FDA Approves Enhertu for HER2-Ultralow Metastatic Breast Cancer

The antibody-drug conjugate improved progression-free survival for patients previously treated with hormone therapy.

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On January 27, the Food and Drug Administration (FDA) expanded the approval of Enhertu (fam-trastuzumab deruxtecan) to cover people with hormone-positive, HER2-ultralow advanced breast cancer following endocrine therapy.

Enhertu, from AstraZeneca and Daiichi Sankyo, is an antibody-drug conjugate (ADC) that delivers strong chemotherapy directly to cancer cells. It combines the monoclonal antibody trastuzumab (Herceptin), designed to target HER2—a receptor for a protein that promotes cell growth—with a topoisomerase inhibitor drug as a payload. Last week, the FDA approved a new ADC from the same partnership, Datroway (datopotamab deruxtecan), which consists of an antibody targeting TROP-2 with the same payload, for HER2-negative metastatic breast cancer.

The FDA initially approved Enhertu in December 2019 for inoperable or metastatic breast cancer with high HER2 expression. Approval was extended to patients with HER2-low breast cancer in August 2022, and now the indication has been further expanded to include those with the lowest HER2 expression.

“We are excited to see more treatment options for these patients which enable more personalized care,” Krissa Smith, Vice President for Education at Susan G. Komen, said in a company news release. “It is critical for patients to understand the HER2 status of their metastatic breast cancer to help them make informed treatment decisions. Patients with tumors that are HER2-low or HER2-ultralow now have more options to consider with their healthcare team.”

Breast cancer is classified by the type of receptors on tumors. Most have estrogen or progesterone receptors that make them treatable with hormone (endocrine) therapy, classified as HR-positive. Around 15% to 20% of breast tumors have high expression of HER2, classified as HER2-positive. However, a majority of tumors traditionally classified as HER2-negative actually have some HER2 receptors, now classified as HER2-low, and perhaps 25% are HER2-ultralow. Triple-negative breast cancer doesn’t express any of these receptors and is harder to treat.

The expanded approval is supported by results from the Phase III DESTINY-Breast06 trial, presented last year at the American Society of Clinical Oncology annual meeting and published in The New England Journal of Medicine. This study focused on previously treated patients with HR-positive metastatic breast cancer who traditionally would have been classified as HER2-negative. It included 713 participants with HER2-low tumors (a score of +1 or +2) and 153 with HER-ultralow tumors (a score of 0 but detectable). They were randomly assigned to receive Enhertu by IV infusion once every three weeks or standard chemotherapy.

Enhertu demonstrated a “statistically significant and clinically meaningful” improvement in progression-free survival compared with chemotherapy, reducing the risk of progression or death by 36%. Median progression-free survival times were 13.2 months versus 8.1 months, respectively. Results were consistent in an exploratory analysis looking at just the HER2-ultralow group.

These results “represent a potential shift in how we classify and treat metastatic breast cancer,” senior study investigator Giuseppe Curigliano, MD, PhD, of the University of Milan, said at the ASCO meeting.

Enhertu is generally safe, though side effects are common. The most frequently reported adverse reactions are decreased white blood cell counts, decreased hemoglobin (anemia), decreased platelet count, nausea, vomiting, diarrhea, constipation, decreased appetite, fatigue, hair loss, musculoskeletal pain, elevated liver enzymes and decreased blood potassium. The product label includes a warning about lung inflammation (interstitial lung disease and pneumonitis). Enhertu can cause fetal harm if used during pregnancy.

“Endocrine therapy is typically used in the initial treatment of HR-positive metastatic breast cancer, and following progression, subsequent chemotherapy is associated with poor outcomes,” said lead study investigator Aditya Bardia, MD, MPH, of UCLA Health Jonsson Comprehensive Cancer Center. “With a median progression-free survival exceeding one year and a response rate of more than 60%, trastuzumab deruxtecan offers a potential new standard of care for patients with HR-positive, HER2-low or HER2-ultralow metastatic breast cancer following endocrine therapy.”

Click here for full prescribing information for Enhertu.

Click here for more news about breast cancer.

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