Poster LB331

First-line trastuzumab deruxtecan with rilvegostomig and fluoropyrimidine in HER2-positive gastric cancer, gastroesophageal junction adenocarcinoma, or esophageal adenocarcinoma: DESTINY-Gastric03 Part 4 arm A results

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Objective

- To report preliminary results for DESTINY-Gastric03 (NCT04379596) Part 4 arm A, evaluating first-line (1L) trastuzumab deruxtecan (T-DXd) 5.4 mg/kg with rilvegostomig and fluoropyrimidine (FP) in advanced or metastatic human epidermal growth factor receptor 2 (HER2)–positive (+) gastric cancer (GC), gastroesophageal junction adenocarcinoma (GEJA), or esophageal adenocarcinoma (EA)

Conclusions

- Preliminary results showed promising antitumor activity with 1L T-DXd 5.4 mg/kg with rilvegostomig and FP in HER2+ GC, GEJA, or EA
- The safety profile of 1L T-DXd 5.4 mg/kg with rilvegostomig and FP was generally consistent with the known profiles of each agent as monotherapy,[1–3] with no new safety signals observed
- Overall, data support further study of this 1L T-DXd (5.4 mg/kg)–based regimen in advanced HER2+ GC, GEJA, or EA

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]) 6.4 mg/kg 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).[5,6] Rilvegostomig is a novel drug that blocks two proteins on the surface of cells in the immune system, called programmed cell death protein 1 and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain, thereby helping the immune system kill cancer cells.[7,8] In previously untreated people with advanced HER2-negative GCs, rilvegostomig plus chemotherapy decreased the size or number of tumors, with no new safety concerns.[8] Here, we present early results for DESTINY-Gastric03 Part 4 arm A, evaluating T-DXd 5.4 mg/kg with rilvegostomig and chemotherapy in HER2+ GCs.

How did we perform this research?

In DESTINY-Gastric03 Part 4 arm A, we evaluated the benefit and possible side effects of T-DXd 5.4 mg/kg with rilvegostomig and chemotherapy (5-fluorouracil or capecitabine) 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?

In this clinical study, 21 out of 30 people (70%) had a confirmed objective response (target tumors decreased in size by at least 30% or disappeared, which was verified by a second follow-up scan) after treatment with T-DXd 5.4 mg/kg with rilvegostomig and chemotherapy. The side effects were generally consistent with the known safety profiles of each agent when used alone,[9–11] and no new safety concerns were observed.

What are the implications of this research?

These early results provide evidence of the benefit of T-DXd 5.4 mg/kg with rilvegostomig and chemotherapy for people with advanced or metastatic HER2+ GC, GEJA, or EA who have 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.

1. Jørgensen JT, Hersom M. *J Cancer*. 2012;3:137–144; 2. Gravalos C, Jimeno A. *Ann Oncol*. 2008;19:1523–1529; 3. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185; 4. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108; 5. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf (Accessed March 12, 2026); 6. Enhertu (trastuzumab deruxtecan): summary of product characteristics. 2025. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed March 12, 2026); 7. Lee K, et al. *J Immunother Cancer*. 2022;10(Suppl. 2) (Abstract 469); 8. Herrero FR, et al. *Ann Oncol*. 2024;35(Suppl. 2):S887 (Abstract 1422P); 9. Peng Z, et al. *EClinicalMedicine*. 2025;87:103404; 10. Arai H, et al. *BMC Cancer*. 2019;19:652; 11. Hiltermann J, et al. Oral presentation at WCLC 2024 (Abstract OA11.03)

Poster

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Poster presented at AACR 2026 by Dr Yelena Y Janjigian. Corresponding author email address: janjigiy@mskcc.org

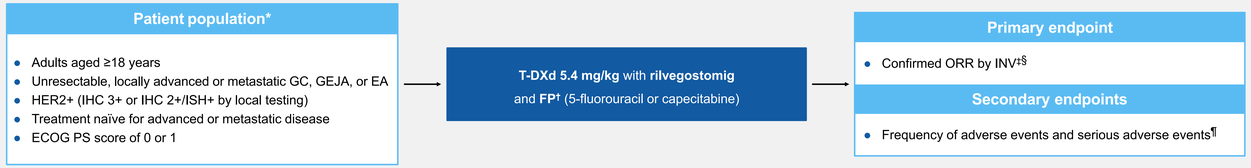
Introduction

- 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[4,5]
- Preliminary results from DESTINY-Gastric03 Part 2 arm 2F showed that 1L T-DXd 5.4 mg/kg with pembrolizumab (an anti-programmed cell death protein 1 [PD-1] antibody) and FP demonstrated antitumor activity, with no new safety signals, in advanced HER2+ GC, GEJA, or EA[6]
- Rilvegostomig is a monovalent, Fc-reduced, dual checkpoint bispecific IgG1 monoclonal antibody against PD-1 and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) receptors[7]
  - Rilvegostomig in combination with chemotherapy showed antitumor activity and a manageable safety profile in previously untreated patients with advanced HER2-negative GC or GEJA[7]
- Here, we report early data from DESTINY-Gastric03 Part 4 arm A evaluating 1L T-DXd 5.4 mg/kg with rilvegostomig and FP in advanced HER2+ GC, GEJA, or EA

