

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

Reference Number: PA.CP.PHAR.456

Effective Date: 10/2020

Last Review Date: 01/2026

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:

- In combination with pertuzumab, for the first-line treatment of unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test.
- As monotherapy, for 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.
- As monotherapy, for 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.
- As monotherapy, for 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.
- As monotherapy, for 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*.
- As monotherapy, for 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.
- As monotherapy, for unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory 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 \geq 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: 12 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 (IHC 3+ or ISH positive);
 - b. HER2-low (IHC 1+ or IHC 2+/ISH-);
 - c. HER2-ultralow (IHC 0 with membrane staining);
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. One of the following (a, b or c):
 - a. For HER2-positive (IHC 3+ or ISH positive) breast cancer, one of the following (i, ii or iii):
 - i. Prescribed in combination with pertuzumab as first-line therapy for unresectable or metastatic disease;
 - ii. Failure of one prior anti-HER2-based regimen (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced;
 - iii. 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-) or ultralow (IHC 0 with membrane staining) breast cancer, one of the following (i, ii, or iii):
 - i. Failure of at least one prior line of chemotherapy and member meets one of the following (1 or 2):
 1. Member's cancer is HR-positive;
 2. Member's cancer is HR-negative and the member does not have a germline BRCA 1/2 mutation;
 - ii. Disease recurrence during or within 6 months of completing adjuvant chemotherapy;
 - iii. If HR-positive, both of the following (1 and 2):
 1. If request is for first-line therapy, member does not have a germline BRCA 1/2 mutation;

2. Failure of one prior endocrine therapy (*see Appendix B for examples*), unless contraindicated, clinically significant adverse effects are experienced, or the member has visceral crisis;
- c. Other NCCN recommendations listed as category 1, 2A, or 2B;
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: 12 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 \geq 18 years;
4. Disease is unresectable locally advanced, recurrent, metastatic or member is not a surgical candidate;
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: 12 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 \geq 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: 12 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 \geq 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: 12 months

F. Other NCCN Recommended Uses (off-label) (must meet all):

1. Diagnosis of one of the following (a-g):
 - a. Recurrent or metastatic HER2-positive cervical cancer;
 - b. Recurrent HER2-positive salivary gland tumors;
 - c. Recurrent or metastatic HER2-positive endometrial carcinoma;
 - d. Recurrent HER2-positive ampullary adenocarcinoma;
 - e. Recurrent and locally advanced or metastatic HER2-positive pancreatic adenocarcinoma;
 - f. Recurrent or metastatic vaginal cancer;
 - g. Other category 1, 2A, or 2B NCCN-recommended uses not listed;
2. Prescribed or in consultation with an oncologist;
3. Age \geq 18 years;
4. For cervical and vaginal cancer: Prescribed as a single agent following failure of \geq 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 \geq 1 prior therapy (see *Appendix B*);
7. For ampullary adenocarcinoma: Prescribed as a single agent and the member has one of the following (a or b):
 - a. Good performance status (ECOG 0-1 with good biliary drainage and adequate nutritional intake);
 - b. Intermediate ECOG PS 2;
8. For pancreatic adenocarcinoma: prescribed as a single agent and the member has one of the following (a or b):
 - a. Good performance status (ECOG PS 0-1, with good biliary drainage and adequate nutritional intake);
 - b. Intermediate performance status (ECOG 2);
9. 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: 12 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

dMMR: mismatch repair deficient
FDA: Food and Drug Administration
GEJ: gastroesophageal junction
HER2: human epidermal growth factor receptor 2
HR: hormone-receptor
IHC: immunohistochemistry (assay)

MSI-H: microsatellite instability-high
NCCN: National Comprehensive Center Network
NSCLC: non-small cell lung cancer
PD-L1: programmed death ligand-1
TMB: tumor mutational burden

