HER2-targeted therapy trastuzumab deruxtecan shows early promise in patients with non-breast and non-gastric cancers

March 25 2020

A HER2-targeted antibody-drug conjugate, fam-trastuzumab deruxtecan-nxki (Enhertu), showed signs of clinical activity in multiple non-breast/non-gastric cancer types, according to results from a phase I study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

Human epidermal growth factor receptor 2 (HER2) is a gene that can promote cancer progression when mutated or expressed at high levels. High expression levels of HER2 have been observed in many different cancer types, including breast, gastric, lung, and colorectal cancers. Several HER2-targeted therapies are approved for the treatment of HER2-overexpressing breast cancer, and one such therapy is approved for gastric cancer.

"HER2-targeted therapies have proven successful for patients with breast and gastric cancers; however, there are no approved HER2-targeted therapies available for patients with other HER2-overexpressing or HER2-mutated malignancies," said Bob Li, MD, medical oncologist at Memorial Sloan Kettering Cancer Center and senior author on the study. "Conventional therapies for these other HER2-overexpressing cancers tend to have limited efficacy and considerable side effects. Additional treatment options are urgently needed for these patients."

"Therapies that target HER2 can be selectively directed to HER2-overexpressing or HER2-mutated cancer cells, which could improve efficacy and help reduce toxicities caused by off-target effects on normal cells," said Junji Tsurutani, MD, PhD, medical oncologist at the Advanced Cancer Translational Research Institute at Showa University in Tokyo and lead author on the study. Moreover, advances in diagnostic testing have improved clinicians' ability to determine a tumor's HER2 status and have thus expanded the population of patients who might benefit from HER2-targeted therapies, explained Tsurutani.

In this phase I study, Tsurutani, Li, and colleagues tested the safety and clinical activity of the HER2-targeted antibody-drug conjugate (ADC) fam-trastuzumab deruxtecan-nxki (T-DXd) in patients with several different advanced HER2-overexpressing or HER2-mutated solid tumors. T-DXd combines a cytotoxic inhibitor of DNA replication called DXd with an antibody directed to HER2. The antibody selectively binds to HER2-expressing cancer cells, and DXd is then released into the target cell, where its inhibitory effect on DNA replication leads to cell death. DXd can also enter and kill neighboring cancer cells due to its ability to pass through cell membranes. Results published within the last year demonstrated promising antitumor activity of T-DXd in HER2-overexpressing breast and gastric cancers. In December 2019, T-DXd was granted accelerated approval by the U.S. Food and Drug Administration for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior treatments with HER2-targeted therapy in the metastatic setting.

The latest publication reports data from 60 patients with HER2-overexpressing non-breast/non-gastric solid tumors and/or HER2-mutated solid tumors. Of the 60 patients, 20 had colorectal cancer, 18 had non-small cell lung cancer (NSCLC), and 22 were classified as having "other" cancer types. "Other" cancer types included salivary gland tumors (eight patients), esophageal cancer (two patients),

endometrial cancer (two patients), biliary tract cancer (two patients), Paget's disease (two patients), pancreatic cancer (one patient), uterine cervix carcinoma (one patient), extraskeletal myxoid chondrosarcoma (one patient), and small intestine adenocarcinoma (one patient). Additionally, two cases of HER2-mutated breast cancer were included in this category.

All 60 patients were evaluated for response. The overall objective response rate was 28.3 percent with a median progression-free survival of 7.2 months. The median overall survival was 23.4 months. The objective response rate was greatest for NSCLC, with 55.6 percent of patients having a confirmed objective response (10 partial responses). In HER2-mutant NSCLC, the objective response rate was 72.7 percent (8 partial responses). The objective response rates for colorectal cancer and "other" cancer types were 5 percent (one partial response) and 27.3 percent (five partial responses and one complete response), respectively.

The frequency of treatment-emergent adverse events (TEAEs) was similar across the different tumor types. Overall, 62.7 percent of patients experienced a TEAE that was grade 3 or higher, and 30.5 percent experienced serious TEAEs. The most common TEAEs were anemia; decreased counts of neutrophils, white blood cells, and platelets; decreased appetite; increased levels of aspartate aminotransferase, which is a biomarker for liver damage; febrile neutropenia; and decreased blood levels of sodium. Five patients had drug-related interstitial lung disease. Five patients experienced an adverse event with a fatal outcome, of which two were reported to be treatment-related. One of the treatment-related deaths was due to drug-related interstitial lung disease. Forty-nine patients discontinued treatment due to disease progression, adverse events, death, patient withdrawal, or other reasons.

"The safety profile of T-DXd is consistent with the previously reported breast and gastric cancer cohorts from this phase I study," said Li.

"Interstitial lung disease is an important identified adverse event that may be serious – even fatal – and thus requires monitoring and prompt intervention. Further research is required to minimize and manage this risk."

"T-DXd demonstrated promising antitumor activity in a heterogeneous patient population," said Tsurutani. "These results indicate that T-DXd should be explored in larger studies as a treatment option for patients with HER2-overexpressing or HER2-mutated solid tumors."

Li noted, "We are very excited by the results of this preliminary study. T-DXd shows early promise for transforming the standard of care for patients with HER2-overexpressing or HER2-mutated cancers and we look forward to continuing this important research in future clinical trials."

Limitations of the study include the small sample size, both overall and within each tumor type, and the limited diversity of HER2 mutations included in the study. Larger clinical trials are ongoing.

In another study published by Li and colleagues in Cancer Discovery, T-DXd led to a partial response in a patient with lung cancer who had relapsed after treatment with another HER2-targeted ADC, ado-trastuzumab emtansine (T-DM1). This study also demonstrated that T-DM1 treatment led to clinical responses in patients with HER2-mutant or amplified lung cancers, and that combining T-DM1 with an irreversible HER kinase inhibitor enhanced cellular uptake of the drug in cell culture. Furthermore, combination treatment with T-DM1 and an irreversible HER kinase inhibitor led to a partial response in a patient with breast cancer who had previously relapsed on T-DM1. Together, results from this second study suggest that T-DXd or a combination of T-DM1 and a HER kinase inhibitor could be explored as potential treatment options for patients with relapse on T-DM1.

"This study shows the power of translational science through bench-to-bedside-and-back discoveries," said Li. "This team approach has provided mechanistic understanding and helped us to develop ADCs as a potential new class of drugs for patients with lung cancers and other solid tumors."

More information: *Cancer Discovery* (2020). DOI: 10.1158/2159-8290.CD-19-1014

Provided by American Association for Cancer Research