

Medical Drug Clinical Criteria

Subject:	Enhertu (fam-trastuzumab deruxtecan-nxki)		
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Overview

This document addresses the use of Enhertu (fam-trastuzumab deruxtecan-nxki). Enhertu is HER2-directed antibody and topoisomerase inhibitor conjugate that selectively delivers chemotherapy to HER2-overexpressing tumor cells. Internalization and intracellular linker cleavage of the drug by lysosomal enzymes within the tumor cell leads to DNA damage and apoptotic cell death.

Breast cancer is a type of tumor comprised of malignant (cancerous) cells that start to grow in the breast and may spread (metastasize) to surrounding tissues and other areas of the body (American Cancer Society, 2016). Breast cancer is commonly treated by various modalities which include combinations of surgery, radiation therapy, chemotherapy and hormone therapy (National Cancer Institute, 2019). The prognosis and selection of therapies can be affected by clinical and pathologic features of the tumor. One of these includes the human epidermal growth factor receptor 2 gene ERBB2 which is commonly referred to as HER2. Other names for this gene include NEU, Her-2, HER-2/neu and c-erb B2. Initially the HER2 gene was detected in frozen breast tumor samples. Amplification of the HER2 gene was later correlated to overexpression of protein levels in samples of breast cancer.

Approximately 255,000 patients are diagnosed with invasive breast cancer each year, with approximately one in five cases being classified as HER-2 positive. Antibody-drug conjugates containing trastuzumab and a second non-specific cytotoxic drug have the ability to more specifically target HER-2 cancer cells and exert their anti-tumor effects. Kadcyla and Enhertu are currently the only two HER2-directed antibody-drug conjugates on the market. Kadcyla is linked to emtansine, a tubulin inhibitor, whereas Enhertu is linked to DXd, a topoisomerase inhibitor.

The FDA approved indications for Enhertu include:

- HER2-positive metastatic breast cancer
- HER2-low metastatic breast cancer
- HER2-mutant unresectable or metastatic non-small cell lung cancer
- HER2-positive locally advanced or metastatic gastric cancer
- HER2-positive (IHC-3+) unresectable or metastatic solid tumors

Enhertu has a black box warning for interstitial lung disease and embryo-fetal toxicity. Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with Enhertu. Patients should be monitored for signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Enhertu should be discontinued in all patients with Grade 2 or higher ILD/pneumonitis.

The National Comprehensive Cancer Network® (NCCN) clinical practice guideline for central nervous system cancers, provides a 2A recommendation is provided for use as a single agent treatment for asymptomatic brain metastases in those with HER 2+ breast cancer. Subgroup analysis from the ongoing open-label phase II DESTINY-Breast01 trial showed that the antibody-drug conjugate fam-trastuzumab deruxtecan-nxki (deruxtecan being a DNA topoisomerase 1 inhibitor) was associated with a 58% ORR in 24 patients with asymptomatic brain metastases from HER2-positive breast cancer who were previously treated with ado-trastuzumab emtansine. 568 Partial intracranial responses were observed in 41%. In the multicenter open label randomized phase III DESTINY-Breast03 trial, in which fam trastuzumab deruxtecan-nxki is being compared to ado-trastuzumab emtansine in patients with metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane, results presented at an annual meeting showed that median PFS was significantly greater in the fam-trastuzumab deruxtecan-nxki arm, compared to the ado-trastuzumab emtansine arm (15.0 months vs. 5.7 months, respectively; HR, 0.38; 95% CI, 0.23–0.64) (Cortes J et.al. 2021).

In the NCCN clinical practice guideline for colon cancer and rectal cancer the NCCN Panel now recommends use of Enhertu (category level 2A) in the treatment of individuals with HER2 mutations in these cancers based on recent published abstracts from small phase 2 trials (Siena S 2020, Smit EF 2020). The data demonstrating safety and efficacy from these trials have not been published. At this time, there is no evidence to support the safety and efficacy of Enhertu in these solid tumors cancers.

