First-line trastuzumab deruxtecan with volrustomig and fluoropyrimidine in patients with HER2-low gastric cancer, gastroesophageal junction adenocarcinoma, or esophageal adenocarcinoma: DESTINY-Gastric03 Part 5

Yelena Y Janjigian,[1] Hanneke van Laarhoven,[2] Roy Rabbie,[3] Caron Lloyd,[4] Zhuoer Sun,[5] Jeeyun Lee[6]

[1]Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, US; [2]Department of Medical Oncology, Amsterdam University Medical Center, University of Amsterdam, Netherlands; [3]Global Medicines Development, Late Development Oncology, Oncology R&D, AstraZeneca, Cambridge, UK; [4]Clinical Development Department, Late Development Oncology, Oncology R&D, AstraZeneca, New York, NY, US; [5]Clinical Research Division, Biometrics Department, Oncology R&D, AstraZeneca, Shanghai, China; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

TPS472

Plain language summary

Why are we performing this research?

Human epidermal growth factor receptor 2 (HER2) is a protein found in some cancers, including those in the stomach (gastric cancer; GC), where the stomach meets the food pipe (gastroesophageal junction adenocarcinoma; GEJA), and in the food pipe itself (esophageal adenocarcinoma; EA).[1,2] These cancers may be referred to as HER2-positive (HER2+; immunohistochemistry [IHC] 3+ or IHC 2+ with positive in situ hybridization [ISH+]) or HER2-low (IHC 1+ or IHC 2+ with negative in situ hybridization [ISH−]). Currently, there are no HER2-directed treatments for HER2-low GCs. Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, comprising a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab). T-DXd binds to HER2 on the surface of cancer cells. Once inside the cell, it releases the chemotherapy that kills the cancer cells.[3,4] Volrustomig is a novel drug that blocks two proteins on the surface of cells in the immune system, called programmed cell death protein 1 and cytotoxic T-lymphocyte-associated protein 4,[5] thereby helping the immune system kill cancer cells.[5,6] Combining cancer treatments has been shown to decrease the size or number of tumors.[7] Part 5 of the DESTINY-Gastric03 study aims to investigate the effects of T-DXd plus volrustomig and chemotherapy in people with HER2-low GCs.

How are we performing this research?

DESTINY-Gastric03 is an ongoing clinical study looking at T-DXd treatment alone and/or in combination with other cancer treatments in people with HER2+ and HER2-low GC, GEJA, or EA. Part 5 of the DESTINY-Gastric03 study will evaluate the benefit and possible side effects of T-DXd with volrustomig and chemotherapy in people with HER2-low GC, GEJA, or EA. The primary outcome of interest is the percentage of participants who have a decrease in the size or number of tumors after treatment.

Who will participate in this study?

Part 5 of the study will include people with HER2-low (IHC 1+ or IHC 2+/ISH−) GC, GEJA, or EA that has spread to other parts of the body (advanced/metastatic) or cannot be removed completely by surgery (unresectable). People cannot participate if they have previously received treatment for their advanced/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. Van Cutsem E, et al. *Gastric Cancer*. 2015;18:476–484; 2. Plum PS, et al. *BMC Cancer*. 2019;19:38; 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. Dovedi SJ, et al. *Cancer Discov*. 2021;11:1100–1117; 6. Voss MH, et al. *Ann Oncol*. 2023;34(Suppl. 2):S1012 (Abstract 1883MO); 7. Janjigian YY, et al. *Ann Oncol*. 2024;35 (Suppl. 2):S878 (Abstract 1401O)

Background

- Approximately 6−28% of gastric cancers (GCs) are human epidermal growth factor receptor 2 (HER2) immunohistochemistry [IHC] 1+, 5−14% are IHC 2+, and 3−14% are IHC 3+[1–5]
- Trastuzumab (a HER2-directed antibody) plus pembrolizumab (an anti-programmed cell death protein 1 [PD-1] antibody) and chemotherapy is a recommended first-line (1L) treatment for HER2-positive (HER2+; IHC 3+ or IHC 2+/in situ hybridization [ISH]–positive [+]) GC or gastroesophageal junction adenocarcinoma (GEJA), with a programmed cell death ligand 1 (PD-L1) combined positive score of ≥1[6–8]
  - There are currently no 1L HER2-directed treatments for advanced or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–negative [−]) GCs; however, given the established benefit in HER2+ GCs,[6–8] HER2-directed combinations could offer promising treatment options for HER2-low disease
- Trastuzumab deruxtecan (T-DXd; 6.4 mg/kg), a HER2-directed antibody-drug conjugate, is approved in several countries for locally advanced or metastatic HER2+ (IHC 3+ or IHC 2+/ISH+) GC or GEJA after a prior trastuzumab-based regimen[9–11]
  - 1L T-DXd with fluoropyrimidine and/or pembrolizumab demonstrated antitumor activity in metastatic HER2+ GC, GEJA, and esophageal adenocarcinoma (EA)[12]
  - T-DXd has also demonstrated clinical benefit in HER2-low metastatic breast cancer[13] and shown preliminary activity in HER2-low GC,[14] suggesting 1L T-DXd-based regimens could be promising treatment options for HER2-low GC, GEJA, and EA
- Volrustomig is a novel, monovalent, PD-1 / cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) bispecific antibody, engineered to fully bind PD-1, while preferentially binding CTLA-4 on PD-1+ activated T cells[15]
  - Volrustomig has shown increased antitumor activity compared with either anti-PD-1 or anti-CTLA-4 antibodies alone in preclinical settings,[15] and is currently being investigated in various solid tumors, either as monotherapy or in combination with chemotherapy or other agents[16]
  - In GCs, the combination of anti-PD-1 and anti-CTLA-4 resulted in higher response rates compared with anti-PD-1 monotherapy[17]

