Phase 2 Study of Tucatinib vs Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer (HER2CLIMB)

ClinicalTrials.gov Identifier: NCT02614794

Recruitment Status : Recruiting
First Posted : November 25, 2015
Last Update Posted : October 1, 2018

See **Contacts and Locations**

Sponsor:
Cascadian Therapeutics Inc.

Information provided by (Responsible Party):
Seattle Genetics, Inc. (Cascadian Therapeutics Inc.)

Study Description

Go to

Brief Summary:
To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on progression-free survival (PFS) per RECIST 1.1 based on independent central radiology review.

Condition or disease	Intervention/treatment	Phase
HER2 Positive Breast Cancer	Drug: Tucatinib Drug: Capecitabine Drug: Trastuzumab Drug: Placebo	Phase 2

Detailed Description:

A randomized, international, multi-center, double-blinded study in patients with progressive unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab and T-DM1. Patients will be randomized in a 2:1 ratio to receive tucatinib or placebo in combination with capecitabine

and trastuzumab.

Stratification factors include presence or history of treated or untreated brain metastases (yes/no), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1), and region of world (US vs Canada vs Rest of World).

No crossover from placebo to tucatinib will be allowed.

Safety assessments will be performed at a minimum of once every three weeks throughout study treatment and 30 days after the last dose of study drugs. Laboratory assessments will be performed locally at sites. Left ventricular ejection fraction will be assessed by MUGA or ECHO at screening and once every 12 weeks thereafter.

Contrast brain MRI will be performed at baseline in all patients. Efficacy assessments (CT of chest, abdomen and pelvis at a minimum) utilize RECIST 1.1 and include patients with evaluable tumors defined as measurable target lesions and non-measurable non-target lesions. RECIST assessment is performed at baseline, every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter. Repeat MRI of the brain will be required on this same schedule only in those patients with brain metastases identified at baseline. All treatment decisions are made based upon investigator assessment. All patients undergo a repeat MRI of the brain within 30 days of the end of treatment unless previously performed at time of disease progression. Patients in both arms of the study will be followed for OS after completion of study treatment.

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	480 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs Placebo in Combination With Capecitabine and Trastuzumab in Patients With Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma (HER2CLIMB)
Study Start Date :	December 2015
Estimated Primary Completion Date :	September 2020
Estimated Study Completion Date :	January 2021

Resource links provided by the National Library of Medicine

Genetics Home Reference related topics:
Breast cancer

MedlinePlus related topics: Breast Cancer

Drug Information available for: Capecitabine Trastuzumab

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Tucatinib in combination with	Drug: Tucatinib Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or

capecitabine & trastuzumab Tucatinib in combination with capecitabine & trastuzumab	placebo will be given orally twice daily (PO BID). Capecitabine will be given at 1000 mg/m2 PO BID on Days 1-14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg once every 21 days. Other Name: ONT-380 Drug: Capecitabine Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or placebo will be given orally twice daily (PO BID). Capecitabine will be given at 1000 mg/m2 PO BID on Days 1-14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg once every 21 days. Other Name: Xeloda Drug: Trastuzumab Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or placebo will be given orally twice daily (PO BID). Capecitabine will be given at 1000 mg/m2 PO BID on Days 1-14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg once every 21 days. In regions where approved, trastuzumab may be given at 600mg subcutaneously once every 3-weeks at either study initiation or crossing over from previous IV trastuzumab. Other Name: Herceptin
Active Comparator: Placebo in combination with capecitabine & trastuzumab Placebo in combination with capecitabine & trastuzumab	Drug: Capecitabine Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or placebo will be given orally twice daily (PO BID). Capecitabine will be given at 1000 mg/m2 PO BID on Days 1-14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg once every 21 days. Other Name: Xeloda Drug: Trastuzumab Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or placebo will be given orally twice daily (PO BID). Capecitabine will be given at 1000 mg/m2 PO BID on Days 1-14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg once every 21 days. In regions where approved, trastuzumab may be given at 600mg subcutaneously once every 3-weeks at either study initiation or crossing over from previous IV trastuzumab. Other Name: Herceptin Drug: Placebo Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or placebo will be given orally twice daily (PO BID). Capecitabine will be given at 1000 mg/m2 PO BID on Days 1-14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg once every 21 days.

