Oral Agent Increases Survival in Advanced HER2-Positive Breast Cancer

Tucatinib, a tyrosine kinase inhibitor, increases survival rates in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer.

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December 18, 2019 – According to a new double-blind study, oral administration of tucatinib, in combination with trastuzumab and capecitabine, led to greater progression-free survival and overall survival in patients previously treated for HER2-positive breast cancer, including those with brain metastases.

Rashmi K. Murthy, MD, of the University of Texas MD Anderson Cancer Center in Houston, Texas, and colleagues reported their findings in the December 11, 2019, issue of the *New England Journal of Medicine*.

Tucatinib is a highly selective inhibitor of the HER2 tyrosine kinase that has little effect on the epidermal growth factor receptor (EGFR). In previous studies, the combination of a HER2 tyrosine kinase inhibitor with capecitabine showed activity in brain metastases associated with HER2-positive breast cancer. However, use of these combinations has been limited by toxic effects, including toxicity associated with EGFR inhibition.

In the current study, patients with HER2-positive metastatic breast cancer who had previously received trastuzumab, pertuzumab, and trastuzumab emtansine were randomly assigned in a 2:1 ratio to receive either tucatinib or placebo, combined with trastuzumab and capecitabine. At baseline, 47.5% of all participants had brain metastases. The researchers note that this population is “typically excluded from clinical trials despite this condition being a common clinical problem.”

The primary end point of the study was progression-free survival, assessed in the first 480 randomized patients. At 1 year, progression-free survival was 33.1% (95% CI = 26.6 to 39.7) in patients receiving tucatinib/trastuzumab/capecitabine, compared with 12.3% (95% CI = 6.0 to 20.9) of those receiving placebo/trastuzumab/capecitabine. The risk of disease progression or death was 46% lower among patients receiving the tucatinib combination compared with those receiving the placebo combination (hazard ratio = 0.54; 95% CI = 0.42 to 0.71; $P<0.001$).

Secondary endpoints, evaluated in the total population of 612 participants, included overall survival and progression-free survival in patients with brain metastases. Overall survival at 2 years was 44.9% (95% CI = 36.6 to 52.8) in patients receiving the tucatinib combination and 26.6% (95% CI = 15.7 to 38.7) in patients receiving the placebo combination. In patients with brain metastases, progression-free survival at 1 year was 24.9% (95% CI = 16.5 to 34.3) with the tucatinib combination and 0% with the placebo combination.

Most adverse events in the tucatinib-combination group were grade 1 or 2; these included diarrhea, palmar-plantar erythrodysesthesia (PPE) syndrome, nausea, fatigue, and vomiting. The most common adverse events of grade 3 or higher observed with the tucatinib combination included PPE syndrome, diarrhea, increases in alanine aminotransferase and aspartate aminotransferase, and fatigue. While most participants receiving the tucatinib combination showed some toxic effects, adverse events due to tucatinib were responsible for the discontinuation of therapy in only 5.7% of patients.

Adding “tucatinib to trastuzumab and capecitabine resulted in a clinically meaningful lower risk of disease progression or death,” the investigators state. The treatment is an “active combination in heavily pretreated patients with HER2-positive metastatic breast cancer, including those with previously untreated, treated and stable, or treated and progressing brain metastases,” they conclude.

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