Enhertu Works for HER2-Low Metastatic Breast Cancer Too

The antibody-drug conjugate improved progression-free and overall survival for patients with low HER2 expression on breast tumors.

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UPDATE: On August 5, the Food and Drug Administration approved Enhertu for HER2-low advanced breast cancer based on the DESTINY-Breast04 trial results.

The antibody-drug conjugate Enhertu (fam-trastuzumab deruxtecan), which was initially approved for the treatment of metastatic breast cancer with high HER2 expression, also works for people with low HER2 levels, according to research presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting and published in The New England Journal of Medicine.

In the Phase III DESTINY-Breast04 trial, Enhertu reduced the risk of disease progression or death—known as progression-free survival (PFS)—by 50% compared with standard chemotherapy, and it also significantly improved overall survival for HER2-low patients. The presentation earned a standing ovation, and some experts are calling the results "practice changing."

"Our study shows that trastuzumab deruxtecan may be a new and highly effective targeted therapy option available for this newly defined patient population," lead investigator Shanu Modi, MD, of Memorial Sloan Kettering Cancer Center, said in an ASCO news release. "It is important for patients to know what level of HER2 their cancer expresses, not just whether it's positive or negative, especially as HER2-low status can be determined using commonly available tests."

Breast cancer is classified by the type of receptors expressed on tumor cells. Most breast tumors have estrogen or progesterone receptors that make them suitable for hormone therapy and are classified as HR-positive. Around 15% to 20% of tumors have a high level of HER2, a receptor for a protein that promotes cell growth, and are classified as HER2-positive. However, some 60% of patient who were traditionally classified as HER2-negative actually have some HER2 receptors, a group now defined as HER2-low. Triple-negative breast cancer doesn't express any of these receptors and is harder to treat.

"This trial's findings show that trastuzumab deruxtecan doubles progression-free survival compared to chemotherapy alone in patients with HR-positive, HER2-low breast cancer," said ASCO expert Jane Lowe Meisel, MD, of Emory University's Winship Cancer Institute. "By effectively

creating a new category of breast cancer, HER2-low, this trial will redefine how we classify breast cancer and will significantly expand the population of patients who can benefit from HER2-targeted therapy."

The DESTINY-Breast04 trial (NCT03734029) included 557 patients with HER2-low metastatic breast cancer in North America, Europe and Asia who had received one or two previous lines of chemotherapy. Almost all were women, about half were white and the median age was approximately 56 years. Most (89%) had HR-positive tumors. The participants were randomly assigned to receive Enhertu administered by IV infusion every three weeks or their physician's choice of chemotherapy.

Enhertu, from Daiichi Sankyo and AstraZeneca, is an antibody-drug conjugate, a new type of treatment that uses antibodies to carry toxic chemotherapy directly to tumors. Enhertu combines the monoclonal antibody trastuzumab (Herceptin), designed to target HER-2, with a topoisomerase inhibitor drug as a payload. In December 2019, the Food and Drug Administration (FDA) granted accelerated approval of Enhertu for the treatment of inoperable or metastatic HER2-positive breast cancer. It was later approved for HER2-positive stomach cancer.

Focusing on the HR-positive patients (the study's primary endpoint), the median progression-free survival time was 10.1 months in the Enhertu group compared with 5.4 months in the chemotherapy group, reflecting a 49% reduction in the risk of disease progression or death. The median overall survival times were 23.9 months versus 17.5 months, respectively, a 36% reduction. Looking at all patients together, the median PFS times were 9.9 months with Enhertu versus 5.1 months with chemotherapy, a 50% reduction. Median overall survival times were 23.4 months and 16.8 months, respectively, again a 36% reduction.

Enhertu was generally safe, but side effects were common in both treatment groups. More than half of patients (53%) assigned to Enhertu and 67% of those who used chemotherapy experienced severe (Grade 3 or higher) adverse events. Side effects were generally similar in the two groups—including nausea, fatigue, hair loss and blood cell depletion—but 12% of Enhertu recipients developed drug-related interstitial lung disease or pneumonitis (lung inflammation).

If the study results are confirmed, the effectiveness of Enhertu for HER2-low metastatic breast cancer could open up a new avenue of treatment for thousands of patients.

"The results of this trial are practice-changing and redefine how a large population of patients with metastatic disease will be treated," Modi said in a Memorial Sloan Kettering press release. "Although this trial focused on patients with breast cancer, we believe that these results could also have implications for the future treatment of people with other types of cancer that express HER2 at low levels."

Click here to read the study abstract.

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