Evolent Clinical Guideline 3035 for Enhertu™ (fam-trastuzumab deruxtecan-nxki)

Guideline Number:	Applicable Codes	
Evolent_CG_3035		
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Original Date:	**Last Revised Date:**	**Implementation Date:**
February 2020	March 2025	March 2025

TABLE OF CONTENTS

STATEMENT

Purpose

To define and describe the accepted indications for Enhertu (fam-trastuzumab deruxtecan-nxki) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

HER-2 Positive Metastatic/Recurrent Breast Cancer

- The member has recurrent or metastatic HER2 positive breast cancer AND Enhertu (fam-trastuzumab deruxtecan-nxki) will be used as monotherapy for any of the following clinical settings:
    - As first line therapy, for recurrent/metastatic disease, in a member who has experienced disease progression within 6 months of neoadjuvant/adjuvant treatment or within 12 months of extended adjuvant treatment with an anti-HER2 containing regimen [e.g., Herceptin (trastuzumab)/trastuzumab biosimilar +/- Perjeta (pertuzumab) +/- chemotherapy].
    - As second line/subsequent therapy in the metastatic setting.

HER-2 LOW Metastatic Breast Cancer

- Enhertu may be used as a single agent in metastatic HER-2 LOW breast cancer. HER-2 LOW is defined as one of the following: HER-2 IHC staining 2+ with a negative ISH/FISH, or HER-2 by IHC of 1+ (in which case FISH/ISH is not required); the above definition is regardless of Hormone Receptor status. Member should have received one or more lines of systemic chemotherapy for metastatic breast cancer excluding hormonal agents [for example Faslodex (fulvestrant) or CDK 4/6 inhibitors [e.g., Ibrance (Palbociclib), Kisqali (ribociclib), Verzenio (abemaciclib)].

(HR)-positive, HER-2 LOW or HER-2 ULTRALOW Metastatic Breast Cancer

- Enhertu (fam-trastuzumab deruxtecan-nxki) may be used as a single agent in adult members with hormone receptor (HR)-positive, HER-2 low (IHC 1+ or IHC 2+/ISH-) or HER-2 ultralow (IHC 0 with membrane staining) breast cancer that has progressed on one or more endocrine therapies in the metastatic setting.

HER-2 positive, Metastatic/Recurrent Gastric, Esophageal and GE Junction Adenocarcinoma

- The member has metastatic/recurrent, HER-2 positive gastric, esophageal or GE Junction adenocarcinoma AND
- The member has experienced disease progression on a prior regimen that included trastuzumab/trastuzumab biosimilar AND
- Enhertu (fam-trastuzumab deruxtecan-nxki) will be used as a single agent.

Non-Small Cell Lung Cancer (NSCLC)

- The member has unresectable or metastatic non-small cell lung cancer with an activating ERBB-2/HER-2 mutation and Enhertu (fam-trastuzumab deruxtecan-nxki) may be used following at least one prior systemic therapy.

Solid Tumors

- Enhertu (fam-trastuzumab deruxtecan-nxki) may be used in adult members with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

CONTRAINDICATIONS/WARNINGS

- None

EXCLUSION CRITERIA

- Enhertu (fam-trastuzumab deruxtecan-nxki) is being used during or after disease progression with the same regimen.
- For HER-2 positive Gastric, Esophageal and GE Junction adenocarcinoma: Use of Enhertu (fam-trastuzumab deruxtecan-nxki) without receiving prior trastuzumab treatment.
- Dosing exceeds single dose limit of Enhertu (fam-trastuzumab deruxtecan-nxki) 5.4 mg/kg (for breast cancer, NSCLC, and solid tumors) and 6.4 mg/kg (for gastric, esophageal, or GE junction cancer).
- Investigational use of Enhertu (fam-trastuzumab deruxtecan-nxki) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:

- Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
- Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
- Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definition of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
- Whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J9358 - Injection, fam-trastuzumab deruxtecan-nxki, 1 mg

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary

March 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1379 Enhertu (fam-trastuzumab deruxtecan-nxki) • Added new indication • Updated exclusion criteria • Updated references
September 2024	• Removed “HER-2 overexpression” statement in exclusion criteria • Updated references
May 2024	• Added “solid tumors” to indication section • Added new references

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Bardia A, et al; DESTINY-Breast06 Trial Investigators. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. *N Engl J Med*. 2024 Dec 5;391(22):2110-2122. doi: 10.1056/NEJMoa2407086.
2. Meric-Bernstam F, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. *J Clin Oncol*. 2024 Jan 1;42(1):47-58. doi: 10.1200/JCO.23.02005.
3. Smit EF, et al. Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial. *Lancet Oncol*. 2024 Apr; 25(4):439-454. doi: 10.1016/S1470-2045(24)00064-0.
4. Li BT, Smit EF, Goto Y, Nakagawa K, Udagawa H, et al; DESTINY-Lung01 Trial Investigators. Trastuzumab Deruxtecan in *HER2*-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med*. 2022;386(3):241-251. doi: 10.1056/NEJMoa2112431.
5. Pratap K, et al. Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer (mCRC): Primary results from the multicenter, randomized, phase 2 DESTINY-CRC02 study. *J Clin Oncol*. 2023 May 31; 41(16): 3501. doi:10.1200/JCO.2023.41.16_suppl.3501.
6. Modi S, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med*. 2022 Jul 7;387(1):9-20. doi: 10.1056/NEJMoa2203690.
7. Shitara K, et al; DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med*. 2020 Jun 18;382(25):2419-2430. doi: 10.1056/NEJMoa2004413.
8. Modi S, et al; DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med*. 2020 Feb 13;382(7):610-621. doi: 10.1056/NEJMoa1914510.
9. Cortés J, et al; DESTINY-Breast03 Trial Investigators. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med*. 2022 Mar 24;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
10. Enhertu prescribing information. Daiichi Sankyo Inc. Basking Ridge, NJ 2025.
11. Clinical Pharmacology Elsevier Gold Standard 2025.
12. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2025.
13. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2025.
14. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2025.
15. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
16. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
17. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.