DESTINY-Gastric03 Part 5 will assess 1L T-DXd with volrustomig and fluoropyrimidine in patients with locally advanced, unresectable, or metastatic HER2-low (IHC 1+ or IHC 2+/ISH−) GC, GEJA, or EA

Study design

DESTINY-Gastric03 (NCT04379596) is a Phase 1b/2, open-label, dose-escalation (Part 1) and -expansion (Parts 2–5) study evaluating T-DXd with chemotherapy and/or immunotherapy in HER2+ (IHC 3+ or IHC 2+/ISH+) and HER2-low (IHC 1+ or IHC 2+/ISH−) locally advanced, unresectable, or metastatic GC, GEJA, or EA[18]

DESTINY-Gastric03 Parts 1 and 2: ENROLLMENT COMPLETE
T-DXd monotherapy or in combination with chemotherapy and/or immunotherapy in previously treated (Part 1) or treatment-naïve (Part 2) patients with HER2+ GC, GEJA, or EA

DESTINY-Gastric03 Part 3: ENROLLMENT COMPLETE
T-DXd with volrustomig and chemotherapy in treatment-naïve patients with HER2+ and HER2-low GC, GEJA, or EA

DESTINY-Gastric03 Part 4: ENROLLMENT COMPLETE
T-DXd with rilvegostomig and chemotherapy in treatment-naïve patients with HER2+ and HER2-low GC, GEJA, or EA

DESTINY-Gastric03 Part 5: RECRUITING

N=30

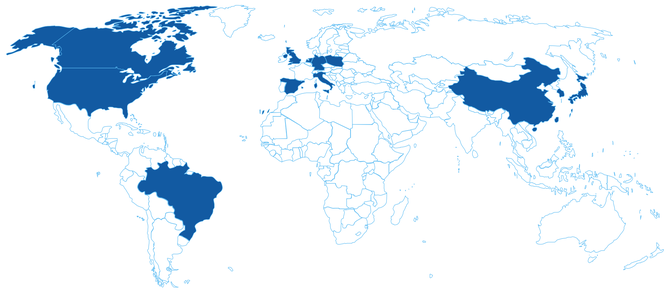
T-DXd IV + **volrustomig** IV + **5-FU*** continuous IV or **capecitabine*** PO in treatment-naïve patients with **HER2-low** GC, GEJA, or EA

The safety profile will be initially assessed in the first six patients who complete ≥3 cycles of treatment

For more information about the DESTINY-Gastric03 study, please visit https://clinicaltrials.gov/study/NCT04379596

*Treatment with 5-FU or capecitabine will be decided by the investigator
5-FU, 5-fluorouracil; EA, esophageal adenocarcinoma; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2(+), human epidermal growth factor receptor 2(−positive); IHC, immunohistochemistry; ISH(+/−), in situ hybridization(−positive/−negative); IV, intravenous; PO, oral; T-DXd, trastuzumab deruxtecan

Enrollment for Part 5: November 4, 2025



Countries with participating study sites

Brazil, Canada, China, Germany, Italy, Japan, Netherlands, Poland, Republic of Korea, Spain, Taiwan, United Kingdom, United States

Key inclusion criteria for Part 5

- Adults aged ≥18 years
- Pathologically documented locally advanced, unresectable, or metastatic GC, GEJA, or EA
- HER2-low status (IHC 1+ or IHC 2+/ISH−) determined by local tissue testing results
- Previously untreated unresectable or metastatic disease; (neo)adjuvant therapies permitted if all systemic therapy was completed and no progression occurred ≥6 months prior to diagnosis of unresectable or metastatic disease
- Local PD-L1 test result before treatment assignment
- Measurable target disease assessed by the investigator based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate organ and bone marrow within 14 days before treatment assignment

