A Phase 1b/2 open-label study evaluating trastuzumab deruxtecan in combination with rilvegostomig and chemotherapy in patients with HER2-positive and HER2-low gastric or gastroesophageal junction adenocarcinoma: DESTINY-Gastric03 Part 4

Yelena Y Janjigian,[1] Caron Lloyd,[2] Victoria de Giorgio-Miller,[3] Yi-Ting Chang,[4] Jeeyun Lee[5]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, US; [2]Clinical Development Department, Late Development Oncology, Oncology R&D, AstraZeneca, New York, NY, US; [3]Clinical Development Department, Global Medicines Development, Oncology R&D, AstraZeneca, Cambridge, UK; [4]Oncology Biometrics, Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD, US; [5]Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea

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Plain language summary

Why are we performing this research?
Human epidermal growth factor receptor 2 (HER2) is a protein found at higher-than-normal levels 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 (esophageal adenocarcinoma).[1,2] These cancers are referred to as HER2-positive (HER2+) and the elevated levels of HER2 can promote tumor growth.[1] Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan [DXd]) joined to an antibody (trastuzumab [T-]). Trastuzumab binds to HER2, where it releases the chemotherapy to kill tumor cells.[3,4] T-DXd is approved in several countries for patients with previously treated HER2+ GC/GEJA that has spread from its original site (advanced/metastatic cancer).[5–7] Rilvegostomig is a drug that helps the immune system to fight cancer. It works by blocking two proteins found on the surface of cells in the immune system, which results in the immune system being activated and able to find and destroy cancer cells.[8] Combining cancer treatments has been shown to decrease the size or number of tumors.[8–10]

How are we performing this research?
DESTINY-Gastric03 is an ongoing clinical study looking at T-DXd treatment alone and in combination with other treatments in people with GC, GEJA, or esophageal adenocarcinoma. Part 4 of the DESTINY-Gastric03 study will evaluate the benefit and safety of combining T-DXd with rilvegostomig and chemotherapy for people with HER2+ GC, GEJA, or esophageal adenocarcinoma. The treatment will also be evaluated for people who have low levels of HER2 (HER2-low cancer). Initially, at least six participants will be enrolled to evaluate the safety of the combination treatment. Following this initial assessment of the safety profile, additional participants will then be enrolled to assess how well the cancers being investigated respond to treatment, the side effects, and the overall health of participants.

Who will participate in this study?
Part 4 of the study will include people with HER2+ or HER2-low GC, GEJA, or esophageal adenocarcinoma. Their cancer must be either advanced/metastatic or unable to be removed completely by surgery (unresectable), and they must not have 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.

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Background

- Approximately 15–18% of gastric cancers (GC), gastroesophageal junction adenocarcinomas (GEJA), and esophageal adenocarcinomas are human epidermal growth factor receptor 2–positive (HER2+), as determined by immunohistochemistry (IHC; IHC 3+ or IHC 2+ with positive in situ hybridization [ISH+]).[1,2] Furthermore, it is estimated that the incidence of patients with HER2-low (IHC 1+ or IHC 2+ with negative in situ hybridization [ISH−]) GC/GEJA is ~21%[3]
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-HER2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload[4]
- T-DXd 6.4 mg/kg is approved for adult patients with locally advanced or metastatic HER2+ (IHC 3+ or IHC 2+ with ISH+) GC/GEJA who have received a prior trastuzumab-based regimen[5]
- In DESTINY-Gastric01, T-DXd demonstrated an objective response rate (ORR) of 51% in pretreated patients with HER2+ GC,[6] and ORRs of 26% and 10% in patients with IHC 2+/ISH− and IHC 1+ tumors (HER2-low), respectively[7]
- Furthermore, recent data from Part 2 of the DESTINY-Gastric03 study showed that first-line (1L) T-DXd combinations with fluoropyrimidine and/or pembrolizumab demonstrated promising antitumor activity in metastatic HER2+ GC/GEJA[8]
- The combination of trastuzumab with pembrolizumab, fluoropyrimidine, and platinum-based chemotherapy is indicated as a 1L treatment for patients with HER2+ GC/GEJA whose tumors express programmed cell death ligand 1 (PD-L1)[9,10]
- Programmed cell death protein 1 (PD-1) inhibition is a well-established treatment approach for advanced gastric cancer,[9–12] and dual blockade of PD-1 and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) has inhibited tumor progression in preclinical models[13]
- Rilvegostomig is a bispecific antibody that targets both PD-1 and TIGIT[14,15]
  - In a recent study, rilvegostomig in combination with platinum-based chemotherapy demonstrated promising antitumor activity and a manageable safety profile in patients with HER2-negative (IHC 0, IHC 1+, IHC 2+ with ISH−) unresectable, locally advanced, or metastatic GC/GEJA[15,16]
  - Moreover, in a preclinical study, T-DXd with a bispecific PD-1/TIGIT antibody (a murine surrogate of rilvegostomig) enhanced tumor growth inhibition compared with T-DXd monotherapy[17]