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[8]
- In Part 4 arm A, 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 were enrolled (**Figure 1**)

Figure 1. DESTINY-Gastric03 Part 4 arm A trial design



DESTINY-Gastric03 Part 4 consists of two arms (A and B); only arm A is presented in this poster. *PD-L1 status was assessed by local test before treatment assignment and by central test retrospectively; †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 adverse events of special interest for T-DXd and rilvegostomig were reported; ILD/pneumonitis was assessed by an ILD adjudication committee
EA, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FP, fluoropyrimidine; 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; INV, investigator assessment; ORR, objective response rate; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Results

Patient characteristics

- At data cutoff (October 16, 2025), 30 patients were enrolled and received treatment in Part 4 arm A; patient demographics and clinical characteristics are presented in **Table 1**

Table 1. Patient demographics and clinical characteristics

	Arm A: T-DXd + rilvegostomig + FP (N=30)
Median age, years (range)	60.5 (27–79)
Sex, n (%)	
Female	6 (20.0)
Race, n (%)	
Asian	8 (26.7)
ECOG PS score, n (%)	
0 / 1	13 (43.3) / 17 (56.7)
Primary tumor site, n (%)	
Gastric	10 (33.3)
GEJ	14 (46.7)
Esophageal	4 (13.3)
Missing	2 (6.7)
HER2 IHC status by local test, n (%)	
IHC 3+ / IHC 2+/ISH+	23 (76.7) / 6 (20.0)
IHC missing	1 (3.3)
HER2 IHC status by central test,* n (%)	
IHC 3+ / IHC 2+/ISH+	11 (36.7) / 7 (23.3)
Missing	8 (26.7)
PD-L1 status by local test, n (%)	
CPS ≥1 / CPS <1	24 (80.0) / 2 (6.7)
Unreported	4 (13.3)
PD-L1 status by central test, n (%)	
CPS ≥1 / CPS <1	11 (36.7) / 6 (20.0)
Unreported	13 (43.3)

*Two patients had HER2 IHC 1+ tumors and two 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

- The median duration of follow up was 7.6 (range 1.9–12.6) months for T-DXd with rilvegostomig and FP
- The confirmed objective response rate (ORR) by investigator assessment was 70.0% (n/N=21/30; 95% confidence interval 50.6, 85.3) in the overall population; investigator-assessed confirmed ORR by HER2 and programmed cell death ligand 1 status is shown in **Table 2**
- Best change from baseline in target lesion size is shown in **Figure 2**

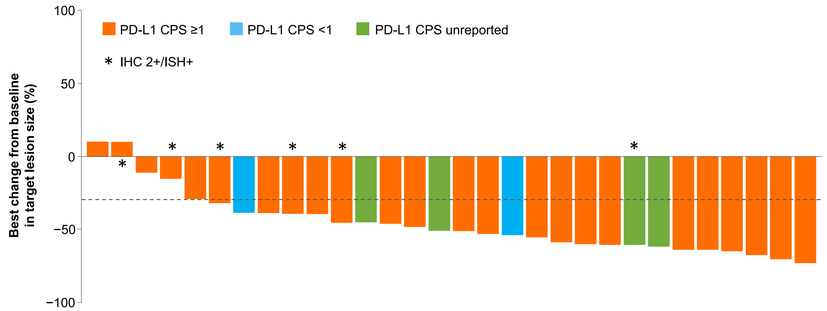
Table 2. Investigator-assessed confirmed ORR by HER2 and PD-L1 status

% (n/n); 95% CI	Arm A: T-DXd + rilvegostomig + FP (N=30)
Local HER2 status*	
IHC 3+	78.3 (18/23); 56.3, 92.5
IHC 2+/ISH+	50.0 (3/6); 11.8, 88.2

% (n/n); 95% CI	Arm A: T-DXd + rilvegostomig + FP (N=30)
Local PD-L1 status†	
CPS ≥1	62.5 (15/24); 40.6, 81.2
CPS <1	100 (2/2); 15.8, 100

