Clinical Policy: Fam-trastuzumab Deruxtecan-nxki (Enhertu)

Reference Number: PA.CP.PHAR.456
Effective Date: 10/2020
Last Review Date: 01/2025

Description
Fam-trastuzumab deruxtecan-nxki (Enhertu®) is a human epidermal growth factor receptor 2 (HER2)-directed antibody and topoisomerase inhibitor conjugate.

FDA Approved Indication(s)
Enhertu is indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive 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.
- Unresectable or metastatic:
  - 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, or
  - 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.
- 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*.
- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.
- Unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no statisfactory alternative treatment options.*

**This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Enhertu is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. IHC 3+ Solid Tumors (must meet all):

1. Diagnosis of HER2-positive, IHC 3+ solid tumor (*see Appendix D*);

2. Disease is unresectable or metastatic;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Failure of at least one prior line of standard systemic regimen for the disease, and have no available standard treatment as a satisfactory alternative treatment option;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 5.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Breast Cancer (must meet all)**:**

1. Diagnosis of recurrent, unresectable, or metastatic breast cancer that is one of the following (a, b or c):
   a. HER2-positive;
   b. HER2-low (IHC 1+ or IHC 2+/ISH-);
   c. HR-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a, b or c):
   a. For HER2-positive breast cancer, one of the following (i or ii):
      i. Failure of one prior anti-HER2-based regimen (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced;
      ii. Rapid disease progression within 6 months of neoadjuvant or adjuvant therapy (12 months for pertuzumab-containing regimens);

      **Prior authorization may be required for anti-HER2-based regimens*
   b. For HER2-low (IHC 1+ or IHC2+/ISH-) breast cancer, one of the following (i or ii):
      i. Failure of at least one prior therapy (e.g., systemic chemotherapy or PARP inhibitor)(if hormone-receptor [HR]-positive, previous therapy should include an endocrine therapy, unless ineligible or with visceral crisis) (*see Appendix B for examples*);
      ii. Disease recurrence during or within 6 months of completing adjuvant chemotherapy;
   c. For HR-positive, HER2-low or ultralow, progressed on one or more endocrine therapies in the metastatic setting;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 5.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

C. Gastric and Gastroesophageal Junction Cancer (must meet all)**:**

1. Diagnosis of HER2-positive gastric or GEJ adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;

3. Age ≥ 18 years;
4. Disease is locally advanced, recurrent or metastatic;
5. Failure of trastuzumab-based regimen (*see Appendix B*);
6. Request meets one of the following (a or b):
   a. Dose does not exceed 6.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of unresectable, recurrent, advanced or metastatic NSCLC;
2. Disease has activating HER2 (ERBB2) mutations;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Failure of one prior systemic therapy (*see Appendix B for examples*);
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 5.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

E. Colon or Rectal Cancer (off label) (must meet all):
1. Diagnosis of advanced or metastatic colon or rectal cancer, including appendiceal adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a, b or c):
   a. Documentation supports failure of or presence of clinically significant adverse effects or contraindication to at least two FDA approved medications for the relevant diagnosis (e.g., oxaliplatin, irinotecan, FOLFOX [fluorouracil, leucovorin, and oxaliplatin] or CapeOX [capecitabine and oxaliplatin], bevacizumab);
   b. Enhertu is prescribed as adjuvant therapy for rectal cancer as a single agent for unresectable metachronous metastases (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) that converted to resectable disease after initial treatment;
   c. Other category 1, 2A, or 2B NCCN-recommended uses not listed;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

F. Other NCCN Recommended Uses (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a, b, c or d):
   a. Recurrent or metastatic HER2-positive cervical cancer;
   b. Recurrent HER2-positive salivary gland tumors;

c. Recurrent or metastatic HER2-positive endometrial carcinoma;
d. Other category 1, 2A, or 2B NCCN-recommended uses not listed;

2. Prescribed or in consultation with an oncologist;
3. Age ≥ 18 years;
4. For cervical cancer: Prescribed as a single agent following failure of ≥ 1 prior therapy (see *Appendix B*);
5. For salivary gland tumors: Prescribed as a single agent and member has one of the following (a or b):
   a. Distant metastases in patients with a performance status (PS) of 0-3;
   b. Unresectable locoregional recurrence or second primary with prior radiation therapy;
6. For endometrial carcinoma: Prescribed as a single agent following failure of ≥ 1 prior therapy (see *Appendix B*);
7. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

G. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b or c):
   a. For breast cancer, NSCLC or IHC 3+ solid cancers: New dose does not exceed 5.4 mg/kg every 3 weeks;
   b. For gastric or GEJ adenocarcinoma: New dose does not exceed 6.4 mg/kg every 3 weeks;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
GEJ: gastroesophageal junction
HER2: human epidermal growth factor receptor 2
HR: hormone-receptor
IHC: immunohistochemistry (assay)
NCCN: National Comprehensive Center Network
NSCLC: non-small cell lung cancer

