An open-label, multicenter, Phase 2 study of trastuzumab deruxtecan (T-DXd) in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) Part 2

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Plain language summary

Why are we performing this research?
Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab). Trastuzumab binds to a protein called human epidermal growth factor receptor 2 (HER2) on the surface of cancer cells, where it releases the chemotherapy to kill these cells.[1,2] In Part 1 of the DESTINY-PanTumor02 clinical study, T-DXd was shown to have beneficial antitumor activity; the greatest effects were seen in participants with the highest tumor level of HER2 (known as immunohistochemistry [IHC] 3+).[3] Based partly on these results, T-DXd is a recommended treatment in the US for people with IHC 3+ solid tumors that have spread to other locations or cannot be completely removed with surgery (known as advanced cancer), and who have received prior systemic treatment and have no other treatment options.[4,5] Part 2 of the study will investigate the benefit and safety of T-DXd treatment in an expanded group of people with HER2-expressing cancers.

How are we performing this research?
DESTINY-PanTumor02 Part 2 is an ongoing clinical study that is taking place at multiple locations worldwide to assess how well T-DXd works as a treatment for HER2 IHC 3+/2+ solid tumors (including non-small cell lung cancer) and in HER2 IHC 2+/1+ endometrial, cervical, and ovarian cancers. The primary outcome of interest is the percentage of people who have a decrease in the size or number of tumors after T-DXd treatment, according to established criteria.

Who will participate in this study?
To participate, people must be aged 18 years or above and have HER2-expressing solid tumors that have advanced, spread, or cannot be completely removed by surgery. People cannot participate if they have been diagnosed with cancer starting in the mucus-producing cells (adenocarcinoma) of the breast, colon, rectum, gastric body, or where the stomach and food pipe meet (gastroesophageal junction), have a history of myocardial infarction (heart attack) within 6 months of taking part, or have a history of non-infectious interstitial lung disease (scarring of the lungs) / pneumonitis (inflammation of lung tissue without infection) that required steroid treatment.

Where can I access more information?
For more information about DESTINY-PanTumor02 Part 2, please visit https://clinicaltrials.gov/study/NCT04482309. You can also speak to your doctor about this and other clinical studies.

1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185; 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108; 3. Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47–58; 4. US FDA. Resources for information. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2 (Accessed October 6, 2024); 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 February 27, 2025)

Background

- Human epidermal growth factor receptor 2 (HER2) expression is seen in a wide range of solid tumors and is associated with biologically aggressive tumor phenotypes, poor prognosis, increased risk of disease recurrence, and limited benefit from chemotherapy[1–3]
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate that is composed of an anti-HER2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload[4,5]
- T-DXd is approved in multiple countries worldwide for the treatment of HER2-positive and HER2-low breast cancer, HER2-positive gastric or gastroesophageal junction carcinoma, and HER2-mutant non-small cell lung cancer[6,7]
- In April 2024, T-DXd received accelerated approval in the US for adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC 3+]) solid tumors that have progressed after prior systemic treatment and have no satisfactory alternative therapies[6,8]
- The approval of T-DXd in this setting was based, in part, on results from Part 1 of the DESTINY-PanTumor02 study, in which T-DXd (5.4 mg/kg once every 3 weeks) demonstrated clinically meaningful benefit and a generally manageable safety profile in pretreated patients with HER2-expressing solid tumors (N=267)[9]
  - In all patients, the investigator-assessed (INV) objective response rate (ORR) was 37.1% (95% confidence interval [CI] 31.3, 43.2), INV median progression-free survival (PFS) was 6.9 months (95% CI 5.6, 8.0), and median overall survival (OS) was 13.4 months (95% CI 11.9, 15.5)[9]
  - The greatest benefit was observed in patients with centrally confirmed HER2 IHC 3+ tumors (n=75): ORR 61.3% (95% CI 49.4, 72.4); median PFS 11.9 months (95% CI 8.2, 13.0); median OS 21.1 months (95% CI 15.3, 29.6)[9]

Here, we describe Part 2 of the DESTINY-PanTumor02 study (NCT04482309; recruitment ongoing), evaluating the efficacy and safety of T-DXd in patients with HER2-expressing unresectable, locally advanced, or metastatic solid tumors

Study design

DESTINY-PanTumor02 Part 1: COMPLETE
T-DXd in HER2-expressing (IHC 3+/2+) solid tumors*

DESTINY-PanTumor02 Part 2: RECRUITING
T-DXd in any HER2 IHC 3+ and IHC 2+/ISH+ solid tumors,† and HER2 IHC 2+/1+ gynecological solid tumors

Patient population for Part 2
- Unresectable, locally advanced, or metastatic solid tumors (excluding breast, colorectal, and gastric cancers). Unlike in Part 1, patients with NSCLC will be eligible
- HER2 status and amplification by central testing
- ≥1 prior lines of therapy in the advanced or metastatic setting
- Prior HER2-directed therapy permitted
- Measurable disease per RECIST 1.1
- WHO/ECOG performance status of 0 or 1

