Clinical Criteria

Subject:	Enhertu (fam-trastuzumab deruxtecan-nxki)		
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Table of Contents

Overview

This document addresses the use of Enhertu (fam-trastuzumab deruxtecan-nxki). Enhertu is HER2-directed antibody and topisomoerase inhibitor conjugate that selectively delivers chemotherapy to HER2-overexpressing tumor cells. Internalization and intracellular linker cleavage of the drug by lyzozomal 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 ENHERTU is indicated for the treatment

- Of those with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
  • in the metastatic setting, or
  • in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.

- Of those with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

The National Comprehensive Cancer Network® (NCCN) currently does not provide recommendations for Enhertu's place in therapy. Herceptin (trastuzumab) plus Perjeta (pertuzumab) and docetaxel (category 1) or paclitaxel (category 2A) are considered preferred first line regimens. Second line agents include other trastuzumab containing regimens, including the second HER2-directed antibody-drug conjugate Kadcyla (ado-trastuzumab emtansine) (category 2A).

Enhertu has a black box warning for interstitial lung disease and embryo-fetal toxicity. Interstitial lung disease (ILD) and pneumonitis, including fata 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.

Other uses

In the NCCN clinical practice guideline for colon cancer, non-small cell lung 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.

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 ≥ 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 < 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 ≤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 ≤ 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 unresectable or metastatic HER2-positive (HER2+) breast cancer (NCCN 1) confirmed by *one* of the following:
   A. Immunohistochemistry (IHC) is 3 +; **OR**
   B. In situ hybridization (ISH) positive; **AND**
~~II. Individual is using as monotherapy; **AND**~~
~~III.~~ II. ~~Individual has had at least two or more prior anti-HER2 therapies in the metastatic phase of breast cancer~~;
~~III.~~ 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

IV. Individual has a diagnosis of HER2+ gastric or gastroesophageal junction adenocarcinoma confirmed by *one* of the following (Label, NCCN 2A):
   A. Immunohistochemistry (IHC) is 3 +; **OR**
   B. In situ hybridization (ISH) positive; **AND**
V. Individual has had received a prior trastuzumab-based regimen.

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
C50.011-C50.929	Malignant neoplasm of the breast
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
Z17.0	Estrogen receptor positive status [ER+]
Z85.3	Personal history of malignant neoplasm of breast

Document History

Revised: 08/19/2022
Document History:

- 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-

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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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    b. Colon Cancer. V3.2021. Revised September 10, 2021.
    c. Esophageal and esophagogastric junction cancers. V1.2022. Revised December 21, 2021.
    d. Gastric Cancer. V2.2022. Revised January 11, 2022.
    e. Head and neck Cancers. V1.2022. Revised December 8, 2021.
    f. Non-Small Cell Lung Cancer. V1.2022. Revised December 7, 2021.
    g. Rectal Cancer. V2.2021. Revised September 10, 2021.
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