NCCN also provides a category 2A recommendation in cervical cancer and endometrial cancer as second-line or subsequent therapy as a single agent in HER2-positive tumors (IHC 3+ or 2+) in local/regional recurrence or stage IVB or recurrence with distant metastases disease. The data is extrapolated from the phase II DESTINY-PanTumor02 interim results. The study looked at 267 patients with solid state tumors that had HER2 expression and had prior HER2 targeted therapy. ORR was 37.1% with a median DOR of 11.8 months. Safety results showed AEs of Grade (G) ≥ 3 occurred in 58.4% of patients, while 11.6% discontinued due to treatment adverse events. 18 patients had drug-related interstitial lung disease/pneumonitis.

NCCN also provides a category 2A recommendation in head and neck cancer—salivary gland tumor. NCCN notes that Enhertu is useful in certain circumstances as a single-agent in systemic therapy for HER2-positive recurrent disease. The evidence cited comes from a retrospective analysis of two phase 1 trials within clinicaltrials.gov that are ongoing and have yet to be published. The analysis showed Enhertu provided an overall response of 47% (8/17) and the best overall response was PR in 8 patients and SD in 9 patients. Median duration of response and PFS were 12.9 months and 14.1 months, respectively. The most common grade 3 or 4 adverse events were neutropenia, decreased white blood cell count, and anemia.

Definitions and Measures

HER2 testing (adapted from American Society of Clinical Oncology/College of American Pathologists):

Positive HER2:

- IHC 3+ based on circumferential membrane staining that is complete, intense. (Observed in a homogeneous and contiguous population and within $> 10\%$ of the invasive tumor cells).
- ISH positive based on:
 - Single-probe average HER2 copy number ≥ 6.0 signals/cell*
 - Dual-probe HER2/CEP 17 ratio $\geq 2.0^*$ with an average HER2 copy number ≥ 4.0 signals/cell
 - Dual-probe HER2/CEP17 ratio $\geq 2.0^*$ with an average HER2 copy number < 4.0 signals/cell
 - Dual-probe HER2/CEP17 ratio $< 2.0^*$ with an average HER2 copy number ≥ 6.0 signals/cell

*(Observed in a homogeneous and contiguous population and within $>10\%$ of the invasive tumor cells. By counting at least 20 cells within the area)

Equivocal HER2:

- IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within $>10\%$ of the invasive tumor cells or complete and circumferential membrane staining that is intense and within $\leq 10\%$ of the invasive tumor cells.
- ISH equivocal based on:
 - Single-probe average HER2 copy number ≥ 4.0 and < 6.0 signals/cell
 - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 4.0 signals/cell

Negative HER2 if a single test (or both tests) performed show:

- IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within $> 10\%$ of the invasive tumor cells
- IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within $\leq 10\%$ of the invasive tumor cells
- ISH negative based on:
 - Single-probe average HER2 copy number < 4.0 signals/cell
 - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Refractory Disease: Illness or disease that does not respond to treatment.

Targeted biologic agent: A newer type of drug developed specifically to target genetic changes in cells that cause cancer. It works differently than standard chemotherapy drugs, often with different side effects.

Unresectable: Unable to be removed with surgery.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Enhertu (fam-trastuzumab deruxtecan-nxki)

Requests for Enhertu (fam-trastuzumab deruxtecan-nxki) may be approved if the following criteria are met:

- I. Individual has a diagnosis of recurrent unresectable or metastatic HER2-positive (HER2+) breast cancer (NCCN 1, 2A) confirmed by *one* of the following:
 - A. Immunohistochemistry (IHC) is 3+; **OR**
 - B. In situ hybridization (ISH) positive; **AND**
- II. Individual has previously received a prior anti-HER2 therapy in either:
 - A. Metastatic setting; **OR**
 - B. In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy;