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
<p>HER2+ Breast Cancer NCCN examples of systemic therapies for recurrent or metastatic disease:</p> <ul style="list-style-type: none"> • Aromatase inhibitor ± trastuzumab • Aromatase inhibitor ± lapatinib • Pertuzumab + trastuzumab + docetaxel 	Varies	Varies
<p>Breast Cancer</p> <ul style="list-style-type: none"> • 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, palbocicib, ribociclib, abemaciclib, tamoxifen, letrozole, anastrozole, exemestane 	Varies	Varies
<p>Gastric and Gastroesophageal Junction Cancer trastuzumab-based regimen</p>	8 mg/kg IV followed by 6 mg/kg IV q 3 weeks	8 mg/kg
<p>NSCLC Examples of systemic therapies include but are not limited to:</p> <ul style="list-style-type: none"> • Carboplatin or cisplatin + pemetrexed + pembrolizumab • Carboplatin + paclitaxel + bevacizumab + atezolizumab • Carboplatin + albumin-bound paclitaxel + atezolizumab • Carboplatin + paclitaxel or albumin-bound paclitaxel + pembrolizumab • Nivolumab + ipilimumab + paclitaxel + carboplatin or cisplatin <p>Examples of targeted therapies include but are not limited to:</p> <ul style="list-style-type: none"> • 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 	Varies	Varies
<p>Cervical Cancer Examples of first-line therapies include but are not limited to:</p> <ul style="list-style-type: none"> • Cisplatin or carboplatin + paclitaxel ± bevacizumab • Topotecan + paclitaxel ± bevacizumab 	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
<ul style="list-style-type: none"> • Cisplatin + topotecan • Cisplatin • Carboplatin <p>Examples of NCCN-preferred second-line or subsequent therapies include but are not limited to:</p> <ul style="list-style-type: none"> • Tisotumab vedotin-tftv • Cemiplimab • Bevacizumab • Paclitaxel • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan 		
<p>Endometrial Carcinoma</p> <p>Examples of first-line therapies include but are not limited to:</p> <ul style="list-style-type: none"> • Carboplatin + paclitaxel + trastuzumab • Carboplatin + docetaxel • Carboplatin + paclitaxel + bevacizumab <p>Examples of NCCN-preferred second-line or subsequent therapies include but are not limited to:</p> <ul style="list-style-type: none"> • 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) 	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
<ul style="list-style-type: none"> • Cisplatin + ifosfamide 		
<p>Vaginal Cancer Examples of first-line therapies for recurrent or metastatic disease include but are not limited to:</p> <ul style="list-style-type: none"> • For PD-L1-positive tumors: <ul style="list-style-type: none"> ○ Cisplatin/paclitaxel + pembrolizumab +/- bevacizumab ○ Carboplatin/paclitaxel + pembrolizumab +/- bevacizumab • Cisplatin/paclitaxel + bevacizumab • Carboplatin/paclitaxel + bevacizumab <p>Examples of NCCN-preferred second-line or subsequent therapies include but are not limited to:</p> <ul style="list-style-type: none"> • For tumor microburden (TMB)-high, PD-L1-positive, or microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) tumors: pembrolizumab • Other recommended: <ul style="list-style-type: none"> ○ Bevacizumab ○ Paclitaxel ○ Albumin-bound paclitaxel ○ Docetaxel ○ Fluorouracil ○ Gemcitabine ○ Pemetrexed ○ Topotecan ○ Vinorelbine ○ Irinotecan ○ Tisotumab vedotin-tftv ○ Cemiplimab <p>Ipilimumab + nivolumab</p>	Varies	Varies

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, oropharyngeal neoplasm, vulvar

cancer, extramammary Paget’s disease, lacrimal gland cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, and esophageal squamous cell carcinoma.

- NCCN guidelines also support the use of Enhertu as a single agent for second-line and subsequent therapy for the following solid tumor types that are IHC 3+: recurrent appendiceal adenocarcinoma or Goblet cell adenocarcinoma.

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.; January 2025. Available at: www.enhertu.com. Accessed December 5, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed December 5, 2025.
3. National Comprehensive Cancer Network Guidelines. Breast Cancer Version 5.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed December 5, 2025.
4. 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	01/2023

Reviews, Revisions, and Approvals	Date
<p>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.</p>	
<p>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.</p>	01/2024
<p>1Q 2025 annual review: RT4: added newly approved indication for IHC 3+ solid tumors.; references reviewed and updated.</p>	01/2025
<p>1Q 2026 annual review: added NCCN-supported uses for recurrent NSCLC (in addition to unresectable or metastatic), ampullary adenocarcinoma, pancreatic adenocarcinoma, and vaginal cancer; per NCCN recs added a requirement for BRCA 1/2 negativity if using Enhertu for HR-negative breast cancer as second-line or later therapy; updated initial auth durations from 6 months to 12 months; references reviewed and updated. RT4: added approved indication for HR-positive, HER2-low or HER2-ultralow breast cancer. RT4: added newly approved indication for use in combination with pertuzumab as first-line therapy for HER2-positive breast cancer.</p>	01/2026