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breast cancer, locally advanced and metastatic

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A phase 2 randomized, double-blinded, controlled study of ONT-380 vs. placebo in combination with capecitabine (C) and trastuzumab (T) in patients with pretreated HER2+ unresectable locally advanced or metastatic breast carcinoma (MBC)

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Background: ONT-380 is a highly selective small molecule inhibitor of HER2 kinase with nanomolar potency. Unlike dual HER2/EGFR agents, it does not inhibit EGFR at clinically relevant concentrations, decreasing the potential for EGFR-related toxicities (severe skin rash and diarrhea). In preclinical studies, ONT-380 demonstrated synergistic activity with T, and was active in HER2+ models of brain metastases (mets). In a Phase 1b study, ONT-380 was combined with C and T in pts with HER2+ MBC previously treated with trastuzumab emtansine (T-DM1) and T. Objective response rate (ORR) was 13/ 24 (54%) in pts with measurable disease treated with ONT-380 + C + T (including 10 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, ONT-380 is now being evaluated in a Phase 2 study in combination with C and T.

Trial design: The primary study objective is to assess the effect of ONT-380 vs placebo given with C + T on progression-free survival (PFS) based on independent central review. Additional secondary objectives include CNS PFS, non-CNS PFS, time to CNS progression, ORR, duration of response, clinical benefit rate, and safety. The study population includes adult pts with progressive HER2+ locally advanced or MBC who have had prior treatment with a taxane, T, pertuzumab and T–DM1 but not C or lapatinib. Pts with brain mets, including untreated or progressive mets, may be enrolled. 180 pts will be enrolled in North America and Europe. Pts will receive C (1000 mg/mg^2 PO BID for 14 days of a 21-day cycle) and T (8 mg/kg IV loading dose; 6 mg/kg IV once every 21 days), and will be randomized in a 2:1 ratio to receive ONT–380 300 mg PO BID or placebo. Pts with isolated CNS progression may continue on study treatment after undergoing local CNS therapy. An independent Data Monitoring Committee will monitor pt safety.

Clinical trial identification: ONT-380-206

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