Adding tucatinib to drug combination extends survival for advanced HER2+ breast cancer patients

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Researchers from The University of Texas MD Anderson Cancer Center today reported study results showing the addition of tucatinib to capecitabine (Xeloda) and trastuzumab (Herceptin) significantly

improved progression-free survival (PFS) and overall survival (OS) in patients with advanced HER2-positive breast cancer, with and without brain metastasis according to results of the HER2CLIMB clinical trial.

The trial results published in the *New England Journal of Medicine* and were presented by Rashmi K. Murthy, M.D., assistant professor of Breast Medical Oncology, during the 2019 San Antonio Breast Cancer Symposium.

The trial met its primary endpoint and showed that the treatment combination reduced the risk of death by 46% compared with trastuzumab and capecitabine alone. The trial also met its secondary endpoints at interim analysis, showing tucatinib prolonged OS, reduced the risk of death by 34% and extended PFS by 52% among patients with brain metastasis. The overall response rate was higher in the tucatinib group at 41% compared with 23% in the standard of care treatment.

"This is a uniquely designed trial in that it allowed patients to enroll if they had untreated, treated stable or previously treated, but progressive brain metastasis," said Murthy. "Brain metastasis is a common clinical problem developing in up to half of patients during the disease course, but there are limited systemic treatment options as most drugs have difficulty crossing the blood brain barrier."

HER2-positive breast cancer tumors have high levels of human epidermal growth factor receptor 2 (HER2). This type of breast cancer has been associated with shorter survival times as well as a higher risk of recurrence and brain metastasis. Approximately 25% of breast cancers are HER2-positive and as many as half of patients with HER2-positive disease will develop brain metastasis over the course of their lifetime. Tucatinib is a tyrosine kinase inhibitor (TKI) that is highly selective for HER2.

The international randomized trial enrolled 612 patients with locally advanced or metastatic HER2-positive breast cancer who received prior treatment with trastuzumab, pertuzumab and ado-trastuzumab emtansine. Researchers randomly assigned patients 2:1 to trastuzumab and capecitabine with or without tucatinib. Nearly half (47.5%) of patients had brain metastasis at baseline.

The triplet combination was generally well tolerated with no unexpected toxicities. The most frequent adverse events in the tucatinib arm included diarrhea, hand-foot syndrome, nausea, fatigue, and vomiting, all mostly low grade. There was a low drug discontinuation rate, 5.7% in the triplet arm compared with 3% in the control arm.

"This trial verified that tucatinib is both a safe and effective treatment," said Murthy. "These results are unprecedented for late line therapy in advanced breast cancer, and are a major advance for patients who have significant unmet medical need. Tucatinib in combination with trastuzumab and capecitabine should be the new standard of care for patients pretreated with multiple anti-HER2 agents including patients with brain metastasis."

These positive trial results led to the decision to unblind the study so that all patients can benefit from the combination. There are plans to submit a New Drug Application to the Food and Drug Administration in the first quarter of 2020.

The HER2CLIMB trial is ongoing but is no longer recruiting patients. Completion of the trial is expected in September 2020. The Phase III HER2CLIMB-02 clinical trial began in October 2019. A similar study assessing the safety and efficacy of the combination of tucatinib and trastuzumab with capecitabine for the treatment of leptomeningeal metastases currently is recruiting patients.

Medical Xpress

More information: Rashmi K. Murthy et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1914609

Provided by University of Texas M. D. Anderson Cancer Center

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