

UTILIZATION MANAGEMENT MEDICAL POLICY

- POLICY:** Oncology (Injectable) – Enhertu Utilization Management Medical Policy
- Enhertu® (fam-trastuzumab deruxtecan-nxki intravenous infusion – Daiichi Sankyo and AstraZeneca)

REVIEW DATE: 02/28/2024; selected revision 06/05/2024, 12/04/2024

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.
- **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 Kadcylla® (ado-trastuzumab emtansine intravenous infusion).

Guidelines

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

- **Breast Cancer:** NCCN guidelines (version 6.2024 – November 11, 2024) 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 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
- **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).⁴

- **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.^{2,5}
- **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.^{2,6}

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

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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 (immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive); OR
 - ii.** Patient has HER2-low disease as shown by HER2 IHC 1+, or IHC 2+ and ISH negative disease and meets ONE of the following (a or b):
 - a)** Patient has hormone receptor (HR) positive disease with visceral crisis or is refractory to endocrine therapy; OR
Note: Visceral crisis is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies, and rapid disease progression.
 - b)** Patient has HR negative disease; AND
 - 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.

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 (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.

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.

4. 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; April 2024.
2. The NCCN Drugs & Biologics Compendium. © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on December 2, 2024. Search term: fam-trastuzumab deruxtecan-nxki.
3. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 6.2024 – November 11, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on December 2, 2024.
4. 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.
5. 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.
6. 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.

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
Selected Revision	Breast Cancer: In patients with HER2-low, hormone receptor-positive disease, added qualifier, “with visceral crisis or..” is refractory to endocrine therapy. Added a Note to define visceral crisis. For criteria referring to a trial of prior regimen, added clarification “...in the metastatic setting”. Also added new criteria that if patient has disease recurrence during or within 6 months of completing adjuvant or neoadjuvant therapy (12 months for Perjeta therapy), Enhertu can be used in first line setting.	12/04/2024