Utilization Review Policy 223

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

EFFECTIVE DATE: 5/1/2020
LAST REVISION DATE: 02/28/2024

COVERAGE CRITERIA FOR: All UCare Plans

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 unresectable or metastatic HER2-positive disease in adults 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 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, in adults who have received 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 locally advanced or metastatic HER2-positive disease, in adults who have received a prior trastuzumab-based regimen.
- **Non-small cell lung cancer,** treatment of unresectable or metastatic disease in adults whose tumors have an activating HER2 (erb-b2 receptor tyrosine kinase 2 [*ERBB2*]) mutation, 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 1.2024 – January 25, 2024) 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). The NCCN compendium recommends Enhertu for brain metastases in patients with HER2 positive breast cancer.[2]
- **Cervical Cancer:** NCCN guidelines (version 2.2024 – February 23, 2024) recommend Enhertu as a second-line or subsequent therapy under "Useful in Certain Circumstances" for HER2-positive tumors (IHC 3+ or 2+) [category 2A].[2,11]
- **Colon or Rectal Cancer:** NCCN colon cancer guidelines (version 1.2024 – January 29, 2024) and NCCN rectal cancer guidelines (version 1.2024 – January 29, 2024) 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 4.2023 – January 26, 2024) 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 3.2023 –January 26, 2024) 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.[2,7]
- **Head and Neck Cancers:** NCCN guidelines (version 2.2023 – May 15, 2023) recommend Enhertu as a systemic therapy option for recurrent, unresectable, or metastatic salivary gland tumors, (Useful in Certain Circumstances), for HER2 positive tumors (category 2A).[2,9]
- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 2.2024 – February 9, 2024) support use of Enhertu as a "Preferred" single-agent subsequent therapy for *ERBB2* or HER2-mutation positive recurrent, advanced, or metastatic disease.[2,8]
- **Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer:** NCCN guidelines (version 1.2024 – January 17, 2024) recommend Enhertu (category 2A) for recurrent therapy for platinum-resistant disease under "Useful in Certain Circumstances" for HER2-positive tumors (IHC 3+ or 2+).[2,10]
- **Uterine Neoplasms:** NCCN guidelines (version 1.2024 – September 20, 2023) recommend Enhertu (category 2A) for recurrent endometrial carcinoma in the second-line or subsequent therapy setting for HER2-positive tumors (IHC 3+ or 2+).[2,12]

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

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1. Breast Cancer. Approve for 1 year if the patient meets ALL of the following (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 (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 (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 (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 (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. Cervical Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent or metastatic disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease (immunohistochemistry [IHC] 3+ or IHC 2+); AND
- **D)** Patient has received at least one prior systemic therapy; AND
  Note: Examples are cisplatin, carboplatin, capecitabine, paclitaxel, gemcitabine, bevacizumab.
- **E)** 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. Colon or Rectal Cancer. Approve for 1 year if the patient meets ALL of the following (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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6. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (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 (immunohistochemistry [IHC] 3+ or IHC 2+); AND
- **C)** Patient has received at least one prior systemic therapy; AND
  Note: Examples are carboplatin, paclitaxel, docetaxel, trastuzumab, cisplatin, doxorubicin, bevacizumab.
- **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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7. Esophageal Cancer. Approve for 1 year if the patient meets ALL of the following (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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8. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND
B) Patient has platinum-resistant disease; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease (immunohistochemistry [IHC] 3+ or IHC 2+); AND
D) Patient has received at least one prior systemic therapy regimen; AND
Note: Examples include combinations of one or more of the following agents such as carboplatin, paclitaxel, docetaxel, 5-fluorouracil, oxaliplatin, capecitabine, cisplatin, liposomal doxorubicin, ifosfamide.
E) 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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9. Salivary Gland Tumors. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

a. Patient is ≥ 18 years of age; AND
b. Patient has recurrent, unresectable, or metastatic disease; AND
c. Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; 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; February 2024.
2. The NCCN Drugs & Biologics Compendium. © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 23, 2024. Search term: fam-trastuzumab deruxtecan-nxki.
3. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – January 25, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 25, 2024.
4. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – January 29, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 26, 2024.
5. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – January 29, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 26, 2024.

6. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 4.2023 – January 26, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 26, 2024.
7. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – January 26, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 26, 2024.
8. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2024 – February 9, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 26, 2024.
9. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (version 2.2024 – December 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 26, 2024.
10. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – January 17, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed February 26, 2024.
11. The NCCN Cervical Cancer Clinical Practice Guidelines in Oncology (version 2.2024 – February 23, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed February 26, 2024.
12. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2024 – September 20, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed February 26, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
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
Annual Revision	**Cervical Cancer:** Indication and criteria were added to Other Uses with Supportive Evidence section based on NCCN guidelines. **Endometrial Carcinoma:** Indication and criteria were added to Other Uses with Supportive Evidence section based on NCCN guidelines. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:** Indication and criteria were added to Other Uses with Supportive Evidence section based on NCCN guidelines. **Salivary Gland Tumors:** Indication and criteria were added to Other Uses with Supportive Evidence section based on NCCN guidelines.	02/28/2024