*One patient had missing HER2 IHC status; †four patients had unreported PD-L1 CPS status
Confirmed ORR required confirmation after at least 4 weeks. Confirmed ORR by centrally assessed PD-L1 status: CPS ≥1 (81.8% [n/n=9/11]; 95% CI 48.2, 97.7), CPS <1 (50.0% [n/n=3/6]; 95% CI 11.8, 88.2)
CI, confidence interval; CPS, combined positive score; FP, fluoropyrimidine; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; ORR, objective response rate; PD-L1, programmed cell death ligand 1; T-DXd, trastuzumab deruxtecan

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



Investigator assessed per RECIST 1.1. Best percentage change in target lesion size is the maximum reduction or the minimum increase from baseline in the absence of a reduction. The dashed line indicates the threshold for partial response (a decrease of at least 30% in target lesion size from baseline). HER2 and PD-L1 status were locally assessed
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

Safety

- The median total duration of treatment exposure was 7.0 (range 1.8–11.3) months for both T-DXd and rilvegostomig, 8.1 (range 2.9–11.3) months for 5-fluorouracil, and 4.8 (range 1.4–9.0) months for capecitabine
- In total, eight patients (26.7%) had drug-related Grade ≥3 adverse events (AEs); a summary of the safety data is shown in **Table 3**
  - The most common (>5%) events were neutrophil count decrease (n=3; 10.0%) and hypokalemia (n=2; 6.7%)
- Drug-related AEs leading to discontinuation of any investigational product occurred in three patients (10.0%); events were fatigue (n=1; 3.3%), pneumonia (n=1; 3.3%), and interstitial lung disease (n=1; 3.3%)
- There were no drug-related AEs with an outcome of death

Table 3. Summary of AEs

n (%)	Arm A: T-DXd + rilvegostomig + FP (N=30)
Any-grade AEs	29 (96.7)
Drug-related any-grade AEs*	26 (86.7)
Grade ≥3 AEs	11 (36.7)
Drug-related Grade ≥3 AEs*	8 (26.7)
Serious AEs	8 (26.7)
Drug-related serious AEs*	4 (13.3)
AEs leading to dose interruption of T-DXd/rilvegostomig	10 (33.3) / 11 (36.7)
AEs leading to dose reduction of T-DXd†	3 (10.0)
AEs leading to discontinuation of any IP	4 (13.3)
Drug-related AEs leading to discontinuation of any IP*	3 (10.0)

*Assessed by the investigator as possibly related to any of the IPs; †per protocol, rilvegostomig dose reductions were not permitted
AE, adverse event; FP, fluoropyrimidine; IP, investigational product; T-DXd, trastuzumab deruxtecan

- Drug-related AEs of special interest are shown in **Table 4**
  - Adjudicated drug-related interstitial lung disease/pneumonitis occurred in two patients (6.7%; both Grade 2)
  - There were no reports of drug-related left ventricular dysfunction
  - Drug-related Grade ≥3 AEs of special interest included diarrhea/colitis (n=1; 3.3%) and dermatitis/rash (n=1; 3.3%)

Table 4. Drug-related AEs of special interest

Any-grade events, n (%)	Arm A: T-DXd + rilvegostomig + FP (N=30)
Diarrhea/colitis*†	9 (30.0)
Dermatitis/rash*†	4 (13.3)
Hepatic events*†	2 (6.7)
ILD/pneumonitis*‡	2 (6.7)
Myositis*†	1 (3.3)
Hypothyroid events*†	1 (3.3)

*Grouped terms; †protocol-specified AE of special interest for rilvegostomig but assessed by the investigator as possibly related to any treatment; ‡protocol-specified AE of special interest for T-DXd (termed 'ILD/pneumonitis', as shown in the table) and rilvegostomig (termed 'pneumonitis'); confirmed as drug related by an ILD adjudication committee (possibly related to any treatment)
AE, adverse event; FP, fluoropyrimidine; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan

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Disclosures

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References

1. Peng Z, et al. *EClinicalMedicine*. 2025;87:103404
2. Arai H, et al. *BMC Cancer*. 2019;19:652
3. Hiltermann J, et al. Oral presentation at WCLC 2024 (Abstract OA11.03)
4. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf (Accessed March 12, 2026)
5. Enhertu (trastuzumab deruxtecan): summary of product characteristics. 2025. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed March 12, 2026)
6. Janjigian YY, et al. Poster presented at ESMO Asia 2025 (Poster 297P)
7. Herrero FR, et al. *Ann Oncol*. 2024;35(Suppl. 2):S887 (Abstract 1422P)
8. NCT04379596. Updated February 23, 2026. Available from: https://clinicaltrials.gov/study/NCT04379596 (Accessed March 12, 2026)

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