An open-label, randomized, multicenter, phase 3 study of trastuzumab deruxtecan (T-DXd) + chemotherapy ± pembrolizumab versus chemotherapy + trastuzumab ± pembrolizumab in first-line metastatic HER2+ gastric or gastroesophageal junction cancer: DESTINY-Gastric05

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Plain Language Summary

Why are we performing this research?

- Up to 17% of patients with gastric or gastroesophageal junction (GEJ) cancer have tumors that express the human epidermal growth factor receptor 2 (HER2) protein.[1-4] HER2-directed therapy is the standard of care for these patients
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody bound to a cytotoxic chemotherapy agent (called an antibody-drug conjugate) that is designed to target and kill tumor cells expressing HER2[5-7] and is approved as monotherapy in the second-line or later setting (following a prior trastuzumab-based regimen) in more than 65 countries[8,9]
- The aim of the DESTINY-Gastric05 study is to provide a potentially improved, platinum-free first-line treatment approach for all patients with HER2+ gastric or GEJ cancer, regardless of programmed death ligand 1 (PD-L1) expression level (measured by combined positive score [CPS] on a diagnostic laboratory test)
- DESTINY-Gastric05 is being conducted to assess T-DXd in combination with chemotherapy ± pembrolizumab (a programmed death 1 inhibitor) versus chemotherapy and trastuzumab ± pembrolizumab (approved standard of care for first-line therapy) in previously untreated patients with unresectable or metastatic HER2+ gastric or GEJ cancer

How are we performing this research?

- DESTINY-Gastric05 includes 2 cohorts:
  - In the main cohort, patients with a tumor PD-L1 CPS ≥1 will be randomly assigned to receive (1) T-DXd + 5-fluorouracil (5-FU) or capecitabine + pembrolizumab or (2) trastuzumab + platinum-based chemotherapy (cisplatin + 5-FU or oxaliplatin + capecitabine) + pembrolizumab
  - In the exploratory cohort, patients with a tumor PD-L1 CPS <1 will be randomly assigned to receive (1) T-DXd in combination with 5-FU or capecitabine or (2) trastuzumab + platinum-based chemotherapy (cisplatin + 5-FU or oxaliplatin + capecitabine)
- The primary endpoint is progression-free survival by blinded independent central review, a measure of the time interval from the date of randomization to the date of radiographic disease progression or death due to any cause

Who will participate in this study?

- Adult patients with pathologically documented (confirmed by pathology report), previously untreated, unresectable, locally advanced or metastatic HER2+ (centrally determined and defined as immunohistochemistry [IHC] score of 3+ or IHC 2+/in situ hybridization–positive) gastric or GEJ adenocarcinoma are eligible for enrollment in DESTINY-Gastric05
- Prior treatment in the perioperative and/or adjuvant setting and prior use of immuno-oncology treatment is allowed provided there is >6 months between the end of treatment and diagnosis of recurrent disease
- Patients must have centrally determined PD-L1 CPS ≥1 (main cohort) or <1 (exploratory cohort)

Where can I access more information?

- This study is expected to end in June 2028
- For more information about DESTINY-Gastric05, please visit https://clinicaltrials.gov/study/NCT06731478
- You may also speak to your doctor about clinical studies

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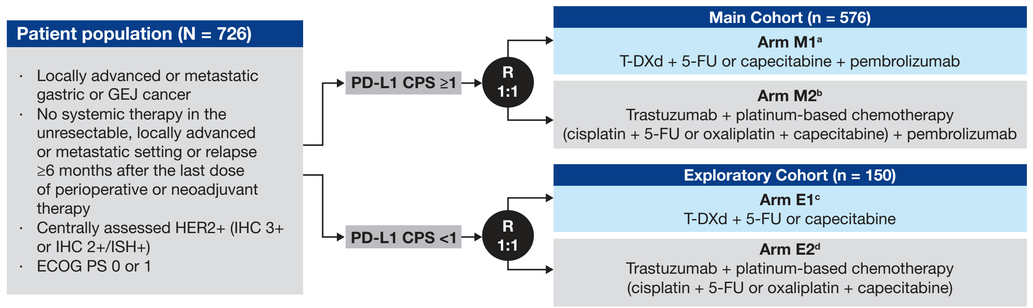
This study is sponsored by Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201). Pembrolizumab is provided under agreement by Merck & Co., Inc., Rahway, NJ, USA.

