Tucatinib Fights Breast Cancer That Spreads to the Brain

New targeted therapy improves survival in people with metastatic HER2-positive breast cancer.

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A new kinase inhibitor delayed disease progression and improved overall survival in people with advanced HER2-positive breast cancer, including those with cancer that had spread to the brain, according to study results presented last week at the San Antonio Breast Cancer Symposium.

“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,” lead investigator Rashmi Murthy, MD, of the University of Texas MD Anderson Cancer Center, said in a press release. “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.”

Around 20% of breast tumors express the HER2 receptor at high levels and can therefore be treated with HER2 inhibitors like Herceptin (trastuzumab). But treatment options are limited for people with cancer that has relapsed and metastasized, or spread elsewhere in the body. Those with brain metastasis are often excluded from clinical trials of new therapies.

Murthy presented findings from the HER2CLIMB trial (ClinicalTrial.gov number NCT02614794), which evaluated tucatinib, an experimental tyrosine kinase inhibitor from Seattle Genetics that targets HER2. Unlike some other HER2 inhibitors, tucatinib has little activity against another target, EGFR, which means it should cause fewer side effects.

This study involved 612 participants, including five men, with HER2-positive metastatic breast cancer. The median age was approximately 55, about 20% were age 65 or older and about three quarters were white. About 60% had cancer that was also hormone receptor positive. Almost 40% already had Stage IV cancer when they were diagnosed. Nearly half (47%) had brain metastasis, and about half had cancer that had spread to their lungs and bones. They were previously treated with the HER2 targeted therapies Herceptin, Perjeta (pertuzumab) and Kadcyla (ado-trastuzumab emtansine, or T-DM1).

The participants were randomly assigned to receive either tucatinib or a placebo in combination with Herceptin and the chemotherapy drug capecitabine (Xeloda and generics). Tucatinib and capecitabine were taken as a twice-daily pills, while Herceptin was administered by IV infusion.

At the conference, Murthy presented efficacy data for the first 480 patients to be randomized; the additional participants were added later to allow for statistically significant conclusions about people with brain metastasis. Safety data were presented for all 612 participants. The results were also published in The New England Journal of Medicine.

After one year of follow-up, 33% of participants in the tucatinib group and 12% in the placebo group were alive without their cancer worsening, known as progression-free survival. This represents a 46% reduction in the risk of disease progression or death. The median progression-free survival duration was 7.8 months versus 5.6 months, respectively.

The overall response rate, meaning cancer regression, was 41% in the tucatinib group compared with 23% in the placebo group. An additional 46% and 8%, respectively, had stable disease.

Among participants with brain metastases, progression-free survival at one year was 25% in the tucatinib group versus 0% in the placebo group, indicating a 52% reduction in the risk of disease progression or death. That is, while everyone in the placebo group worsened, a quarter of those who took tucatinib saw no disease progression. In this subset of patients, the median progression-free survival duration was 7.6 months versus 5.4 months.

Overall survival at one year was 76% in the tucatinib group and 62% in the placebo group. At two years, the corresponding figures were 45% and 27%, representing a 34% improvement. The median overall survival duration was 21.9 months versus 17.4 months, respectively.

Treatment was generally safe, though almost everyone in both groups experienced side effects; about half of which were severe (Grade 3 or higher). Common adverse events included diarrhea (81% in the tucatinib group versus 53% in the placebo group), nausea (58% versus 44%, respectively), vomiting (36% versus 25%) and fatigue (45% versus 43%). More than half in both groups (63% and 53%, respectively) developed hand-foot syndrome or palmar-plantar erythrodysesthesia, with redness, swelling and pain on the palms of the hands and soles of the feet.

Although side effects were mostly mild or moderate, 13% of people taking tucatinib had severe diarrhea or hand-foot syndrome. People taking tucatinib were more likely than those in the placebo group to develop severe liver enzyme elevations (5% versus 0.5%). However, few people in either group stopped treatment prematurely (6% versus 3%).

Given the good outcomes in the tucatinib group, the blinded randomized portion of the study was halted so that everyone could receive the new drug.

“Our results show that for this group of patients, for whom effective standard treatment options are extremely limited, the addition of tucatinib to trastuzumab and capecitabine provided a clinically meaningful reduction in the risk of disease or death,” lead investigator Eric Winer, MD, of Dana-Farber Cancer Institute in Boston, said in a press release. “Most importantly, tucatinib reduced the risk of death by a third, which is unprecedented in a population of patients who had received extensive prior therapy.”

The Phase III HER2CLIMB-02 trial (ClinicalTrials.gov number NCT03975647), comparing tucatinib versus placebo in combination with Kadcyla, is currently enrolling participants with advanced HER2-positive breast cancer with or without brain metastasis. Tucatinib is also being studied for HER2-positive colorectal cancer in the Phase II MOUNTAINEER trial (ClinicalTrials.gov number NCT03043313).

Seattle Genetics indicated that it plans to submit a new drug application for tucatinib to the Food and Drug Administration by the first quarter of 2020.

Click here to read the study abstract.

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