OR

- III. Individual has a diagnosis of recurrent unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (Label, NCCN 1, 2A); **AND**
- IV. Individual is using as single-agent therapy;

OR

- V. Individual has a diagnosis of HER2-positive (IHC 3+ or 2+), cervical cancer, including vaginal cancer (NCCN 2A); **AND**
 - A. Individual is using as second-line or subsequent therapy; **AND**
 - B. Individual is using as a single agent; **AND**
 - C. Using in one of the following disease states:
 - 1. Local/regional recurrence; **OR**
 - 2. Stage IVB or recurrence with distant metastases;

OR

- VI. Individual has a diagnosis of colorectal cancer (including appendiceal adenocarcinoma) (NCCN 2A); **AND**
 - A. Individual is using as initial treatment; **AND**
 - 1. Individual is using as a single agent; **AND**
 - 2. Individual has HER2-amplified (defined as IHC 3+ or ISH positive) and RAS and BRAF wild-type disease; **AND**
 - 3. Individual has unresectable metachronous metastases pMMR/MSS only and previous FOLFOX or CapeOX treatment within the past 12 months;

OR

- B. Individual is using as subsequent therapy; **AND**
 - 1. Individual is using as a single agent; **AND**
 - 2. Using in one of the following disease states:
 - a. Individual has advanced disease; **OR**
 - b. Individual has metastatic disease which is proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) who are HER2-amplified (defined as IHC 3+ or ISH positive) and RAS and BRAF wild-type;

OR

- VII. Individual has a diagnosis of HER2-Positive (IHC 3+) disease in solid tumors (Label, NCCN 2A); **AND**
 - A. Individual has an unresectable or metastatic solid tumor; **AND**
 - B. Individual has had prior systemic treatment; **AND**
 - C. Individual has no satisfactory alternative treatment options; **AND**
 - D. Individual is using as a single agent;

- I. Individual has a diagnosis of salivary gland tumor (NCCN 2A); **AND**
 - A. Individual is using in recurrent, unresectable, or metastatic disease with no surgery or radiation therapy options; **AND**
 - B. Individual is using for HER2-positive tumors; **AND**
 - C. Individual is using as single-agent systemic therapy;

OR

- ±VIII. Individual has a diagnosis of unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations and who have received a prior systemic therapy (Label, NCCN 2A);

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OR
~~III.X.~~ Individual has a diagnosis of HER2+ gastric or esophageal and esophagogastric junction cancers confirmed by *one* of the following (Label, NCCN 2A):
A. Immunohistochemistry (IHC) is 3+; **OR**
B. In situ hybridization (ISH) positive;

AND

~~IV.X.~~ Individual has had received a prior trastuzumab-based regimen (or trasztuzumab biosimilars)-based regimen;

OR

~~V.XI.~~ Individual has a diagnosis of endometrial carcinoma (NCCN 2A); **AND**
A. Individual is using as second-line or subsequent therapy; **AND**
B. Individual is using for recurrent disease; **AND**
C. Disease is HER2-positive (IHC 3+ or 2+);

OR

~~VI.XII.~~ Individual has a diagnosis of metastatic HER2 + breast cancer with brain metastases and the following criteria are met (NCCN 2A):
A. Individual has a primary diagnosis of HER2+ breast cancer; **AND**
B. Using in one of the following ways:
1. In those with asymptomatic brain metastases as primary or initial therapy; **OR**
2. In those with stable brain metastases disease in relapsed/recurrent disease;
AND
C. Individual is using as a single-agent treatment.