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
HER2+ Breast Cancer NCCN examples of systemic therapies for recurrent or metastatic disease: • Aromatase inhibitor ± trastuzumab • Aromatase inhibitor ± lapatinib • Pertuzumab + trastuzumab + docetaxel	Varies	Varies
Breast Cancer • Examples of systemic therapies include but are not limited to: eribulin, capecitabine, gemcitabine, nab-paclitaxel, paclitaxel • Examples of endocrine therapies for HR+ disease include but are not limited to: sacituzumab, palbociclib, ribociclib, abemacicilib, tamoxifen, letrozole, anastrozole, exemestane	Varies	Varies
Gastric and Gastroesophageal Junction Cancer trastuzumab-based regimen	8 mg/kg IV followed by 6 mg/kg IV q 3 weeks	8 mg/kg
NSCLC Examples of systemic therapies include but are not limited to: • Carboplatin or cisplatin + pemetrexed + pembrolizumab • Carboplatin + paclitaxel + bevacizumab + atezolizumab	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• Carboplatin + albumin-bound paclitaxel + atezolizumab • Carboplatin + paclitaxel or albumin-bound paclitaxel + pembrolizumab • Nivolumab + ipilimumab + paclitaxel + carboplatin or cisplatin Examples of targeted therapies include but are not limited to: • EGFR mutation positive: afatinib, erlotinib, dacomitinib, gefitinib, osimertinib, erlotinib + ramucirumab, erlotinib + bevacizumab (non-squamous) • BRAF: dabrafenib/trametinib, dabrafenib, vemurafenib • ALK: alectinib, brigatinib, ceritinib, crizotinib, lorlatinib • ROS1: ceritinib, crizotinib, entrectinib		
Cervical Cancer Examples of first-line therapies include but are not limited to: • Cisplatin or carboplatin + paclitaxel ± bevacizumab • Topotecan + paclitaxel ± bevacizumab • Cisplatin + topotecan • Cisplatin • Carboplatin Examples of NCCN-preferred second-line or subsequent therapies include but are not limited to: • Tisotumab vedotin-tftv • Cemiplimab • Bevacizumab • Paclitaxel • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan	Varies	Varies
Endometrial Carcinoma Examples of first-line therapies include but are not limited to: • Carboplatin + paclitaxel + trastuzumab • Carboplatin + docetaxel • Carboplatin + paclitaxel + bevacizumab	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of NCCN-preferred second-line or subsequent therapies include but are not limited to: • Cisplatin + doxorubicin • Cisplatin + doxorubicin + paclitaxel • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel • Albumin-bound paclitaxel • Topotecan • Bevacizumab • Temsirolimus • Cabozantinib • Docetaxel • Ifosfamide (for carcinosarcoma) • Ifosfamide + paclitaxel (for carcinosarcoma) • Cisplatin + ifosfamide		

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): interstitial lung disease and pneumonitis; embryo-fetal toxicity

Appendix D: IHC 3+ Solid Tumors

- In DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 clinical trials, the following were solid tumor types that were included in the study: colorectal cancer, bladder cancer, biliary tract cancer, NSCLC, endometrial cancer, ovarian cancer, cervical cancer, salivary gland cancer, pancreatic cancer, orophanryngeal neoplasm, vulvar cancer, extramammary Paget's disease, lacrimal gland cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, and esophageal squamous cell carcinoma.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Breast cancer, NSCLC, ICH 3+ solid tumors	5.4 mg/kg IV every 3 weeks	5.4 mg/kg
Gastric, GEJ cancer	6.4 mg/kg IV every 3 weeks	6.4 mg/kg

VI. Product Availability

Single-dose vial: 100 mg lyophilized powder

VII. References

1. Enhertu Prescribing Information. Basking Ridge, NJ: Daiichi Sankyo, Inc.; April 2024. Available at: www.enhertu.com. Accessed October 21, 2024.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium.Accessed April 24, 2025.
3. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2019; doi: 10.1056/NEJMoa1914510.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9358	Injection, fam-trastuzumab deruxtecan-nxki, 1 mg

Reviews, Revisions, and Approvals	Date
Policy created	10/2020
1Q 2021 annual review: recurrent breast cancer added per NCCN; added criteria for new FDA-approved gastric cancer indication; updated coding implications; therapeutic alternatives and references reviewed and updated	01/2021
1Q 2022 annual review: references reviewed and updated.	01/2022
1Q 2023 annual review: added criteria for new FDA-approved indications for NSCLC and HER2-low breast cancer, references reviewed and updated. added off-label use for advanced or metastatic colon and rectal cancers per NCCN; for NSCLC removed the criterion to require treatment of non-HER2 mutations first, to align with NCCN recommendations; added recurrent gastric or GEJ cancer as a covered indication per NCCN; RT4: added language to the FDA Approved Indications section re: using an FDA-approved test to identify HER2-low breast cancer; references reviewed and updated.	01/2023
1Q 2024 annual review: per NCCN guidelines, clarified that off-label use for appendiceal adenocarcinoma is included as a colorectal cancer, added criteria for use as adjuvant therapy in rectal cancer, added criteria for off-label use for cervical cancer, salivary gland tumors, and endometrial carcinoma; references reviewed and updated.	01/2024
1Q 2025 annual review: RT4: added newly approved indication for IHC 3+ solid tumors.; references reviewed and updated.	01/2025