

Specialty Guideline Management

Enhertu

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Enhertu	fam-trastuzumab deruxtecan-nxki

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications¹

HER2-Positive Early Breast Cancer

Enhertu followed by a taxane, trastuzumab, and pertuzumab (THP) is indicated for the neoadjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive [immunohistochemistry score (IHC) 3+ or in situ hybridization test (ISH)+] stage II or III breast cancer as determined by an FDA-authorized test.

Enhertu is indicated for the adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment.

HER2-Positive Metastatic Breast Cancer

Enhertu, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) 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.

Enhertu, in combination with pertuzumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer as determined by an FDA-approved test.

HER2-Low and HER2-Ultralow Metastatic Breast Cancer

Enhertu, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic

- HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an 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.
- hormone receptor (HR)-positive HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting.

HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Enhertu, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer

Enhertu, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH+) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

Enhertu, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Compendial Uses²⁻⁵

- HER2-positive breast cancer, treatment of recurrent disease
- HER2-low and ultralow breast cancer, treatment of recurrent disease
- Non-small cell lung cancer with HER2 mutations, treatment of recurrent and advanced disease
- HER2-positive esophageal, gastric or gastroesophageal junction cancer
- HER2-positive solid tumors
 - HER2-amplified colorectal cancer (including appendiceal and anal adenocarcinoma)

- HER2-positive cervical cancer
- HER2-positive endometrial carcinoma
- HER2-positive ovarian cancer
- HER2-positive vaginal cancer
- HER2-positive vulvar cancer
- HER2-positive ampullary adenocarcinoma
- HER2-positive salivary gland tumor
- HER2-positive pancreatic adenocarcinoma
- HER2-amplified small bowel adenocarcinoma
- HER2-positive occult primary
- HER2-positive appendiceal neoplasms and cancers
- HER2-positive bladder cancer
- HER2-positive biliary tract cancer
- HER2-positive esophageal and esophagogastric adenocarcinoma
- HER2-positive gastric adenocarcinoma

All other indications are considered experimental/investigational and not medically necessary.

Documentation

Submission of the following information is necessary to initiate the prior authorization review: human epidermal growth factor receptor 2 (HER2) status (e.g., immunohistochemistry [IHC] score, in situ hybridization [ISH] test) and hormone receptor (HR) status.

Coverage Criteria

Breast cancer^{1,2}

Authorization of 12 months may be granted for treatment of breast cancer when any of the following criteria are met:

- Member has HER2-positive breast cancer and meets any of the following criteria:
 - The requested medication will be used as neoadjuvant treatment for stage II or III disease followed by a taxane, trastuzumab, and pertuzumab (THP).
 - The requested medication will be used as a single agent when the disease had no response to preoperative systemic therapy, or the disease is recurrent, metastatic, or unresectable.

- The requested medication will be used in combination with pertuzumab as first line treatment when the disease had no response to preoperative systemic therapy, or the disease is unresectable or metastatic.
- The requested medication will be used as adjuvant therapy for residual disease in members with high risk of recurrence (i.e., inoperable cancer at presentation prior to neoadjuvant therapy or operable cancer with axillary node-positive disease following preoperative therapy).
- Member has HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer and meets all of the following criteria:
 - The disease had no response to preoperative systemic therapy, or the disease is recurrent metastatic, or unresectable.
 - The requested medication will be used as a single agent.
- Member has HER2-ultralow (IHC 0 with membrane staining) breast cancer and meets all of the following criteria:
 - The disease is recurrent, metastatic, or unresectable.
 - The disease is hormone receptor positive with visceral crisis or endocrine therapy refractory or the disease is hormone receptor negative.
 - The requested medication will be used as a single agent.
- Member has HER2-negative breast cancer and meets all of the following criteria:
 - The disease had no response to preoperative systemic therapy, or the disease is recurrent unresectable or metastatic.
 - The disease is hormone receptor positive with visceral crisis or endocrine therapy refractory.
 - The requested medication will be used as a single agent.

Non-Small Cell Lung Cancer^{1,2}

Authorization of 12 months may be granted for subsequent therapy of non-small cell lung cancer with HER2 (ERBB2) mutations or HER2 overexpression (IHC 3+) when all of the following criteria are met:

- The disease is recurrent, advanced, metastatic, or unresectable.
- The requested medication will be used as a single agent.
- The member has not experienced disease progression on a HER2 targeted drug (e.g., Kadcycla).

Esophageal, Gastric or Gastroesophageal Junction Adenocarcinoma^{1,2}

Authorization of 12 months may be granted for members with HER2-positive disease who are not surgical candidates or for subsequent treatment of HER2-positive unresectable locally advanced, recurrent, or metastatic esophageal, gastric, or gastroesophageal junction adenocarcinoma as a single agent.

Solid Tumors¹⁻⁴

Authorization of 12 months may be granted for treatment of solid tumors when all of the following criteria are met:

- The disease is unresectable, metastatic, advanced, recurrent, or persistent.
- The tumor is HER2-positive (IHC 3+ or 2+).
- The member received prior systemic treatment and has no satisfactory alternative treatment options.
- The requested medication will be used as a single agent.

Biliary Tract Cancer²

Authorization of 12 months may be granted for subsequent treatment of unresectable or resected gross residual (R2) disease or metastatic HER2-positive (IHC 3+) biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer) when used as a single agent.

Continuation of Therapy

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in the coverage criteria section when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

References

1. Enhertu [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; May 2026.
2. The NCCN Drugs & Biologics Compendium® © 2026 National Comprehensive Cancer Network, Inc. Available at: <https://www.nccn.org>. Accessed May 18, 2026.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 4.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf. Accessed September 3, 2025.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 4.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed September 3, 2025.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 5.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed September 3, 2025.