A Phase 2 Randomized, Double-Blinded, Placebo-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

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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)
  - Active in murine tumor models of HER2+ disease as a single agent and is synergistic in combination with trastuzumab or chemotherapy[1]
  - Superior activity compared to lapatinib or neratinib in preclinical models of HER2+ CNS disease[2]
  - Initial Phase 1 single-agent study showed objective responses with no treatment-related Grade 3 diarrhea[3]
    - Dose limiting toxicity of reversible Grade 3 elevation of AST/ALT in 2 patients
- In a Phase 1b study, tucatinib was combined with capecitabine and trastuzumab in patients with HER2+ metastatic breast cancer[4]:
  - Prior treatment with T-DM1 and trastuzumab required
    - 74% of patients also had prior treatment with pertuzumab
  - Objective response rate (ORR) was 13/ 24 (54%) in patients with measurable disease (including 10 pts with brain metastases)
  - Combination was well tolerated, with low rates of Grade 3 diarrhea at the recommended dose (tucatinib 300 mg BID)
  - Responses in brain metastases seen in patients with measurable disease at baseline[5]

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

Study Objectives

- Primary objective:
  - Progression-free survival (PFS) per RECIST 1.1 based on independent central review
- Secondary objectives:
  - PFS based on investigator assessment
  - ORR
  - Duration of response
  - Clinical benefit rate (% CR + PR + SD ≥ 6 months)
  - Overall survival
  - PFS in patients with brain metastases
  - Safety
- Exploratory objectives:
  - Effect on brain metastases based on RANO-BM
  - Biomarker identification
  - Brain metastases progression in patients with or without brain metastases at baseline

Eligibility Criteria

Key Inclusion Criteria:

- Histologically confirmed HER2+ breast carcinoma
- Received previous treatment with a taxane, trastuzumab, pertuzumab, and T-DM1
- Progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy
- Measurable or non-measurable disease per RECIST 1.1
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
- Adequate laboratory values:
  - Total bilirubin ≤1.5 X upper limit of normal (ULN)
  - AST and ALT ≤ 2.5 X ULN (≤ 5 X ULN if liver metastases are present)
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^3/μL
  - Platelet count ≥ 100 x 10^3/μL
  - Hemoglobin ≥ 9 g/dL
  - Creatinine clearance ≥ 50 mL/min
  - Activated partial thromboplastin time (aPTT) ≤ 1.5 X ULN
- Left ventricular ejection fraction (LVEF) ≥ 50% as assessed by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)

Key Exclusion Criteria:

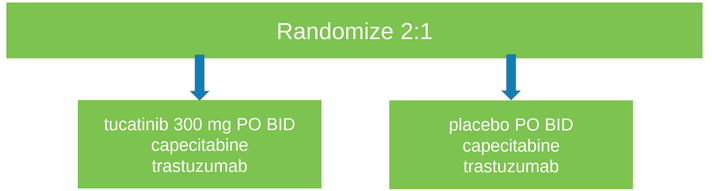
- Previous treatment with:
  - Lapatinib within 12 months of starting study treatment
  - Neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor (EGFR) or HER2 tyrosine kinase inhibitor (TKI)
  - Capecitabine for metastatic disease
- Treatment with any systemic anti-cancer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

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
  - Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of > 4mg of dexamethasone (or equivalent)
  - Any lesion thought to require immediate local therapy
  - Known leptomeningeal disease (LMD)
  - Poorly controlled seizures

Treatment Regimen

N = 180



- Patients will be stratified based upon presence of CNS metastases at baseline, ECOG status, and Region of World
- Treatment is double-blinded, placebo-controlled; all patients receive:
  - Capecitabine administered as 1000 mg/mg^2 PO BID for 14 days of a 21-day cycle
  - Trastuzumab administered as 8 mg/kg IV loading dose; 6 mg/kg IV once every 21 days
  - Tucatinib 300 mg PO BID or Placebo PO BID
- Assessments:
  - Physical and laboratory measurements on Day 1 of each cycle and on Day 12 of Cycles 1 and 2
  - CT scan every 6 weeks for first 24 weeks then every 9 weeks
  - MRI brain 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 they complete study
- Patients may continue participation in the study until unacceptable toxicity, disease progression (except for patients with brain metastases-only progression who may be able to continue on study treatment after initial brain metastases-only progression), withdrawal of consent, or study closure.

Study Status

- Enrollment currently open in United States and Canada
  - First patient enrolled February 2016
  - Enrollment planned to begin in Europe in early 2017
- Sponsored by Cascadian Therapeutics, Inc.

HER2CLIMB

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Data presented in the abstract and on this poster are from an unlocked database as of 02 May 2016 and are subject to change.