

## Corporate Medical Policy

### Fam-Trastuzumab Deruxtecan-nxki (Enhertu<sup>®</sup>)

<b>File Name:</b>	fam_trastuzumab_deruxtecan_enhertu
<b>Origination:</b>	2/2020
<b>Last CAP Review:</b>	4/2020
<b>Next CAP Review:</b>	4/2021
<b>Last Review:</b>	4/2020

#### Description of Procedure or Service

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Fam-trastuzumab deruxtecan-nxki (Enhertu) is a HER2-directed antibody and topoisomerase inhibitor conjugate that is indicated for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

HER2-positive breast cancer is a breast cancer that tests positive for the protein called human epidermal growth factor receptor 2 (HER2), which promotes the growth of cancer cells. In the presence of too many HER2 proteins, cancer cells are fast multiplying. Immunohistochemistry (IHC) is the test used to count the number of HER2 receptors. Cancer cells with more than two *HER2* gene copies or too many HER2 receptors are called "HER2 positive." Breast cancer accounts for nearly 1 in 3 cancer diagnoses in women in the U.S., and it is the most common cancer after non-melanoma skin cancer among women. After lung cancer, breast cancer ranks second for cancer mortality. Metastatic breast cancer has a poor prognosis. In a cohort of 3,524 women with de novo Stage IV or relapsed breast cancer diagnosed between 1992 and 2007, the median overall survival was 39.2 months among patients with de novo Stage IV and 27.2 months among patients with relapsed disease (estimates independent of HER2 status). Factors associated with reduced survival for patients with metastatic breast cancer include age  $\geq 50$  years, visceral disease, shorter disease-free interval, negative hormone receptor status, and HER2-positive status. Systemic treatment for metastatic breast cancer is mainly palliative. The goals of treatment are to prolong survival, alleviate symptoms, and maintain or improve quality of life. Treatment is primarily with chemotherapeutic and other anti-tumor drugs. The National Comprehensive Cancer Network (NCCN) guidelines on treatment of metastatic breast cancer include specific recommendations for first-line treatment of HER2-positive metastatic breast cancer. All recommended treatment regimens in the guidelines include trastuzumab. Recommended agents that are used as monotherapy or in combination with trastuzumab are paclitaxel, docetaxel, vinorelbine, capecitabine, and carboplatin.

Fam-trastuzumab deruxtecan-nxki (Enhertu) is an antibody-drug conjugate (ADC) composed of a humanized anti-HER2 monoclonal antibody, a topoisomerase inhibitor, and a cleavable linker. It was approved by the U.S. Food and Drug Administration (FDA) in December 2019 for the treatment of unresectable or metastatic HER2-positive breast cancer. Fam-trastuzumab deruxtecan binds to HER2 on tumor cells, then is internalized and intracellular linker cleavage occurs via lysosomal enzymes. Upon release, the membrane permeable topoisomerase inhibitor causes DNA damage and apoptotic cell death.

This policy addresses fam-trastuzumab deruxtecan-nxki (Enhertu). Enhertu is not interchangeable with trastuzumab (Herceptin) or ado-trastuzumab emtansine (Kadcyla). Trastuzumab and ado-trastuzumab emtansine are each addressed separately in individual policies as referenced below.

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## **Related Medical Policies:**

Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER-2 Positive Malignancies  
Pertuzumab for Treatment of Malignancies  
Trastuzumab

## **Related Pharmacy Policies:**

Tykerb<sup>®</sup> (Lapatinib)

*\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.*

## **Policy**

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**BCBSNC will provide coverage for fam-trastuzumab deruxtecan-nxki (Enhertu<sup>®</sup>) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

## **Benefits Application**

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## **When Fam-Trastuzumab Deruxtecan-nxki (Enhertu) is covered**

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### **Initial Therapy**

Fam-trastuzumab deruxtecan-nxki (Enhertu) is considered medically necessary for the treatment of adult patients with HER2-positive breast cancer when the following criteria are met:

- The patient has unresectable or metastatic disease; and
- The patient has received prior treatment with two or more anti-HER2-based regimens in the metastatic setting (e.g., ado-trastuzumab, trastuzumab, pertuzumab, lapatinib).

