event; FP, fluoropyrimidine; IP, investigational product; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Poster

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Disclosures

Dr. Yelena Y Janjigian reports consulting or being an invited speaker for AmerisourceBergen, Arcus Biosciences, Astellas, AstraZeneca, Basilea Pharmaceutica, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Clinical Care Options, ED Medresources (OncInfo), Geneos Therapeutics, HC Wainwright & Co., LLC, HMP Education, Imedex, Inspirna, Merck, Merck Serono, Mersana Therapeutics, Michael J Hennessy Associates, Paradigm Medical Communications, PeerView Institute, Pfizer, Physicians' Education Resource®, LLC, Research to Practice, Silverback Therapeutics, Talem Health, and TotalCME; participation on an advisory board with AbbVie, Arcus Biosciences, AskGene Pharma, Inc., AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Eisai Co., Ltd, Eli Lilly, GSK, Gilead Sciences, Guardant Health, Imugene, Lynx Health, Merck, Sanofi Genzyme, Seagen, and Zymeworks Inc.; personal or institutional research funding from Arcus Biosciences, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Cycle for Survival, Eli Lilly, Fred's Team, Genentech/Roche, Inspirna, Merck, National Cancer Institute, Stand Up To Cancer, Transcenta Holding Ltd; stock options or shares in Inspirna and Veda Life Sciences; and membership on the steering committees for AstraZeneca, Michael J Hennessy Associates, and Transcenta Holding Ltd.

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