Key exclusion criteria for Part 5

- History of another primary malignancy
- Lack of physiological integrity of the upper gastrointestinal tract or malabsorption syndrome
- Uncontrolled intercurrent illness that would limit compliance with study requirements or substantially increase risk of adverse events (AEs)
- Lung-specific intercurrent clinically significant illnesses, including any underlying pulmonary disorders, and prior pneumonectomy
- Any autoimmune, connective tissue, or inflammatory disorders
- History of non-infectious interstitial lung disease (ILD)/pneumonitis, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Spinal cord compression, any leptomeningeal disease, or clinically active central nervous system metastases

Key study endpoints for Part 5

1° Primary endpoint

- Confirmed objective response rate (ORR) determined by investigator assessment per RECIST 1.1

2° Secondary endpoints

- Investigator-assessed per RECIST 1.1
  - Disease control rate (DCR)
  - Duration of response (DOR)
  - Progression-free survival (PFS)
- Overall survival (OS)
- Frequency and severity* of AEs
- Changes in laboratory parameters, vital signs, body weight, and electrocardiogram results
- Serum concentrations of T-DXd, total anti-HER2 antibody, deruxtecan, and volrustomig
- Presence of anti-drug antibodies for T-DXd and volrustomig
- Comparison of ORR, DCR, DOR, PFS, and OS based on local and central HER2 test results†

*Per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; †from tumor samples with evaluable results; central testing will be assessed retrospectively

Poster

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of this poster. Alternatively, please visit: https://bit.ly/44bVwx1.

Copies of this poster obtained through this QR code are for personal use only and may not be reproduced without permission from ASCO GI and the authors of this poster.

This study is sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

Acknowledgments

We thank the patients who are participating in this study, as well as their families and caregivers.

Under the guidance of the authors and in accordance with Good Publication Practice, medical writing and editorial support was provided by Doriana Di Bella, PhD, of Helios Medical Communications, part of the Helios Global Group, and was funded by AstraZeneca.

Disclosures

Dr. Yelena Y Janjigian reports consulting and/or being an invited speaker for Cencora, Arcus Biosciences, Astellas, AstraZeneca, Basilea Pharmaceutica, BeOne Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Clinical Care Options, ED Medresources Inc., 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, Gilead Sciences, GSK, Guardant Health, Imugene, Lynx Healthcare, Merck, Physicians' Education Resource®, LLC, Sanofi, Seagen, and Zymeworks Inc.; 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, and Transcenta Holding Ltd.; stock options or shares in Inspirna and Veeda Life Sciences; and membership on the steering committees of AstraZeneca, Michael J Hennessy Associates, and Transcenta Holding Ltd.

References

1. Uzunparmak B, et al. *Ann Oncol*. 2023;34:1035–1046
2. Van Cutsem E, et al. *Gastric Cancer*. 2015;18:476–484
3. Subasinghe D, et al. *J Int Med Res*. 2023;51:3000605231154403
4. Gao X, et al. *Int J Surg*. 2023;109:1330–1341
5. Yang Y, et al. *Acta Biochim Biophys Sin (Shanghai)*. 2021;53:547–557
6. Shah MA, et al. *J Clin Oncol*. 2023;41:1470–1491
7. ESMO Gastric Cancer Living Guideline, version 1.4, September 2024. Available from: https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-gastric-cancer (Accessed November 24, 2025)
8. Lordick F, et al. *Ann Oncol*. 2022;33:1005–1020
9. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf (Accessed October 16, 2025)
10. 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 October 16, 2025)
11. Enhertu (trastuzumab deruxtecan): summary of product characteristics. 2025. Available from: https://www.medicines.org.uk/emc/product/12135/smpc/print (Accessed October 16, 2025)
12. Janjigian YY, et al. *Ann Oncol*. 2024;35(Suppl. 2):S878 (Abstract 1401O)
13. Curigliano G, et al. *J Clin Oncol*. 2024;42(Suppl. 17):LBA1000 (Abstract)
14. Yamaguchi K, et al. *J Clin Oncol*. 2023;41:816–825
15. Dovedi SJ, et al. *Cancer Discov*. 2021;11:1100–1117
16. NCT06535607. Updated October 29, 2025. Available from: https://www.clinicaltrials.gov/study/NCT06535607 (Accessed November 19, 2025)
17. Janjigian YY, et al. *J Clin Oncol*. 2018;36:2836–2844
18. NCT04379596. Updated December 2, 2025. Available from: https://clinicaltrials.gov/study/NCT04379596?a=12 (Accessed October 20, 2025)

DESTINY Gastric03

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