Utilization Review Policy 223

POLICY: Oncology (Injectable) – Enhertu Utilization Management Medical Policy

- Enhertu® (fam-trastuzumab deruxtecan-nxki intravenous infusion – Daiichi Sankyo and AstraZeneca)

EFFECTIVE DATE: 5/1/2020
LAST REVISION DATE: 02/19/2025

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** (immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive) 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** (IHC 1+ or IHC 2+/ ISH negative) breast cancer, as determined by an 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.
  - Treatment of unresectable or metastatic hormone receptor (HR)-positive HER2-low (IHC 1+ or IHC 2+/ISH negative) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, in adults who have progressed on one or more endocrine therapies in the metastatic setting.
- **Gastric or gastroesophageal junction adenocarcinoma**, treatment of locally advanced or metastatic HER2-positive disease (IHC 3+ or IHC 2+/ISH positive), 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.
- **Solid tumors**, treatment of unresectable or metastatic HER2-positive (IHC 3+) solid tumors in adults who have received prior systemic treatment and have no satisfactory alternative treatment options.

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 1.2025 – January 31, 2025) recommend Enhertu as a "Preferred" second-line 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 0+, 1+, or 2+ and ISH negative disease that is HR positive with visceral crisis or endocrine therapy refractory (category 1 as second-line). In this setting, it is also recommended as "Other Recommended Regimen" for first-line setting for no germline BRCA mutation and/or IHC HER2 0+, 1+, or 2+/ISH-negative. For HR-negative, HER2 IHC 0+, 1+, or 2+/ISH-negative disease with no germline *BRCA* mutation, Enhertu is a category 1, "Preferred" option in the second-line setting. It can also be considered for later line therapy, if not used in second line. Or it may be considered first-line therapy when disease has progressed during or within 6 months after completing adjuvant chemotherapy. The NCCN compendium recommends Enhertu for brain metastases in patients with HER2 positive breast cancer.[2]

- **Esophageal and Esophagogastric Junction Cancers**: NCCN guidelines (version 5.2024 – December 20, 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).[4]
- **Gastric Cancer:** NCCN guidelines (version 5.2024 –December 20, 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.[2,5]
- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 3.2025 – January 14, 2025) support use of Enhertu as a "Preferred" single-agent subsequent therapy for *ERBB2* or HER2-mutation positive recurrent, advanced, or metastatic disease.[2,6]

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 – HER2-Positive Disease**. 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 has human epidermal growth factor receptor 2 (HER2)-positive disease (immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive); OR
D) Patient meets ONE of the following (i or ii):
  i. Patient has tried at least one prior regimen in the metastatic setting; OR
  ii. Patient has had disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy (within 12 months for Perjeta [pertuzumab injection]-containing regimens) and the medication is used as first-line 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.

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2. Breast Cancer – Hormone Receptor-Positive, HER2-Low or Ultra-Low Disease. 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 recurrent, unresectable, or metastatic disease; AND
C) Patient has hormone receptor (HR) positive disease with visceral crisis or is refractory to endocrine therapy; AND
  Note: Visceral crisis is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies, and rapid disease progression.
D) Patient has human epidermal growth factor receptor 2 (HER2)-low or HER2-ultra-low disease as shown by immunohistochemistry [IHC] 0+, 1+, 2+ or in situ hybridization [ISH] negative; AND
E) Patient meets ONE of the following (i or ii):
  i. The medication will be used as first-line therapy and meets BOTH of the following (a and b):
    a) The disease is negative for germline *BRCA* 1/2 mutation; AND
    b) Patient has tried at least one line of endocrine-based therapy in the metastatic setting; OR
  ii. The medication will be used as second-line therapy; AND
F) 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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3. Breast Cancer – Hormone Receptor-Negative, HER2-Low or Ultra-Low Disease. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, F, and G):
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent, unresectable, or metastatic disease; AND
C) Patient has hormone receptor (HR)-negative disease; AND
D) The disease is negative for germline *BRCA* 1/2 mutation; AND
E) Patient has human epidermal growth factor receptor 2 (HER2)-low or HER2-ultra-low disease as shown by immunohistochemistry [IHC] 0+, 1+, 2+ or in situ hybridization [ISH] negative; AND
F) Patient meets ONE of the following (i or ii):
  i. The medication is considered for first-line therapy after the disease has progressed during or within 6 months after completing adjuvant chemotherapy; OR
  ii. The medication is used in the subsequent therapy setting (second- or later-line).
G) 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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4. **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 (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH] positive); 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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5. **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.

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6. **Solid Tumors.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   Note: Examples include bladder cancer, biliary tract cancer, cervical cancer, colorectal cancer, endometrial cancer, ovarian cancer, pancreatic cancer, salivary gland tumors.
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has unresectable or metastatic disease; AND
   - **C)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease (immunohistochemistry [IHC] 3+); AND
   - **D)** Patient has received prior systemic treatment; AND
   - **E)** According to the prescriber, there are no satisfactory alternative treatment options; AND
   - **F)** 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.

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; January 2025.
2. The NCCN Drugs & Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 17, 2025. Search term: fam-trastuzumab deruxtecan-nxki.
3. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – January 31, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 17, 2025.
4. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 5.2024 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 17, 2025.
5. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 5.2024 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 17, 2025.
6. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – January 14, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 17, 2025.

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
Selected Revision	**Breast Cancer:** For criterion referring to human epidermal growth factor 2 (HER2)-positive disease, added qualifier "(immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive)" based on updated FDA indication. **Gastric or Gastroesophageal Junction Cancer:** For criterion referring to human epidermal growth factor 2 (HER2)-positive disease, added qualifier "(immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive)" based on updated FDA indication. **Solid Tumors:** Added new FDA-approved indication and approval criteria. **Cervical Cancer:** Deleted approval condition since it is covered under "Solid Tumors" indication. **Colon or Rectal Cancer:** Deleted approval condition since it is covered under "Solid Tumors" indication. **Endometrial Carcinoma:** Deleted approval condition since it is covered under "Solid Tumors" indication. **Esophageal Cancer:** Deleted approval condition since it is covered under "Solid Tumors" indication. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:** Deleted approval condition since it is covered under "Solid Tumors" indication. **Salivary Gland Tumors:** Deleted approval condition since it is covered under "Solid Tumors" indication.	06/05/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	**Breast Cancer – HER2-Positive Disease.** Added qualifier "HER2-positive disease" to indication. Deleted criteria for HER2-low disease since it is now addressed separately. **Breast Cancer – Hormone Receptor-Positive, HER2-Low or Ultra-Low Disease.** Added new approval condition and criteria for HER2 ultra-low disease. Separated criteria for HER2-low disease from "HER2-Positive Disease" indication above. **Breast Cancer – Hormone Receptor-Negative, HER2-Low or Ultra-Low Disease.** Added new approval condition and criteria for HER2 ultra-low disease.	02/19/2025

	Separated criteria for HR negative, HER2-low disease from "HER2-Positive Disease" indication above.	
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025