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Adding Tucatinib to Trastuzumab and Chemotherapy Improves Survival for Patients with Metastatic HER2-Positive Breast Cancer

HER2CLIMB trial results to be presented at 2019 San Antonio Breast Cancer Symposium

SAN ANTONIO — Results from the HER2CLIMB trial will be presented at this year's San Antonio Breast Cancer Symposium (SABCS). This phase II trial compared the tyrosine kinase inhibitor tucatinib in combination with trastuzumab and capecitabine to trastuzumab and capecitabine alone in patients with pretreated HER2-positive metastatic breast cancer. The tucatinib arm demonstrated improved progression-free survival and overall survival.

Topline results were announced in October 2019. The full study will be presented at SABCS and simultaneously published in the *New England Journal of Medicine* on Wednesday, Dec. 11, at 8:45 a.m. CT.

To schedule an interview with a study author and for other inquiries, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896.

ABSTRACT

Tucatinib vs Placebo Added to Trastuzumab and Capecitabine for Patients with Pretreated HER2+ Metastatic Breast Cancer with and without Brain Metastases (HER2CLIMB)

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Background: There is a significant unmet medical need among patients with HER2+ metastatic breast cancer who have progressed after receiving multiple anti-HER2 agents, particularly in the up to 50% of

patients who develop brain metastases during the course of their disease. Tucatinib is an investigational oral tyrosine kinase inhibitor that is highly selective for HER2 with minimal inhibition of EGFR. Tucatinib has shown antitumor activity in preclinical models of HER2+ breast cancer and intracranial tumor models.

Methodology: HER2CLIMB (NCT02614794) is a global, randomized, double-blind, controlled trial in patients with locally advanced or metastatic HER2+ breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1, including patients with untreated, treated stable, or treated progressive brain metastases. Patients were randomized 2:1 to receive tucatinib (300 mg BID) or placebo, in combination with trastuzumab (6 mg/kg once every 21 days with a loading dose of 8 mg/kg on cycle 1 Day 1), and capecitabine (1000 mg/m^2 BID, Days 1–14 of each 21-day cycle). Randomization was stratified by brain metastases, ECOG status, and geographic region. Prophylactic antidiarrheals were not required. The primary endpoint was PFS (defined as disease progression or death) per RECIST 1.1 by blinded independent central review in the first 480 patients. Multiplicity-adjusted secondary endpoints evaluated in the whole population included OS, PFS in patients with brain metastases, and confirmed ORR in patients with measurable disease. Safety data were evaluated using CTCAE v4.03.

Results: HER2CLIMB enrolled 612 patients between Feb-2016 and May-2019. Data cutoff was 4-Sep-2019. Demographics and disease characteristics were balanced across treatment arms, including 47.5% of patients with brain metastases, with a median of 4 prior regimens, 3 in the metastatic setting. Median follow-up for the overall population was 14 mos. The primary endpoint and all multiplicity-adjusted secondary endpoints were met. There was a 46% reduction in the risk of progression or death in the tucatinib arm (HR=0.54 [95% CI: 0.42, 0.71]; P<0.00001). Median PFS was 7.8 mos vs 5.6 mos and 1-year PFS was 33% vs 12%. The risk of death was reduced by 34% in the tucatinib arm (HR=0.66 [95% CI: 0.50, 0.88], P=0.0048). Median OS was 21.9 mos vs 17.4 mos and 2-year OS was 45% vs 27%. Among patients with brain metastases, there was a 52% reduction in the risk of progression or death (HR=0.48 [95% CI: 0.34, 0.69], P<0.00001). Median PFS was 7.6 mos vs 5.4 mos and 1-year PFS was 25% vs 0%. For all these endpoints, outcomes in all subgroups were consistent with the overall outcomes. The confirmed ORR was significantly higher in the tucatinib arm vs the control arm (41% vs. 23%, respectively; P=0.00008). Most frequent adverse events in the tucatinib arm included: diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Grade ≥3 adverse events in the tucatinib arm vs the control arm included: diarrhea 12.9% vs. 8.6%, increased AST 4.5% vs. 0.5%, increased ALT 5.4% vs. 0.5%, and increased bilirubin 0.7% vs. 2.5%. Adverse events leading to discontinuation of tucatinib or placebo were infrequent in both arms (5.7% and 3.0%).

Conclusions: The HER2CLIMB trial demonstrated that the addition of tucatinib to trastuzumab and capecitabine in heavily pretreated patients with HER2+ metastatic breast cancer, including those with brain metastases, was associated with statistically significant and clinically meaningful prolongation of progression-free and overall survival. If approved, tucatinib in combination with trastuzumab and capecitabine has the potential to become a new standard of care in patients who have previously received 3 HER2-targeted agents.

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Since 1977 the San Antonio Breast Cancer Symposium® (SABCS®) has been the leading scientific conference for basic scientists, physician-scientists, clinical investigators and breast care providers, and advocates seeking an exchange of new information in experimental biology, etiology, prevention, diagnosis, and therapy of premalignant breast disease and breast cancer. Founded, owned, and operated by UT Health San Antonio, the symposium has grown to a five-day event attended by an international audience of academic investigators and private physicians from over 80 countries to attain information through abstract presentations, panel discussions, research findings, and state-of-the-art educational sessions. UT Health San Antonio, the American Association for Cancer Research

(AACR), and Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine support SABCS, which provides education and accessibility to the latest information regarding the prevention, diagnosis, and treatment of premalignant breast cancer and breast disease. For more information about the symposium, please visit www.sabcs.org.