FDA Approves Enhertu for HER2-Positive Stomach Cancer

The antibody-drug conjugate improved response rates and survival compared with chemotherapy.

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On January 15, the Food and Drug Administration (FDA) approved Enhertu (fam-trastuzumab deruxtecan) for the treatment of adults with locally advanced or metastatic HER2-positive gastric (stomach) or gastroesophageal junction cancer who previously received trastuzumab (Herceptin).

Enhertu, from Daiichi Sankyo and AstraZeneca, is an antibody-drug conjugate. The antibody, trastuzumab, targets HER2—a protein that promotes cancer cell growth—and carries a chemotherapy payload that kills cancer cells. Around 20% of breast and stomach tumors overexpress HER2. Trastuzumab alone is approved for breast and gastric cancers with high HER2 expression. Enhertu was approved for advanced HER2-positive breast cancer in December 2019.

Gastric cancer is the fifth most common cancer worldwide, but it is uncommon in the United States, with an estimated 27,600 new cases diagnosed in 2020. The gastroesophageal junction is the region where the stomach connects to the esophagus.

Gastric cancer is usually diagnosed at a late stage, and the five-year survival rate is only about 5%. The recommended first-line therapy for advanced HER2-positive gastric cancer is a combination of chemotherapy plus trastuzumab, but there are few options if disease progresses despite treatment.

Approval of Enhertu was based on findings from the Phase II DESTINY-Gastric01 trial (ClinialTrials.gov NCT03329690), which enrolled 188 patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma in Japan and South Korea, where this type of cancer is more common. About three quarters were men, and the median age was 65 years. Their cancer had progressed despite using two or more prior therapies, including trastuzumab and chemotherapy.

The 188 participants in this open-label study were randomly assigned to receive Enhertu alone, administered by IV infusion every three weeks, or the treating physician’s choice of either irinotecan or paclitaxel chemotherapy. Treatment continued until they experienced disease progression or unacceptable side effects.

The overall response rate was 40.5% (including 7.9% with complete responses) in the Enhertu group compared with 11.3% (with no complete responses) in the chemotherapy group. The median response duration was nearly three times longer in the Enhertu group (11.3 versus 3.9 months, respectively).

The median overall survival time was 12.5 months in the Enhertu group versus 8.4 months in the chemotherapy group—a 41% reduction in the risk of death. The median progression-free survival time was 5.6 months versus 3.5 months, respectively.

Earlier data presented at the American Society of Clinical Oncology (ASCO) virtual annual meeting last May and published in The New England Journal of Medicine showed that the overall survival rate at one year was 52.1% in the Enhertu group, compared with 28.9% in the chemotherapy group. The one-year progression-free survival rates were 29.9% versus 0%, respectively.

Enhertu is generally safe. The most common adverse reactions include nausea, vomiting, decreased appetite, diarrhea, constipation, fever, hair loss, elevated liver enzymes and other lab test abnormalities. Enhertu can cause depletion of red blood cells (anemia), white blood cells (neutropenia) and platelets (thrombocytopenia), which can lead to fatigue, infections and easy bleeding. Potential serious adverse events include interstitial lung disease and heart problems. Enhertu can cause fetal harm if used during pregnancy.

Enhertu received an FDA breakthrough therapy designation, intended to speed approval of treatments that address an unmet medical need, as well as orphan drug status, intended to encourage development of therapies for rare diseases.

“Patients with metastatic HER2-positive gastric cancer with progression following first-line treatment have historically faced poor outcomes, including low response to treatment and rapid disease progression,” Ronan Kelly, MD, of the Charles A. Sammons Cancer Center at Baylor University Medical Center in Dallas, said in an AstraZeneca press release. “This approval represents the first time a HER2-directed medicine has demonstrated a significant improvement in survival compared to chemotherapy for patients following initial treatment in the metastatic setting, and it has the potential to become the new standard of care for this patient population.”

An additional Phase II trial of Enhertu alone for gastric and gastroesophageal junction cancer (DESTINY-Gastric02) is currently underway. DESTINY-Gastric03 is evaluating Enhertu in combination with chemotherapy and checkpoint inhibitor immunotherapy.

In other studies reported at the ASCO meeting, Enhertu showed promise as a treatment for HER2-positive non-small-cell lung cancer, with an overall response rate of 61.9% (DESTINY-Lung01), and for HER-positive colorectal cancer, with an overall response rate of 45.3% (DESTINY-CRC01).

Click here for more information about Enhertu.

Click here to learn more about stomach cancer.