Requests for Enhertu (fam-trastuzumab deruxtecan-nxki) may not be approved for the following:

- I. When Enhertu is used in combination with other targeted biologic agents or chemotherapy agents; **OR**
- II. When the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9358 Injection, fam-trastuzumab deruxtecan-nxki, 1 mg (Enhertu)

ICD-10 Diagnosis

C16.0	Malignant neoplasm of gastro-esophageal junction
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C50.011-C50.929	Malignant neoplasm of the breast
C52	Malignant neoplasm of vagina
C53.0-C53.9	Malignant neoplasm of cervix uteri
C54.0-C54.9	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C79.51-C79.52	Secondary malignant neoplasm of bone
C78.00-C78.39	Secondary malignant neoplasm of lung and pleura
C77.0-C77.9	Secondary malignant neoplasm of lymph nodes
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31-C79.32	Secondary malignant neoplasm of brain

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Z17.0	Estrogen receptor positive status [ER+]
Z85.3	Personal history of malignant neoplasm of breast

Document History

- Revised: 05/17/2024
- Document History:
- 05/17/2024 – Select Review: Add FDA label criteria for use in HER2-Positive (IHC 3+) unresectable or metastatic solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. Removed duplicative criteria for salivary gland tumors. Clarify IHC scores for colorectal, cervical, and vaginal cancer. Coding Reviewed: Added ICD-10-CM C52.
 - 02/23/2024 – Annual Review: Add category 2A recommendations from NCCN for Cervical cancer, Colorectal cancer salivary gland tumors, and endometrial cancer. Update nomenclature for esophageal and esophagogastric junction cancers. Clarify disease state in existing breast cancer criteria from NCCN. Coding Reviewed: No changes.
 - 02/24/2023 – Annual Review: Update existing HER-low breast cancer criteria to ensure use as a single-agent. Coding Reviewed: No changes. 06/02/2024: Effective 02/23/2024 added ICD-10-CM C18.0-C18.9, C19, C20, C53.0-C53.9, C54.0-C54.9, C55.
 - 9/12/2022 – Select Review: Add clinical criteria for FDA approvals in HER2-Low Metastatic breast cancer and Unresectable or Metastatic HER2-mutated NSCLC. Coding reviewed: Added ICD-10-CM C34.10-C34.92.
 - 08/19/2022 – Select Review: Update existing breast cancer criteria for FDA approval in unresectable or metastatic HER2 positive breast cancer in the metastatic or neoadjuvant/adjuvant settings. Coding Reviewed: No changes.
 - 02/25/2022 – Annual Review: Update references for Gastric cancers. Minor wording and formatting updates. Coding reviewed: No changes.
 - 02/19/2021 – Annual Review: Update Enhertu criteria for FDA approved indication in locally advanced or metastatic HER2-positive gastric or gastroesophageal junction cancer, with prior trastuzumab-based therapy. Coding Reviewed: Added ICD-10-CM C16.0, Z17.0.
 - 02/21/2020 – Annual Review: Add new clinical criteria document for Enhertu. Coding Reviewed: Added HCPCS J3490, J3590, J9999, C9399. Added ICD-10 C50.011-50.929, C79.51-C79.52, C78.00-C78.39, C77.00-C77.9, C78.7, C79.31-C79.32, Z85.3. Coding Reviewed 5/15/2020-Added HCPCS codes J9358 (Effective 7/1/2020), Deleted: J3490, J3590, J9999, C9399 (Effective 6/30/2020)

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 - Breast Cancer. V5.2023. Revised December 5, 2023.
 - Central Nervous System Cancers. V1.2023. Revised March 24, 2023.
 - Cervical Cancer. V1.2024. Revised September 20, 2023.
 - Colon Cancer. V4.2023. Revised November 16, 2023.
 - Esophageal and esophagogastric junction cancers. V3.2023. Revised August 29, 2023.
 - Gastric Cancer. V2.2023. Revised August 29, 2023.
 - Head and neck Cancers. V2.2024. Revised December 08, 2023.
 - Non-Small Cell Lung Cancer. V1.2024. Revised December 21, 2023.
 - Rectal Cancer. V6.2023. Revised November 16, 2023.
 - Uterine Neoplasms. V1.2024. Revised September 20, 2023.
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