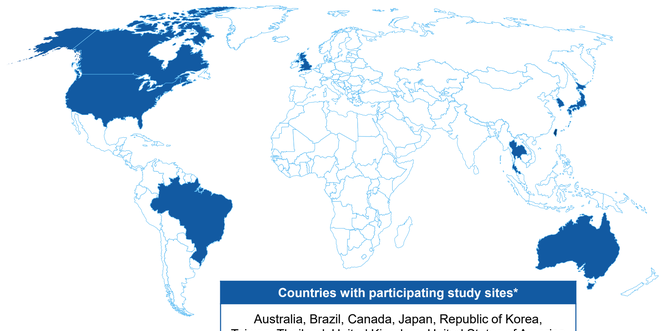
T-DXd 5.4 mg/kg IV Q3W

- **Cohort 2A (n≈40)** Any HER2 IHC 3+ tumors†
- **Cohort 2B (n≈40)** Any HER2 IHC 2+/ISH+ tumors†
- **Cohort 2C (n≈40)** HER2 IHC 2+/1+ endometrial cancer‡
- **Cohort 2D (n≈40)** HER2 IHC 2+/1+ ovarian cancer‡
- **Cohort 2E (n≈40)** HER2 IHC 2+/1+ cervical cancer‡

For more information about Part 2 of the DESTINY-PanTumor-02 study, please visit https://clinicaltrials.gov/study/NCT04482309

*Across seven tumor cohorts: biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, and other tumors (excluding breast, colorectal, gastric, and NSCLC); †patients with breast, gastric, gastroesophageal junction, or colorectal cancer will not be enrolled. Recruitment of patients with endometrial, ovarian, and cervical cancer will be limited to n=20 in Cohort 2A; ‡if no objective responses are observed in the first 15 patients with IHC 1+ tumors, the cohort will be closed to further IHC 1+ recruitment, and will continue to recruit only patients with IHC 2+ tumors
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; IV, intravenous; NSCLC, non-small cell lung cancer; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

Part 2 start date: May 2024 | Currently recruiting patients



Countries with participating study sites*
Australia, Brazil, Canada, Japan, Republic of Korea, Taiwan, Thailand, United Kingdom, United States of America

*Additional countries to be considered for participation

Key inclusion criteria

- Age ≥18 years
- Locally advanced, unresectable, or metastatic solid tumors
- HER2 expression (IHC 3+/2+/1+) and amplification (in situ hybridization–positive [ISH+]) determined by central testing. HER2 IHC scoring will be based on current American Society of Clinical Oncology / College of American Pathologists guidelines for scoring HER2 for gastric cancer[10]
- Measurable target disease as assessed by the investigator based on Response Evaluation Criteria in Solid Tumours 1.1
- World Health Organization / Eastern Cooperative Oncology Group performance status of 0 or 1
- Protocol-defined adequate organ and bone marrow function within 14 days of receiving study treatment
- Left ventricular ejection fraction ≥50% within 28 days of randomization

Key exclusion criteria

- Primary diagnosis of adenocarcinoma of the breast, colon, rectum, gastric body, or gastroesophageal junction
- Known somatic DNA mutation of *HER2* without tumoral HER2 expression
- History of myocardial infarction (<6 months prior to randomization) or symptomatic congestive heart failure
- Pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy
- Uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals
- History of non-infectious interstitial lung disease (ILD) / pneumonitis requiring steroids, or current/suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- History of another primary malignancy within 3 years prior to first dose, except for adequately resected non-melanoma skin cancer and malignancy treated with curative intent
- Lung-specific intercurrent, clinically significant illnesses
- Autoimmune, connective tissue, or inflammatory disorders with documented or suspected pulmonary involvement at screening
- Spinal cord compression or clinically active central nervous system metastases
- Unresolved toxicities (other than alopecia) from previous anticancer therapies that have not been resolved to Grade ≤1 or baseline

Key study endpoints

1° Primary endpoint
- Confirmed ORR*

2° Secondary endpoints
- Duration of response*
- Disease control rate*
- PFS*
- OS
- Presence of anti-drug antibodies for T-DXd
- Frequency of adverse events (AEs) and serious AEs,† and changes from baseline in laboratory parameters and vital signs‡
- Serum concentration of T-DXd, total anti-HER2 antibody, and MAAA-1181 (deruxtecan)

*Investigator assessed per Response Evaluation Criteria in Solid Tumours 1.1; †AEs and serious AEs graded according to the Medical Dictionary for Regulatory Activities and National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; ‡plus electrocardiogram, echocardiogram / multiple gated acquisition results

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Alternatively, please visit: https://bit.ly/3FFonk2

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