Outcome Measures

Go to

Primary Outcome Measures :

1. Progression-free survival (PFS) per RECIST 1.1 based on independent central radiology review [Time Frame: 42 months]

Secondary Outcome Measures :

1. Effect of tucatinib in combination with capecitabine and trastuzumab on overall survival (OS) [Time Frame: 52 months]
2. Progression-free survival (PFS) in the subgroup of patients with baseline brain metastases per RECIST 1.1 based on central review [Time Frame: 42 months]
3. Quality of life as measured by EQ-5D questionnaire [Time Frame: 52 months]

Eligibility Criteria

Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria

Histologically confirmed HER2+ breast carcinoma, with HER2+ defined by in situ hybridization (ISH) or fluorescence in situ hybridization (FISH) methodology

Received previous treatment with trastuzumab, pertuzumab, and T-DM1

Progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy

Have measurable or non-measurable disease assessable by RECIST 1.1

At least 18 years of age at time of consent

Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1

Adequate hepatic and renal function

Left ventricular ejection fraction (LVEF) ≥ 50%

CNS Inclusion - Based on screening brain magnetic resonance imaging (MRI), patients must have one of the following:

- No evidence of brain metastases
- Untreated brain metastases not needing immediate local therapy
- Previously treated brain metastases not needing immediate local therapy

1. Brain metastases previously treated with local therapy may either be stable since treatment or may have

progressed since prior local CNS therapy

2. Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if the following criteria are met:

i. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days.

ii. Other sites of evaluable disease are present

c. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

Exclusion Criteria

Previously been treated with:

1. lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤ 21 days and was discontinued for reasons other than disease progression or toxicity)
2. neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) at any time previously
3. previously been treated with capecitabine for metastatic disease except in cases where capecitabine was given for < 21 days and was discontinued for reasons other than disease progression or toxicity. Patients who have received capecitabine for adjuvant or neoadjuvant treatment at least 12 months prior to starting study treatment are eligible.

Clinically significant cardiopulmonary disease

Carriers of Hepatitis B or Hepatitis C or have other known chronic liver disease

Positive for human immunodeficiency virus (HIV)

Unable for any reason to undergo MRI of the brain

CNS Exclusion - Based on screening brain MRI, patients must not have any of the following:

Any untreated brain lesions > 2.0 cm in size, unless discussed with medical monitor

Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of > 2 mg of dexamethasone (or equivalent)

Any brain lesion thought to require immediate local therapy. Patients who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria

Known or concurrent leptomeningeal disease (LMD)

Poorly controlled seizures

Contacts and Locations

Go to

Contacts

Contact: Seattle Genetics Trial Information Support 866-333-7436 clinicaltrials@seagen.com

Show 187 Study Locations

Sponsors and Collaborators

Cascadian Therapeutics Inc.

Investigators

Study Director: Luke Walker, MD Seattle Genetics, Inc.

More Information

Go to

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Murthy R, Borges VF, Conlin A, Chaves J, Chamberlain M, Gray T, Vo A, Hamilton E. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018 Jul;19(7):880-888. doi: 10.1016/S1470-2045(18)30256-0. Epub 2018 May 24.

Responsible Party:	Cascadian Therapeutics Inc.
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Keywords provided by Seattle Genetics, Inc. (Cascadian Therapeutics Inc.):

Tucatinib
Capecitabine
Trastuzumab
Xeloda
Herceptin
Breast Cancer
ARRY-380
ONT-380
HER2 Positive Breast Carcinoma
HER2 Positive Locally Advanced Breast Cancer
HER-2 Positive Breast Cancer
HER-2 Positive Breast Carcinoma
HER-2 Positive Locally Advanced Breast Cancer
Recurrent Breast Carcinoma
Stage IV Breast Cancer
Metastatic Breast Cancer
Breast Carcinoma
Metastatic Malignant Neoplasm in the Brain
Brain Metastases in Breast Cancer
Asymptomatic Brain Metastases in Breast Cancer
Low Symptomatic Brain Metastases in Breast Cancer

Additional relevant MeSH terms:

Breast Neoplasms
Neoplasms by Site
Neoplasms
Breast Diseases
Skin Diseases
Capecitabine
Trastuzumab
Antimetabolites, Antineoplastic
Antimetabolites
Molecular Mechanisms of Pharmacological Action
Antineoplastic Agents