**POLICY:** Enhertu® (fam-trastuzumab deruxtecan-nxki injection for intravenous use)

**EFFECTIVE DATE:** 5/1/2020
**LAST REVISION DATE:** 02/22/2023

**COVERAGE CRITERIA FOR:** All UCare Plans

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## OVERVIEW

Enhertu is a human epidermal growth factor receptor 2 (HER2)-directed antibody and topoisomerase inhibitor conjugate indicated for the following uses:[1]

- **Breast cancer**
  - Treatment of adults with unresectable or metastatic HER2-positive disease 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.
  - Treatment of adults with unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/ in situ hybridization [ISH] negative) breast cancer, as determined by a FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- **Gastric or gastroesophageal junction adenocarcinoma**, treatment of adults with locally advanced or metastatic HER2-positive disease, who have received a prior trastuzumab-based regimen.
- **Non-small cell lung cancer,** treatment of adults with unresectable or metastatic disease whose tumors have an activating HER2 (erb-b2 receptor tyrosine kinase 2 [*ERBB2*]) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

Enhertu cannot be substituted for or with trastuzumab or Kadcyla® (ado-trastuzumab emtansine intravenous infusion).

## Guidelines

Enhertu is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Breast Cancer:** NCCN guidelines (version 2.2023 – February 7, 2023) recommend Enhertu as a "Preferred" second-line therapy regimen for the treatment of recurrent, unresectable (local or regional), or Stage IV metastatic disease that is HER2-positive (category 1).[2,3] The guidelines note that Enhertu may be considered in the first-line setting as an option for select patients (i.e., those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for Perjeta® {pertuzumab intravenous infusion}-containing regimens]) [category 2A]. The guidelines recommend Enhertu as a "Preferred" single-agent for recurrent unresectable (local or regional) or stage IV HER2 IHC 1+, or 2+ and ISH negative disease that is HR negative or HR positive with visceral crisis or endocrine therapy refractory (category 1 as second-line; category 2A as later-line therapy). NCCN compendium recommends Enhertu for brain metastases in patients with HER2 positive breast cancer.[2]
- **Colon or Rectal Cancer:** NCCN colon cancer guidelines (version 3.2022 – January 25, 2023) and NCCN rectal cancer guidelines (version 4.2022 – January 25, 2023) recommend Enhertu as primary treatment as a single agent in patients with HER2-amplified and *RAS* and *BRAF* wild-type after previous adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months (category 2A). Enhertu is also

recommended as subsequent therapy for HER-2 amplified and *RAS* and *BRAF* wild-type disease (category 2A).[2,4,5]

- **Esophageal and Esophagogastric Junction Cancers**: NCCN guidelines (version 5.2022 – December 5, 2022) recommend Enhertu as a "Preferred Regimen" for second-line or subsequent therapy for unresectable locally advanced, recurrent, or metastatic disease (where local therapy is not indicated) for HER2 overexpression positive adenocarcinoma (category 2A).[6]
- **Gastric Cancer:** NCCN guidelines (version 2.2022 –January 11, 2022) recommend Enhertu as a "Preferred Regimen" for second-line or subsequent therapy for unresectable locally advanced, recurrent, or metastatic disease (where local therapy is not indicated) for HER2 overexpression positive adenocarcinoma (category 2A).[7] Trastuzumab is recommended as a preferred regimen in addition to first-line chemotherapy (fluorouracil or capecitabine + oxaliplatin [category 2A] or cisplatin [category 1]) in HER2 overexpression positive adenocarcinoma.
- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 2.2023 – February 17, 2023) support use of Enhertu as a preferred single-agent subsequent therapy for *ERBB2* or HER2-mutation positive recurrent, advanced, or metastatic disease.[2,8]

## POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Enhertu. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enhertu, as well as the monitoring required for adverse events and long-term efficacy, approval requires Enhertu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enhertu is recommended in those who meet one of the following criteria:

### FDA-Approved Indications

**1. Breast Cancer**. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent or metastatic breast cancer; AND
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; OR
  - **ii.** Patient has HER2-low disease as shown by HER2 immunohistochemistry (IHC) 1+, or IHC 2+ and in situ hybridization (ISH) negative disease and meets one of the following criteria (a or b):
    - **a)** Patient has hormone receptor (HR) positive disease and is refractory to endocrine therapy; OR
    - **b)** Patient has HR negative disease; AND
- **D)** Patient has tried at least one prior regimen; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

