

**Category**

Best Biotechnology Product

**Drug / Device Name**

ENHERTU

**Compound/ Tech Name**

Trastuzumab deruxtecan (fam-trastuzumab deruxtecan-nxki in the United States only; trastuzumab deruxtecan in rest of world; T-DXd, formerly DS-8201)

**Trade Name**

ENHERTU

**Date of Approval**

2019-12-20

**Indications**

ENHERTU® is currently approved globally for certain patients with breast cancer (BC), gastric or gastroesophageal junction (GEJ) adenocarcinoma, and non-small cell lung cancer (NSCLC; accelerated approval); further details follow.

ENHERTU® is approved in more than 40 countries for the treatment of adult patients with unresectable or metastatic HER2-positive BC who have received 1 or more prior anti-HER2-based regimen(s), either in the metastatic setting or in the neoadjuvant or adjuvant setting, and who have developed disease recurrence during or within 6 months of completing therapy, based on the results from the DESTINY-Breast03 trial. ENHERTU® is also approved in approximately 40 countries for the treatment of adult patients with unresectable or metastatic HER2-positive BC who have received 2 or more prior anti-HER2-based regimens, based on results from the DESTINY-Breast01 trial.

ENHERTU® is approved in more than 30 countries for the treatment of adult patients with unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization [ISH]-) BC who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy, based on the results of the DESTINY-Breast04 trial.

ENHERTU® is approved in more than 30 countries for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 and/or DESTINY-Gastric02 trials.

ENHERTU® is approved under accelerated approval in the United States for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy, based on the results from the DESTINY-Lung02 trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

## Therapeutic Categories

HER2-expressing or HER2-mutant solid tumors

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## Background information and need for drug/device

ENHERTU® is an antibody-drug conjugate (ADC) composed of a humanized monoclonal antibody specifically targeting HER2, a cleavable linker, and a potent topoisomerase I inhibitor as the cytotoxic payload. HER2, a key oncologic therapeutic target, is aberrant (amplified, overexpressed, mutated) in multiple cancer types and its expression is associated with poorer prognosis, aggressive disease course, and increased risk of recurrence.

Approximately 15%-20% of BCs are associated with HER2 overexpression or amplification (traditionally defined as “HER2-positive”), which is associated with more aggressive disease. Although existing treatments are effective for HER2-positive BC, most cancers develop resistance to currently available therapies and metastatic BC (mBC) remains incurable; therefore, a need for new therapies remains. In addition, approximately 60% of traditionally HER2-negative mBCs express low levels of HER2 (IHC1+ or IHC2+/ISH-), a BC patient group newly defined as “HER2-low” (following development of ENHERTU®). HER2-directed therapies have previously not improved clinical outcomes for patients with low HER2 expression (historically treated as HER2-negative disease), with limited targeted treatment options available after progressing on primary therapy.

Approximately 15%-20% of advanced gastric or GEJ tumors show HER2 overexpression or amplification. Prior to ENHERTU® approval, trastuzumab was the only approved anti-HER2 therapy for HER2+ gastric cancer. Other HER2-targeted therapies have not significantly improved overall survival (OS) vs standard chemotherapy in second-line or later treatment of HER2+ advanced gastric or GEJ cancer.

In other malignancies, such as metastatic colorectal cancer, for which 3% of cancers show HER2 overexpression, and NSCLC, wherein 2%-4% of lung adenocarcinomas exhibit a HER2 alteration (mutation or amplification), and many others, there are limited or no other HER2-targeted therapies approved in any line of therapy.

Based on proportions of tumors with HER2 aberrations, a huge population of patients with cancer may potentially benefit now or in the future from ENHERTU® therapy.

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## History of the development of the drug/device

Based on promising preclinical and phase 1 data, multiple phase 2-3 studies have demonstrated ENHERTU®’s potential across a variety of HER2-expressing or -mutated cancer types. Major results from registrational clinical studies are summarized below; most disclosures to date have been published in the highest tier of scientific journals, including NEJM (5), Lancet (2), and Lancet Oncology (3), reinforcing the practice-changing nature of the data.

Most recently, ENHERTU® was approved for HER2-low mBC, an innovative new classification of

patients, based on the phase 3 DESTINY-Breast04 study. ENHERTU® demonstrated statistically significant and clinically meaningful improvement versus physician's choice of chemotherapy in progression-free survival (PFS; HR: 0.51) and OS (HR: 0.64), prompting an exceptionally rare standing ovation upon disclosure of this seminal data during the Plenary Session at ASCO 2022. ENHERTU® is the first HER2-directed therapy with survival benefit in these patients, representing ground-breaking progress for more than half of the mBC patient population.

DESTINY-Breast03, a randomized phase 3 study, demonstrated superiority of ENHERTU® over the HER2-targeted ADC ado-trastuzumab emtansine (T-DM1; KADCYLA®) in patients with HER2+ mBC previously treated with trastuzumab and taxane. ENHERTU® demonstrated a highly statistically significant improvement in PFS versus T-DM1 (HR: 0.33); 79% of patients demonstrated a response vs 35% for T-DM1. These results supported ENHERTU® becoming the standard of care in second-line or later HER2+ mBC and approved in numerous countries.

In DESTINY-Lung01 and DESTINY-Lung02, pivotal phase 2 studies of ENHERTU® in previously treated patients with HER2-mutant NSCLC, 55% and 54% of patients treated with ENHERTU® demonstrated a response, with disease control in 92.3% and 90.4%. Based on these results, ENHERTU® received accelerated approval for the treatment of patients with HER2-mutant NSCLC (USA).

The development program, a global collaboration between Daiichi Sankyo and AstraZeneca, continues across many other HER2-targetable cancers (see next section for additional details).

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**Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition**

ENHERTU® was designed and engineered with 7 key attributes using a novel payload-linker technology to address limitations of previous compounds. The innovative payload-linker of ENHERTU® allows for a high drug-to-antibody ratio while retaining a favorable pharmacokinetic profile. The payload-linker is stable in plasma and is cleaved by lysosomal enzymes upregulated in tumors, preferentially releasing the payload in cancer cells. The released payload has a short half-life, minimizing systemic exposure, and easily crosses the cell membrane, potentially allowing for potent cytotoxic effects on neighboring tumor cells regardless of HER2 expression.

Aside from the established efficacy across HER2+ cancers in the approved indications, ENHERTU® is the first HER2-targeted agent to demonstrate efficacy in BC patients with low HER2 expression, and thus has redefined BC classification and treatment for these patients with limited targeted therapy options. The safety profile of ENHERTU® is consistent across tumor types, with the most common treatment-related grade 3+ adverse events including nausea, fatigue, and blood disorders (eg, platelet or white-cell count decreased, anemia, neutropenia). Interstitial lung disease is an important identified risk that requires careful management.

In BC, ENHERTU® is currently under investigation in patients with even lower HER2 tumor expression (>IHC 0 and

The novel payload-linker technology used for ENHERTU® was also used to create additional ADC candidates, which are currently under investigation in multiple clinical trials across several solid tumor

indications and include TROP2-directed and HER3-directed ADCs.

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**Please provide appropriate references (ie Pubmed links)**

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