Part 4 of the open-label Phase 1b/2 DESTINY-Gastric03 study (NCT04379596) will evaluate the efficacy and safety of T-DXd in combination with rilvegostomig and chemotherapy as 1L therapy for patients with HER2+ and HER2-low GC / GEJA / esophageal adenocarcinoma[18]

Study design and population

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 esophageal adenocarcinoma (parts 2D–2F only)

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

DESTINY-Gastric03 Part 4: RECRUITING

Rilvegostomig safety cohort
N≈6

T-DXd IV Q3W + **rilvegostomig** IV Q3W + **5-FU** continuous IV infusion Q3W on Days 1–5* or **capecitabine** orally BID Q3W on Days 1–14*

The combination regimen will be tested in an initial treatment-naïve safety cohort comprising patients with **HER2+** (IHC 3+ or IHC 2+/ISH+) and **HER2-low** (IHC 2+/ISH− or IHC 1+) GC, GEJA, or esophageal adenocarcinoma

Rilvegostomig main cohort: parts 4A and 4B
N≈24–30 per arm (target)

Arms 4A and **4B** will comprise patients with **HER2+** and **HER2-low** disease, respectively

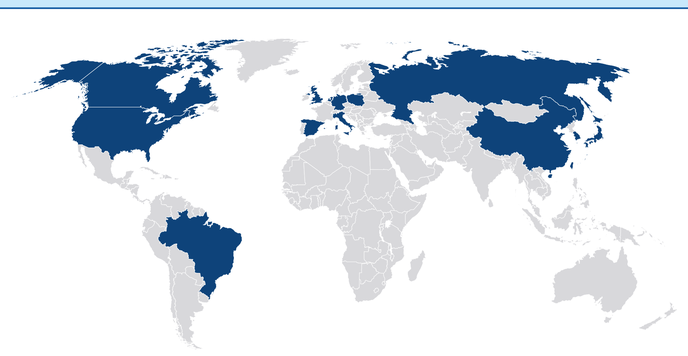
Recommendations on dose expansion will be made following review of the safety cohort

Safety and efficacy will be assessed

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; BID, twice daily; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; Q3W, once every 3 weeks; T-DXd, trastuzumab deruxtecan

Enrollment for Part 4 began May 20, 2024



Countries with participating study sites

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

Key inclusion criteria

- Aged ≥18 years
- Unresectable, locally advanced, or metastatic disease based on most recent imaging
- Pathologically documented locally advanced HER2+ (IHC 3+ or IHC 2+/ISH+) or HER2-low (IHC 2+/ISH− or IHC 1+) GC, GEJA, or esophageal adenocarcinoma determined by local tissue testing results
- Treatment-naïve disease for 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
- Eastern Cooperative Oncology Group performance status of 0 or 1

Key exclusion criteria

- Multiple primary malignancies within the previous 3 years
- 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)
- Active or prior documented autoimmune or inflammatory disorders
- History of non-infectious interstitial lung disease (ILD) / pneumonitis or current/suspected ILD/pneumonitis that cannot be ruled out by imaging at screening

Key study endpoints

1° Primary endpoint

- Confirmed ORR determined by investigator per Response Evaluation Criteria in Solid Tumors (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 of AEs and serious AEs; dose-limiting toxicities; and changes in laboratory parameters, vital signs, body weight, and electrocardiogram results
- Serum concentration of T-DXd, total anti-HER2 antibody, MAAA-1181, and rilvegostomig
- Presence of anti-drug antibodies for T-DXd and rilvegostomig
- Comparison of ORR, DCR, DOR, PFS, and OS between patients based on local and central HER2 test results

E Exploratory endpoints

- Candidate biomarker identification by mutation, protein expression analysis, and morphological assessment of tissue and blood

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Poster

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DESTINY Gastric03

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