Initial authorization: 12 months

### **Continuation Therapy**

Continuation of treatment with fam-trastuzumab deruxtecan-nxki (Enhertu) beyond 12 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of unresectable or metastatic HER2-positive breast cancer when the following criteria are met:

1. The patient is currently receiving fam-trastuzumab deruxtecan and continues to meet initial criteria; and
2. The patient has continued clinical benefit on fam-trastuzumab deruxtecan therapy as demonstrated by tumor response or lack of disease progression, and an acceptable toxicity profile.

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Use of fam-trastuzumab deruxtecan-nxki (Enhertu) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, (see Policy Guidelines); **OR**
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

## **When Fam-Trastuzumab Deruxtecan-nxki (Enhertu) is not covered**

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Fam-trastuzumab deruxtecan-nxki (Enhertu) is considered **investigational** and therefore not covered when the above criteria are not met.

Fam-trastuzumab deruxtecan-nxki (Enhertu) is considered investigational when used for:

1. Non-cancer indications; **OR**
2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under “When Fam-Trastuzumab Deruxtecan-nxki (Enhertu) is covered.”

## **Policy Guidelines**

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### Dosing and Administration

The recommended dose of Enhertu is 5.4 mg/kg administered as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Enhertu is not to be substituted for or with trastuzumab (Herceptin) or ado-trastuzumab emtansine (Kadcyla).

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with Enhertu. Patients should be monitored and promptly investigated for signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Enhertu should be permanently discontinued in all patients with Grade 2 or higher ILD/pneumonitis. Other warnings and precautions include neutropenia and left ventricular dysfunction.

According to the manufacturer’s safety information for Enhertu, the most common adverse reactions ( $\geq 20\%$  incidence) include nausea, fatigue, vomiting, hair loss, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, and thrombocytopenia.

### Evidence Summary

The efficacy of fam-trastuzumab deruxtecan-nxki was evaluated in a multicenter, single-arm, phase 2 clinical trial (DESTINY-Breast01; NCT03248492) that enrolled 184 adult female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients with a history of treated interstitial lung disease (ILD) or current ILD at screening were excluded from the trial. In addition, patients were

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excluded who had untreated or symptomatic brain metastases. The median number of prior cancer regimens in the locally advanced/metastatic setting was five (range, 2 to 17), and all patients received prior treatment with trastuzumab and ado-trastuzumab emtansine, and 66% had prior pertuzumab. In the trial, patients received fam-trastuzumab deruxtecan 5.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. The median treatment duration was 10.0 months (range, 0.7 to 20.5 months), and the median duration of follow-up was 11.1 months (range, 0.7 to 19.9 months). The primary efficacy endpoint was confirmed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which was 60.9% (95% CI, 53.4% to 68.0%), including a 6.0% complete response rate (CR) and 54.9% partial response rate (PR). Other key secondary endpoints included duration of response and progression-free survival. The median duration of response was 14.8 months (95% CI, 13.8 to 16.9).

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), “Investigational (Experimental) Services.”

Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: J9358, S0353, S0354*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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Daiichi Sankyo, Inc. Enhertu (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Highlights of prescribing information. December 2019. Available at: <https://dsi.com/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true>. Last accessed February 2020.

U.S. Food and Drug Administration. FDA approves new treatment option for patients with HER2-positive breast cancer who have progressed on available therapies. December 20, 2019. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-option-patients-her2-positive-breast-cancer-who-have-progressed-available>. Last accessed February 2020.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Breast Cancer, version 2.2020. Revised February 5, 2020. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). Last accessed February 2020.

Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382:610-21. Available at: <https://www-nejm-org.libproxy.lib.unc.edu/doi/pdf/10.1056/NEJMoa1914510?articleTools=true>. Last accessed February 2020.

Medical Director review 2/2020

Specialty Matched Consultant Advisory Panel 4/2020

## Policy Implementation/Update Information

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- 2/25/20 New policy developed. Enhertu is considered medically necessary for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer when specified medical criteria and guidelines are met. Added HCPCS codes C9399, J3490, J3590, J9999, S0353, and S0354 to Billing/Coding section. References added. Medical Director review 2/2020. (krc)
- 6/9/20 Specialty Matched Consultant Advisory Panel review 4/15/2020. No change to policy statements. (krc)
- 6/30/20 Added HCPCS code J9358 to Billing/Coding section effective 7/1/2020 and deleted code C9399, J3490, J3590, and J9999 termed 6/30/2020. (krc)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.