Enhertu and Trodelvy Show Promise for First-Line Metastatic Breast Cancer Treatment

The two antibody-drug conjugates could offer new options for women receiving their first treatment for advanced disease.

July 31, 2025 By Liz Highleyman

Two antibody-drug conjugates, Enhertu (trastuzumab deruxtecan) and Trodelvy (sacituzumab govitecan), delayed disease progression for women receiving initial treatment for locally advanced or metastatic breast cancer, according to a pair of Phase III studies presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting.

First-line treatment with Enhertu plus Perjeta (pertuzumab) reduced the risk of disease progression or death by 44% for patients with HER2-positive advanced breast cancer, while Trodelvy plus Keytruda (pembrolizumab) lowered the risk by 35% compared with Keytruda plus chemotherapy for those with advanced triple-negative breast cancer. The median duration of response exceeded three years in the Enhertu trial and one year in the Trodelvy study.

Breast cancer is classified by the types of receptors it expresses. A majority of breast tumors carry estrogen or progesterone receptors (known as HR-positive) and can be treated with hormone therapy. About 20% express the HER2 receptor and can be treated with HER2 inhibitors such as Herceptin (trastuzumab). Triple-negative breast cancer, accounting for about 10% of cases, does not carry any of these receptors and is harder to treat.

Traditional chemotherapy kills both malignant and healthy cells, leading to adverse effects. Enhertu, from AstraZeneca and Daiichi Sankyo, and Trodelvy, from Gilead Sciences, are antibody-drug conjugates that use monoclonal antibodies to deliver strong chemotherapy directly to tumors, helping to minimize side effects.

DESTINY-Breast09

The DESTINY-Breast09 trial evaluated Enhertu plus Perjeta as initial treatment for HER2-positive locally advanced or metastatic breast cancer. The Food and Drug Administration (FDA) initially approved Enhertu in 2019 for previously treated inoperable or metastatic breast cancer with high HER2 expression. Approval was extended to patients with HER2-low breast cancer in 2022 and to

those with ultralow HER2 expression this year.

In this study, 770 participants were randomly assigned to receive Enhertu plus Perjeta or standard first-line therapy consisting of taxane chemotherapy plus Herceptin and Perjeta. This treatment, known as THP, has long been the standard of care, but most patients experience disease progression within two years. (Another group, not presented, received Enhertu alone.)

Just over half already had metastatic breast cancer at the time of diagnosis, while 48% experienced recurrence after treatment for early-stage disease. A majority were younger than 65, and about half were enrolled in Asia.

After a median follow-up of 29 months, those who received Enhertu plus Perjeta had a 44% lower risk of disease progression or death. The median progression-free survival time was 40.7 months in the Enhertu plus Perjeta group and 26.9 months in the THP group. At two years, 70% of patients in the Enhertu plus Perjeta group were still alive without further progression, compared with 52% in the THP group. Objective response rates, indicating tumor shrinkage, were similar at 85% and 79%, respectively, but Enhertu plus Perjeta recipients were more likely to see a complete response (15% versus 9%). The median duration of response was 39.2 months versus 26.4, respectively. Overall survival data are not yet mature, but there was a trend toward improvement in the Enhertu plus Perjeta group.

Treatment was generally safe, but nearly two thirds of patients in both groups experienced severe (Grade 3 or higher) side effects. Severe nausea, vomiting and diarrhea were more common in the Enhertu plus Perjeta group. About 12% of Enhertu plus Perjeta recipients developed interstitial lung disease (lung inflammation); most cases were mild to moderate, but there were two deaths.

“The DESTINY-Breast09 trial has the potential to establish a new first-line standard of care for metastatic HER2-positive breast cancer, a setting which hasn’t seen significant innovation in more than a decade,” lead study author Sara Tolaney, MD, MPH, of Dana-Farber Cancer Institute, said in an ASCO news release.

ASCENT-04/KEYNOTE-D19

The ASCENT-04/KEYNOTE-D19 trial evaluated Trodelvy plus Keytruda as first-line treatment for unresectable (inoperable) locally advanced or metastatic triple-negative breast cancer that tests positive for PD-L1.

“There is a huge unmet need for new therapies for patients with triple-negative breast cancer,” Tolaney, who also led this study, said in a Dana-Farber news release. “It is important that we work toward shifting these very effective novel drugs to the first line of therapy to move the needle and improve outcomes for these patients.”

While Enhertu uses trastuzumab as the antibody vehicle to deliver chemotherapy to tumors, Trodelvy uses a monoclonal antibody targeting Trop-2, a protein found on most triple-negative breast tumors. The FDA granted accelerated approval to Trodelvy for previously treated metastatic

triple-negative breast cancer in 2020, later expanded to full approval. In 2023, approval was extended to previously treated HR-positive/HER2-negative breast cancer.

Keytruda is an immune checkpoint inhibitor that targets the PD-1 receptor on T cells. Drugs that block the interaction between PD-1 and its binding partner, PD-L1, can restore T-cell activity against cancer. People with higher PD-L1 expression on tumors often respond better to this type of treatment.

This trial enrolled 443 patients in 26 countries. A third were newly diagnosed with advanced breast cancer, and the rest had received systemic treatment for early-stage disease at least six months ago. They were randomized to receive either Trodelvy plus Keytruda or Keytruda plus chemotherapy (a taxane or gemcitabine plus carboplatin), with treatment continuing until they experienced disease progression or unacceptable side effects. Those assigned to Keytruda plus chemotherapy could cross over to receive Trodelvy if they progressed, and 43% did so.

After a median follow-up of 14 months, patients who received Trodelvy plus Keytruda had a 35% lower risk of disease progression or death than those on Keytruda plus chemotherapy, with progression-free survival times of 11.2 months versus 7.8 months. At the 12-month mark, 48% of Trodelvy plus Keytruda recipients were still alive without disease progression compared with 33% in the Keytruda plus chemotherapy group. Objective response rates were 60% versus 53%, respectively, including 13% and 8% with complete remission. The median duration of response was substantially longer with Trodelvy plus Keytruda (16.5 months versus 9.2 months). A preliminary survival analysis suggested an 11% reduction in the risk of death, but again, these data are not yet mature.

Here, too, treatment was generally safe, but side effects were common in both groups. The most frequent severe adverse events in the Trodelvy plus Keytruda group were neutropenia. or low white blood cells (43%) and diarrhea (10%). Neutropenia also exceeded 40% in the Keytruda plus chemotherapy arm.

“These results are an important advancement for patients with PD-L1-positive metastatic triple-negative breast cancer, a population for whom first-line options remain limited,” Tolaney said in a Gilead news release. “By combining sacituzumab govitecan with pembrolizumab, we’re seeing meaningful gains in progression-free survival and a promising trend in overall survival—findings that could support a new frontline standard of care for this aggressive disease.”

Gilead recently announced that Trodelvy also worked better than chemotherapy as a first-line treatment for people with locally advanced or metastatic triple-negative breast cancer without PD-L1 expression, meaning they are not eligible for Keytruda.

AstraZeneca/Daiichi Sankyo and Gilead intend to submit these new data to the FDA, which could expand the indications for Enhertu and Trodelvy to include first-line treatment for advanced breast cancer.

Taken together, these studies offer good news for women with previously untreated metastatic breast cancer, but side effects are a concern. Some experts have suggested that it might not be necessary to continue such regimens until disease progression but rather it may be feasible to use antibody-drug conjugates as part of an induction regimen followed by less intensive maintenance therapy.

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