Study Design

- DESTINY-Gastric05 (NCT06731478) is an open-label, randomized, multicenter, phase 3 trial of T-DXd + chemotherapy ± pembrolizumab versus trastuzumab + chemotherapy ± pembrolizumab in first-line treatment of patients with metastatic HER2+ gastric or GEJ cancer
  - The study aims to bring a potentially improved platinum-free treatment approach for all patients with HER2+ gastric or GEJ cancer, regardless of PD-L1 CPS
- In the main cohort, approximately 576 patients with PD-L1 CPS ≥1 will be randomly assigned in a 1:1 ratio to receive:
  - Arm M1: T-DXd 5.4 mg/kg + either 5-FU or capecitabine 750 mg/m^2/day + pembrolizumab
  - Arm M2: Trastuzumab + platinum-based chemotherapy (either cisplatin + 5-FU or oxaliplatin + capecitabine) + pembrolizumab
- An exploratory cohort of approximately 150 patients will evaluate the efficacy and safety of T-DXd in combination with 5-FU or capecitabine versus trastuzumab + standard-of-care chemotherapy in patients with PD-L1 CPS <1



[a]T-DXd 5.4 mg/kg IV Q3W on day 1 plus 5-FU 600 mg/m^2/day IV on days 1 to 5 or capecitabine 750 mg/m^2 PO BID on days 1 to 14 plus pembrolizumab 200 mg IV Q3W on day 1.

[b]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m^2/day IV on day 1 plus 5-FU 800 mg/m^2/day IV on days 1 to 5 or oxaliplatin 130 mg/m^2/day IV on day 1 plus capecitabine 1000 mg/m^2 PO BID on days 1 to 14) plus pembrolizumab 200 mg IV Q3W on day 1.

[c]T-DXd 5.4 mg/kg IV Q3W on day 1 plus 5-FU 600 mg/m^2/day IV on days 1 to 5 or capecitabine 750 mg/m^2 PO BID on days 1 to 14.

[d]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m^2/day IV on day 1 plus 5-FU 800 mg/m^2/day IV on days 1 to 5 or oxaliplatin 130 mg/m^2/day IV on day 1 plus capecitabine 1000 mg/m^2 PO BID on days 1 to 14).

Countries with participating study sites

Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Portugal, Romania, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, United States, Vietnam

Study start: February 27, 2025 | Recruiting patients

The study is being conducted at 246 study sites in 26 countries across 4 regions (North America, South America, Europe, Asia/Pacific).

Japan and South Korea are separate from the rest of Asia/China as a stratification factor due to the specific screening programs in these countries, which lead to different prognoses.

Background

- Human epidermal growth factor receptor 2 (HER2) is a validated target in up to 17% of patients with gastric or gastroesophageal junction (GEJ) cancer, and few treatment options are available for this patient population[1-4]
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate (ADC) approved as monotherapy in the second-line or later setting in more than 65 countries for the treatment of adult patients with locally advanced or metastatic HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]+) gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen[5,6]
- In DESTINY-Gastric01 (NCT03329690) and DESTINY-Gastric02 (NCT04014075), treatment with T-DXd exhibited clinically meaningful activity, durable responses, and acceptable safety in patients with HER2+ gastric or GEJ cancer whose disease progressed after ≥2 previous regimens (including fluoropyrimidine, a platinum agent, and trastuzumab) and in patients whose disease progressed on a trastuzumab-containing regimen, respectively.[1,7,8] In DESTINY-Gastric06 (NCT04989816), T-DXd demonstrated clinically meaningful and durable responses and no new safety signals in patients from China with HER2+ gastric or GEJ cancer who had received ≥2 prior regimens (including fluoropyrimidine and a platinum agent) for advanced or metastatic disease.[9,10] In DESTINY-Gastric04 (NCT04704934), T-DXd showed statistically significant and clinically meaningful improvement in overall survival versus ramucirumab plus paclitaxel in second-line treatment of patients with HER2+ gastric or GEJ cancer (Shitara K et al. ASCO 2025 abstract LBA4002)[11]
- In KEYNOTE-811, adding pembrolizumab to trastuzumab and chemotherapy improved progression-free survival (PFS) and OS versus placebo and versus trastuzumab + chemotherapy for first-line treatment of patients with HER2+ gastric or GEJ cancer with a programmed death ligand 1 combined positive score (PD-L1 CPS) ≥1[12]
- In DESTINY-Gastric03 (NCT04379596), first-line combinations of T-DXd and fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) ± pembrolizumab showed encouraging efficacy in patients with HER2+ gastric or GEJ cancer, irrespective of PD-L1 CPS[13]

