Enhertu Improves Survival for Women with HER2-Positive Breast Cancer

Research also showed that treatment before surgery benefits patients with HER2-low breast cancer.

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Enhertu (fam-trastuzumab deruxtecan) improved survival for women with previously treated HER2-positive metastatic breast cancer, according to two studies presented this week at the San Antonio Breast Cancer Symposium. A third study showed that neoadjuvant, or pre-surgery, treatment for people with HER2-low breast cancer yielded good response rates.

Breast cancer is classified by the type of receptors expressed on tumor cells. 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.

Enhertu is a new antibody-drug conjugate (ADC), a type of treatment that uses antibodies to carry toxic chemotherapy directly to tumors. It combines the monoclonal antibody trastuzumab (Herceptin and generic equivalents), 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. This August, the FDA also approved Enhertu for HER2-low advanced breast cancer.

Enhertu Versus Kadcyla

In the first study, Sara Hurvitz, MD, of the Jonsson Comprehensive Cancer Center at the University of California Los Angeles, and colleagues compared the safety and efficacy of Enhertu versus the older ADC Kadcyla (ado-trastuzumab emtansine) in people with HER2-positive metastatic breast cancer that had progressed during or after first-line treatment.

The DESTINY-Breast03 trial previously showed that people treated with Enhertu had significantly longer progression-free survival (PFS) compared to those who received Kadcyla. PFS is a measure of how long patients survive without their cancer worsening. The new interim results show that Enhertu also improves overall survival.

“While PFS benefits are important, the gold standard measure of efficacy is overall survival,”

Hurvitz said in an American Association for Cancer Research (AACR) press release.

After a median follow-up period of just over two years, people treated with Enhertu had a 36% lower risk of death than those who received Kadcyla, according to AACR. At one year, 94% of Enhertu recipients were still alive, compared with 86% of Kadcyla recipients. At two years, the corresponding overall survival rates were 77% and 70%. PFS rates also continue to favor Enhertu. Overall response rates (tumor shrinkage) were 79% with Enhertu versus 35% with Kadcyla.

Both treatments were generally safe, but side effects were common: 56% of Enhertu recipients and 52% of Kadcyla recipients experienced severe (Grade 3 or higher) adverse events. Drug-related interstitial lung disease or pneumonitis was more common in the Enhertu group (15% versus 3%).

“With this overall survival analysis, we can confirm that the previously demonstrated benefit from [Enhertu] in PFS improvement transforms into a statistically significant improvement in overall survival, a substantial advantage for our patients,” Hurvitz said.

Enhertu After Kadcyla

In the second study, Ian Krop, MD, PhD, of Yale Cancer Center, presented results from the DESTINY-Breast02 trial, which compared Enhertu versus a combination chemotherapy regimen for people with HER2-positive metastatic breast cancer who had progressed during or after treatment with Kadcyla. The comparator regimen consisted of capecitabine plus either trastuzumab or lapatinib (Tykerb).

This Phase III trial was designed to confirm the findings of the smaller Phase II DESTINY-Breast01 study, which led to Enhertu’s accelerated approval.

“In addition to confirming the favorable benefit-to-risk profile of [Enhertu] in this population, this research was also important to evaluate the efficacy of one antibody-drug conjugate, [Enhertu], in patients whose cancer has already progressed on another antibody-drug conjugate, [Kadcyla,” Krop said in another AACR press release. “This is the first randomized trial to ask this important question.”

Enhertu led to longer survival and higher response rates than the capecitabine-based regimens in this third-line setting, according to AACR. The median overall survival times were 39.2 months with Enhertu versus 26.5 months with the chemotherapy regimen. The median PFS times were 17.8 months and 6.9 months, respectively, reflecting a 64% lower risk of disease progression. The corresponding overall response rates were 70% and 29%.

Adverse events were generally consistent with prior studies, according to Krop. About 10% of Enhertu recipients developed interstitial lung disease, which led to two deaths.

“The results of DESTINY-Breast02 confirm the findings of DESTINY-Breast01, demonstrating high levels of efficacy of [Enhertu] in patients with HER2-positive metastatic breast cancer previously treated with [Kadcyla],” Krop said. “Furthermore, they extend these findings, demonstrating that

[Enhertu] is not only highly active, but also superior to conventional chemotherapy-based regimens in this patient population."

Given the good results seen so far for Enhertu as a follow-up treatment for patients who have progressed despite prior therapies, the drug is now being evaluated as a first-line therapy for people with metastatic breast cancer and those with early-stage cancer.

Enhertu for HER2-Low Breast Cancer

The Phase III DESTINY-Breast04 trial previously showed that Enhertu improved progression-free survival by 50% and significantly improved overall survival compared with standard chemotherapy for patients with HER2-low metastatic breast cancer.

The Phase II TRIO-US B-12 TALENT trial, presented at the conference, evaluated Enhertu as neoadjuvant therapy for people with earlier localized, hormone receptor-positive, HER2-low breast cancer. People with high-risk localized breast cancer often receive neoadjuvant chemotherapy to shrink tumors as much as possible prior to surgery, but the response rate is low for those with hormone receptor-positive cancer.

"While [Enhertu] demonstrated impressive efficacy in metastatic HER2-low breast cancer, to date, no trial has evaluated [Enhertu] in localized, early-stage, potentially curable HER2-low breast cancer, which led us to design this neoadjuvant clinical trial," Hurvitz, one of the study co-investigators, said in a third AACR press release.

Study participants received neoadjuvant Enhertu either alone or in combination with the aromatase inhibitor anastrozole. According to the AACR release, 17 patients had completed eight planned cycles of Enhertu alone, and 16 had completed six planned cycles of Enhertu plus anastrozole, at the time of first data cutoff on October 5. Some patients were still on treatment, had not yet received scans or had not yet undergone surgery, so the results are not considered mature.

According to data available at the time of the AACR press release, the overall response rates were 75% in the Enhertu-only group and 63% in the Enhertu plus anastrozole group. However, just one person (5%) in the Enhertu monotherapy group and none in the combination therapy group experienced pathologic complete response, defined as complete tumor regression and no lymph node involvement at the time of surgery, which was the study's primary endpoint.

Treatment was generally safe. The most common treatment-related severe adverse events were low potassium, diarrhea, neutropenia, fatigue, headache, vomiting dehydration, and nausea, each of which occurred in less than 6% of patients. One patient developed Grade 2 interstitial lung disease, which resolved after treatment discontinuation.

"The study demonstrated that [Enhertu] was relatively safe in HER2-low, hormone receptor-positive, localized breast cancer," said study co-investigator Aditya Bardia, MD, MPH, of Mass General Cancer Center. "It provides translational framework for future studies, including

combination regimens in the neoadjuvant setting to further improve clinical outcomes.”

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