A Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib (ONT-380) vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated HER2+ Unresectable Locally Advanced or Metastatic Breast Carcinoma (HER2CLIMB)

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Tucatinib Background

- Tucatinib is an orally bioavailable, potent HER2 selective tyrosine kinase inhibitor
  - Highly selective for HER2 (IC_{50} 8 nM) > EGFR (IC_{50} >10,000 nM); decreased potential for EGFR-related toxicities (e.g. diarrhea, skin rash)
  - Active in murine HER2+ tumor models as a single agent and synergistic in combination with trastuzumab or chemotherapy[1]
  - Improved outcome compared to lapatinib or neratinib in preclinical HER2+ CNS models[2]
  - Initial Phase 1 single-agent study showed objective responses with no treatment-related Grade 3 diarrhea[3]
- In a Phase 1b study, tucatinib was combined with capecitabine and trastuzumab in patients with HER2+ metastatic breast cancer[4, 5]:
  - Combination was well tolerated, with low rates of Grade 3 diarrhea at the recommended dose (tucatinib 300 mg PO BID)
  - Response and prolonged stable disease reported in heavily pre-treated patients including most with prior pertuzumab treatment
  - Responses and prolonged stable disease reported in patients with brain metastases

[1] Koch et al. AACR 2011; [2] Dinkel et al. AACR 2012 ; [3]Borges et al, AA CR Special Conference on Advances in Breast Cancer Research: Genetics, Biology, and Clinical Applications 2013; [4]Hamilton et al. ASCO 2015; [5]http://ir.cascadianrx.com/events.cfm

HER2CLIMB Study Endpoints

- Primary endpoint:
  - Progression-free survival (PFS) per RECIST 1.1 based on independent central review
- Secondary endpoints:
  - PFS in patients with brain metastases based on independent central review
  - Overall Survival
  - PFS based on investigator assessment
  - Objective response rate
  - Duration of response
  - Clinical benefit rate (% SD ≥ 6 months + CR + PR)*
  - Safety
- Exploratory endpoints:
  - Response in brain metastases per RANO-BM
  - Time to CNS progression

* SD = stable disease; CR = complete response; PR = partial response

Eligibility Criteria

Key Inclusion Criteria:

- Unresectable HER2+ locally advanced or metastatic breast cancer
- Prior therapy includes a taxane, trastuzumab, pertuzumab, and T-DM1
- Measurable or non-measurable disease per RECIST 1.1
- ECOG PS 0 or 1
- Adequate hematologic, renal, and hepatic function
- Left ventricular ejection fraction (LVEF) ≥ 50%

Eligibility Criteria (Continued)

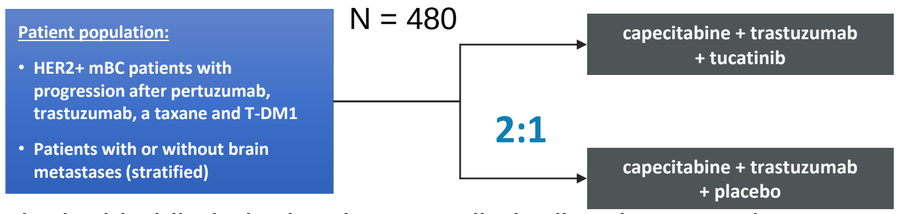
Key Exclusion Criteria:

- Previous treatment with:
  - Lapatinib within 12 months of starting study treatment
  - Neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor (EGFR) or HER2 tyrosine kinase inhibitor (TKI)
  - Capecitabine for metastatic disease
- Treatment with any systemic anti-cancer therapy ≤ 3 weeks of first dose of study treatment

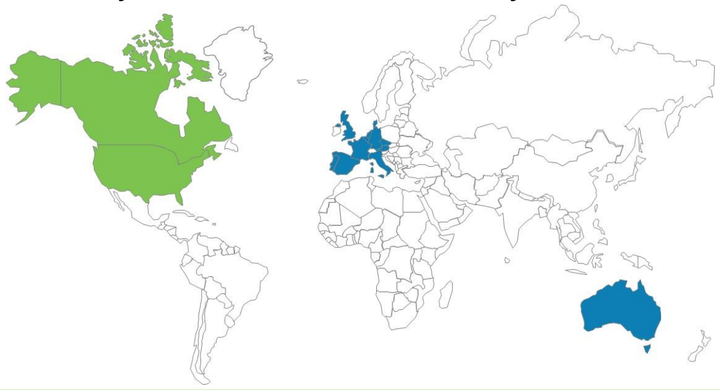
Brain Metastases Criteria:

- All patients will be screened at baseline with brain MRI
- May have any of the following:
  - No brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated brain metastases
- Exclusion:
  - Any untreated lesions > 2.0 cm in size
  - Any lesion thought to require immediate local therapy
  - Known leptomeningeal disease (LMD)

HER2CLIMB Study Design



- Treatment is double-blinded, placebo-controlled; all patients receive:
  - Capecitabine 1000 mg/m^2 PO BID for 14 days of a 21-day cycle
  - Trastuzumab 8 mg/kg IV loading dose; 6 mg/kg IV once every 21 days
  - Tucatinib 300 mg PO BID or Placebo PO BID
  - No anti-diarrheal prophylaxis required
- Assessments:
  - Physical and laboratory measurements: on Day 1 of each cycle and on Day 12 of Cycles 1 and 2
  - Tumor assessments: every 6 weeks for first 24 weeks then every 9 weeks
  - Brain MRI in patients with brain metastases at baseline: every 6 weeks for first 24 weeks and then every 9 weeks. All patients will undergo brain MRI at baseline and after completion of study
- Patients may continue participation in the study until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.
- Patients with isolated brain progression may be able to continue on study treatment after CNS radiation or surgery



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