Key inclusion criteria

- Adults aged ≥18 years
- Pathologically documented, previously untreated, unresectable, locally advanced or metastatic gastric or GEJ adenocarcinoma
- Prior treatment in the perioperative and/or adjuvant setting is allowed[a]
- Prior use of immuno-oncology (IO; ie, anti–programmed death 1/PD-L1) therapy in the (neo)adjuvant setting is allowed[a]
- Centrally determined HER2+ (IHC 3+ or IHC 2+/ISH+) gastric or GEJ cancer as classified by the American Society of Clinical Oncology–College of American Pathologists guidelines[14]
- Centrally determined tumor PD-L1 CPS using the PD-L1 22C3 PharmDx assay:
  - For the main cohort: PD-L1 CPS ≥1
  - For the exploratory cohort: PD-L1 CPS <1
- Presence of at least 1 measurable lesion on computed tomography or magnetic resonance imaging, assessed by the investigator based on Reponse Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1)
- Left ventricular ejection fraction ≥50% within 28 days before randomization
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Protocol-defined adequate organ and bone marrow function within 14 days before randomization

[a]Provided there is >6 months between the end of perioperative or neoadjuvant treatment and the diagnosis of recurrent disease.

Key exclusion criteria

- Prior exposure to other HER2-targeting therapies (including ADCs)
- Known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency
- Cardiovascular disease including myocardial infarction within 6 months before randomization or symptomatic congestive heart failure
- Corrected QT interval prolongation to >470 ms for female patients or >450 ms for male patients
- History of noninfectious ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Spinal cord compression, clinically active central nervous system metastases (defined as untreated and symptomatic), and/or carcinomatous meningitis
- Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder
- Active primary immunodeficiency, history of receiving a live, attenuated vaccine within 30 days before exposure to study drug, or uncontrolled infection
- Active autoimmune disease that has required systemic treatment in the past 2 years[a]
- Diagnosis of immunodeficiency or is receiving chronic systemic therapy or immunosuppressive therapy[a]
- History of active tuberculosis or allogenic tissue/organ transplant[a]

[a]Main cohort only.

Key study endpoints

1° Primary Endpoint

- PFS by blinded independent central review (BICR), defined as the time interval from the date of randomization to the date of radiographic disease progression or death due to any cause

2° Secondary Endpoints

- OS (key secondary endpoint)
- Objective response rate
- PFS by investigator assessment (per RECIST v1.1)
- Duration of response
- Time to response by BICR (per RECIST v1.1)
- Time to second progression-free survival
- Treatment-emergent adverse events and other safety parameters
- Patient-reported outcomes (PROs)

Exploratory Endpoints

- Health economics and outcomes research, hospital admissions
- Other PROs
- Correlation of PD-L1 expression levels and other biomarkers with efficacy and safety

Poster

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Abbreviations

5-FU, 5-fluorouracil; ADC, antibody-drug conjugate; AE, adverse event; BICR, blinded independent central review; BID, twice daily; CPS, combined positive score; DPD, dihydropyrimidine dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; IO, immuno-oncology; ISH, in situ hybridization; IV, intravenous; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T-DXd, trastuzumab deruxtecan.

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Disclosures

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DESTINY Gastric05

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