**Dosing.** Approve up to 5.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

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**2. Gastric or Gastroesophageal Junction Cancer.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient has received at least one prior trastuzumab-based regimen; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

**Dosing.** Approve up to 6.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

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**3. Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable or metastatic disease; AND
- **C)** The disease has activating human epidermal growth factor receptor 2 (HER2) mutations; AND
- **D)** Patient has tried at least one prior systemic therapy; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

**Dosing.** Approve up to 5.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

**Other Uses with Supportive Evidence**

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**4. Colon or Rectal Cancer.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable, advanced, or metastatic disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-amplified disease; AND
- **D)** Patient has wild-type *RAS* and *BRAF* disease; AND
- **E)** Patient has tried at least one chemotherapy; AND
  Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
- **F**) The medication is prescribed by or in consultation with an oncologist.

**Dosing.** Approve up to 6.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

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**5. Esophageal Cancer.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND

**B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
**C)** Patient has received at least one prior trastuzumab-based regimen; AND
**D)** The medication is prescribed by or in consultation with an oncologist.

**Dosing.** Approve up to 6.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enhertu is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Enhertu® intravenous infusion [prescribing information]. Basking Ridge, NJ and Wilmington, DE: Daiichi Sankyo and AstraZeneca; November 2022.
2. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023. Search term: fam-trastuzumab deruxtecan-nxki.
3. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
4. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
5. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 4.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
6. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 5.2022 – December 5, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
7. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2022 – January 11, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
8. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.

## HISTORY

| Type of Revision | Summary of Changes* | Review Date |
|---|---|---|
| Annual Revision | **Breast Cancer**: The requirement that the patient has "unresectable or metastatic" breast cancer was reworded to patient has "recurrent or metastatic" breast cancer. The requirement to try two prior anti-human epidermal growth factor receptor 2 (HER2) regimens in the metastatic setting was changed to a trial of one HER2 regimen and "in the metastatic setting" was removed.<br>**Colon or Rectal Cancer:** The requirement that the patient has "unresectable or metastatic" disease was removed from "the patient is not a candidate for intensive therapy, according to the prescriber" and added as a separate criteria requirement along with advanced disease. The requirement that the patient has HER2-positive tumor was changed to HER2-amplified disease and *RAS* and *BRAF* wild-type tumors was reworded to wild-type *RAS* and *BRAF* disease.<br>**Esophageal Cancers**: Indication and criteria were added to Other Uses with Supportive Evidence section based on NCCN guidelines.<br>**Non-Small Cell Lung Cancer**: The requirement that the patient has HER2-positive disease was reworded to "patient has a HER2 mutation." | 02/02/2022 |
| Update | **05/09/2022: Breast Cancer:** The FDA approval for breast cancer was changed from "treatment of adults with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive disease who have received two or more prior anti-HER2-based regimens in the metastatic setting" to "treatment of adults with unresectable or | N/A |

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|---|---|---|
| | metastatic HER2-positive disease 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." | |
| Selected Revision | **Breast Cancer**: Criteria was added for a patient that has human epidermal growth factor receptor 2 (HER2)-low disease as shown by HER2 immunohistochemistry (IHC) 1+, or IHC 2+ and in situ hybridization negative disease with hormone receptor (HR) positive disease and is refractory to endocrine therapy OR has HR negative disease. The requirement that patient has tried at least one prior anti-HER2 regimen was reworded to "patient has tried at least one prior regimen," and the Note with examples of anti-HER2 regimen was removed. | 08/03/2022 |
| Update | **08/08/2022: Breast Cancer:** The following new FDA approval was added to the overview section: Treatment of adults with unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/ in situ hybridization [ISH] negative) 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. | 08/08/2022 |
| Selected Revision | The following new FDA approval was added to the overview section: Non-small cell lung cancer, treatment of adults with unresectable or metastatic disease who tumors have an activating HER2 (erb-b2 receptor tyrosine kinase 2 [*ERBB2*]) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.<br>**Non-Small Cell Lung Cancer:** This condition of approval was moved from the other uses with supportive evidence section into the FDA approved indications section. The criteria requirement that the patient has unresectable or metastatic disease and the requirement that the patient has to try at least one systemic therapy were added. The criterion, "Patient has HER2 mutation" was reworded to "The disease has an activating HER2 mutations." | 08/17/2022 |
| Annual Revision | **Colon or Rectal Cancer:** The criterion, "Patient is not a candidate for intensive therapy, according to the prescriber" was removed. | 02/22/2023 |