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Online Article

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IN BRIEF

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Fam-trastuzumab deruxtecan-nxki (*Enhertu* – Daiichi Sankyo/AstraZeneca), which received accelerated approval by the FDA in 2019 for treatment of **HER2-positive** breast cancer based on its rate and duration of response,[1] has been granted regular approval for treatment of adults with unresectable or metastatic HER2-positive breast cancer who received a prior anti-HER2-based regimen in the metastatic setting or in the neoadjuvant or adjuvant setting and developed recurrence during or within 6 months of completing treatment.

Fam-trastuzumab deruxtecan has also been approved by the FDA for treatment of unresectable or metastatic **HER2-low** breast cancer in patients who received prior chemotherapy for metastatic disease or who developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. It is the first HER2-directed therapy to be approved for patients with HER2-low metastatic breast cancer.

Pronunciation Key

Fam-trastuzumab deruxtecan-nxki: fam tras tooz' ue mab der" ux tee' kan
***Enhertu*:** en her' too

The four-letter suffix -nxki has no pronunciation or meaning; such suffixes are added to biologic drugs to distinguish reference products from their biosimilars.

STANDARD TREATMENT — Both the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend a combination of the anti-HER2 monoclonal antibodies trastuzumab *(Herceptin)* and pertuzumab *(Perjeta)* plus a taxane for first-line treatment of most patients with advanced **HER2-positive** breast cancer. NCCN and ASCO guidelines were recently updated to include fam-trastuzumab deruxtecan as a preferred second-line option.[2,3]

About 60% of **HER2-negative** metastatic breast cancers express low levels of HER2. NCCN guidelines recommend fam-trastuzumab as a preferred systemic treatment option for patients with unresectable or metastatic HER2-low (immunohistochemical [IHC] score of 1+ or IHC score of 2+ and a negative result on *in situ* hybridization [ISH-]) breast cancer. HER2-low was previously classified as HER2-negative.[4]

MECHANISM OF ACTION — HER2, a transmembrane receptor protein involved in normal cell growth, is overexpressed in about 20% of breast cancers. Amplification and/or overexpression of HER2 is associated with more aggressive disease and reduced survival. *Enhertu* contains the humanized anti-HER2 monoclonal antibody fam-trastuzumab covalently linked to a topoisomerase I inhibitor payload. Fam-trastuzumab binds to HER2 on tumor cells and delivers DXd, resulting in apoptosis and cell death.

CLINICAL STUDIES — Regular FDA approval of fam-trastuzumab deruxtecan for **HER2-positive** breast cancer was based on the results of an open-label trial (DESTINY-Breast03) in 524 patients with unresectable or metastatic HER2-positive breast cancer that had progressed during or after treatment with trastuzumab and a taxane. Patients were randomized to receive fam-trastuzumab deruxtecan 5.4 mg/kg or trastuzumab emtansine 3.6 mg/kg IV every 3 weeks. Median progression-free survival (PFS) was not reached with fam-trastuzumab deruxtecan and was 6.8 months with trastuzumab emtansine. At 12 months, median PFS was 75.8% with fam-trastuzumab deruxtecan and 34.1% with trastuzumab emtansine.[5]

FDA approval of fam-trastuzumab deruxtecan for **HER2-low** breast cancer was based on the results of an open-label trial (DESTINY-Breast04) in 557 patients with unresectable or metastatic HER2-low breast cancer who received 1-2 prior lines of chemotherapy and were randomized to receive fam-trastuzumab deruxtecan (5.4 mg/kg IV once every 3 weeks) or investigator-selected chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). About 89% of patients had hormone receptor-positive disease; median PFS in such patients was 10.1 months with fam-trastuzumab deruxtecan and 5.4 months with investigator-selected chemotherapy and median overall survival was 23.9 months with fam-trastuzumab deruxtecan and 17.5 months with chemotherapy; these differences were statistically significant. Among the overall patient population, median PFS was 9.9 months in the fam-trastuzumab deruxtecan group and 5.1 months in the chemotherapy group and overall survival was 23.4 months with fam-trastuzumab deruxtecan and 16.8 months with chemotherapy; these differences were also statistically significant.[6]

ADVERSE EFFECTS – Fam-trastuzumab deruxtecan can cause nausea, myelosuppression, decreased hemoglobin levels, vomiting, alopecia, increases in liver enzymes, fatigue, and musculoskeletal pain. The label contains a boxed warning about the risks of interstitial lung disease and pneumonitis associated with use of the drug.

DOSAGE, ADMINISTRATION, AND COST – The recommended dosage of fam-trastuzumab deruxtecan is 5.4 mg/kg given intravenously once every 3 weeks until disease progression or unacceptable toxicity occurs. The labeling specifies a number of dosage adjustments that should be made if adverse effects occur. One dose of *Enhertu* for a 70-kg patient costs about $9700.[7]

CONCLUSION – Fam-trastuzumab deruxtecan *(Enhertu)* is FDA-approved for treatment of unresectable or metastatic HER2-positive or HER2-low breast cancer. In clinical trials, the drug extended progression-free survival in previously treated patients. Fam-trastuzumab is now a preferred option for second-line treatment of unresectable or metastatic HER2-positive breast cancer and a preferred systemic treatment option for unresectable or metastatic HER2-low breast cancer. ■

1. Two drugs for advanced HER2-positive breast cancer (Enhertu and Tukysa). Med Lett Drugs Ther 2020; 62:182.
2. SH Giordano et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update summary. J Oncol Pract 2018; 14:501.
3. NCCN. NCCN guidelines for patients. Metastatic breast cancer, 2022. Available at: https://bit.ly/415nIOv. Accessed March 30, 2023.
4. P Tarantino et al. HER2-low breast cancer: pathological and clinical landscape. J Clin Oncol 2020; 38:1951.
5. J Cortes et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 2022; 386:1143.
6. S Modi et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022; 387:9.
7. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. March 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/drug-pricing-policy.

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