

**A randomized, double-blinded pivotal study of tucatinib (ONT-380) vs. placebo in combination with capecitabine and trastuzumab in patients with pretreated HER2-pos. unresectable locally advanced or metastatic breast cancer: HER2CLIMB**

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**Purpose:** Treatment options for HER2-pos. breast cancer patients after trastuzumab/pertuzumab and T-DM1 are not well examined, especially for those patients with brain metastases. Tucatinib (ONT-380) is a highly selective small molecule inhibitor of HER2 kinase. In preclinical studies, tucatinib demonstrated synergistic activity with trastuzumab (Tz), and was active in models of brain metastases. In a Phase 1b study, tucatinib was combined with capecitabine (C) and Tz in pts with HER2+ MBC previously treated with T-DM1 and Tz. Objective responses were seen, including in pts with brain mets. The combination was well tolerated, with low rates of Gr 3 diarrhea at the recommended dose (300 mg PO BID, equivalent to the single agent MTD). Based on these data, tucatinib is now being evaluated in a study in combination with C and Tz (HER2CLIMB).

**Methods:** The primary study objective is to assess the effect of tucatinib vs. placebo given with C + Tz on progression-free survival (PFS) based on independent central review. Additional objectives include PFS in patients with brain mets, overall survival, ORR, duration of response, clinical benefit rate, and safety. The study population includes adult patients with progressive HER2+ locally advanced or MBC who have had prior treatment with a taxane, Tz, pertuzumab and T-DM1. Patients with brain mets, including untreated or progressive brain mets, may be enrolled. 480 patients will be enrolled in North America, Europe, Israel, and Australia. Patients are receiving C (1000 mg/m<sup>2</sup> PO BID for 14 days of a 21-day cycle) and Tz (6 mg/kg IV once every 21 days), and are being randomized in a 2:1 ratio to tucatinib 300 mg PO BID or placebo. Patients with isolated CNS progression may continue on study treatment after undergoing local CNS therapy.

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