

Tucatinib plus trastuzumab emtansine may benefit patients with advanced or metastatic HER2-positive breast cancer

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A combination of two HER2-targeted drugs, tucatinib (Tukysa) and trastuzumab emtansine (Kadcyla, T-DM1), extended progression-free survival among patients with unresectable locally advanced or metastatic HER2-positive breast cancer, compared with T-DM1 alone, according to results from the [HER2CLIMB-02](#) trial presented at the [San Antonio Breast Cancer Symposium](#), held December 5–9, 2023.

T-DM1 is an antibody-drug conjugate comprised of trastuzumab (Herceptin) and the cytotoxic drug emtansine. It was approved for use as a monotherapy in 2013 for patients with late-stage HER2-positive breast cancer and in 2019 for patients with early-stage HER2-positive breast cancer.

However, not all patients have durable responses to T-DM1, and a combination approach may boost the drug's efficacy, explained Sara A. Hurvitz, MD, professor and head of the Division of Hematology and Oncology at the University of Washington Department of Medicine and [senior vice president](#) and director of the Clinical Research Division at Fred Hutchinson Cancer Center.

Tucatinib, a small-molecule inhibitor of HER2, has been shown to delay [disease progression](#) in the central nervous system, unlike most other HER2-targeted drugs. For patients with brain metastases, such a drug can make a significant difference, Hurvitz noted.

"HER2-positive breast cancer has a predilection to spread to the brain, and when this occurs, prognosis is poor," Hurvitz said. "Few options exist for the successful management of breast cancer brain metastases, making this an area of unmet need."

A previous trial, [HER2CLIMB](#), found that the addition of tucatinib to a regimen containing the HER2-targeted antibody trastuzumab and the chemotherapy capecitabine (Xeloda) significantly improved progression-

free and overall survival in heavily pretreated patients, including those with brain metastases.

This trial led to the 2020 [approval](#) of tucatinib, trastuzumab, and capecitabine by the U.S. Food and Drug Administration, but advances in HER2-targeting therapies prompted Hurvitz and colleagues to investigate other tucatinib-based combinations.

In the phase III HER2CLIMB-02 trial, 463 patients with unresectable locally advanced or metastatic HER2-positive breast cancer were enrolled and randomly assigned to receive tucatinib plus T-DM1 (228 patients) or placebo plus T-DM1 (235 patients); 44.1% had brain metastases at baseline.

The median time to disease progression or death was 9.5 months for patients in the tucatinib arm and 7.4 months for patients in the placebo arm, with tucatinib plus T-DM1 reducing the risk of disease progression or death by 24.1%.

Among patients who had brain metastases at baseline, the median time to disease progression or death was 7.8 months for those in the tucatinib arm and 5.7 months for those treated in the placebo arm, with tucatinib plus T-DM1 reducing the risk of disease progression or death by 36.1%. The overall survival data remain immature after a median of 24.4 months of follow-up.

Hurvitz noted that the rate of certain treatment-related side effects, especially those related to liver and gastrointestinal function, was higher among patients treated with tucatinib than those treated with placebo, resulting in a higher rate of dose adjustments and treatment discontinuation in the tucatinib arm. However, these effects were largely manageable with monitoring and clinical intervention, she said.

"This study is one of very few large breast cancer studies prospectively designed to evaluate novel systemic therapies in patients with brain metastases," Hurvitz said. "While there is much interest in improving outcomes for [patients](#) with HER2-positive breast cancer [brain metastases](#), most studies evaluating systemic agents have been limited by a [small size](#), a retrospective design, or an exploratory analysis of a larger study."

Limitations of this study include as-of-yet immature overall survival data. Further, the study was not designed to compare tucatinib plus T-DM1 to tucatinib plus trastuzumab and capecitabine or any regimens containing the antibody-drug conjugate trastuzumab deruxtecan (Enhertu, T-DXd).

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