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

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
Cascadian Therapeutics Inc.

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

ClinicalTrials.gov Identifier:
NCT02614794

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

See Contacts and Locations

Study Description

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.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
</tr>
</thead>
</table>

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...
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**

- **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**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Intervention/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental: Tucatinib in combination with</td>
<td>Drug: Tucatinib</td>
</tr>
<tr>
<td></td>
<td>Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or</td>
</tr>
</tbody>
</table>
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
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

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 \( \geq 21 \) days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is \( \geq 7 \) days prior to first dose of study treatment, or time since surgical resection is \( \geq 28 \) 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 \( \leq 21 \) 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

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): NCT02614794
Sponsors and Collaborators

Cascadian Therapeutics Inc.

Investigators

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

More Information

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


Responsible Party: Cascadian Therapeutics Inc.
ClinicalTrials.gov Identifier: NCT02614794 History of Changes
Other Study ID Numbers: ONT-380-206
2015-002801-12 ( EudraCT Number )
First Posted: November 25, 2015 Key Record Dates
Last Update Posted: October 1, 2018
Last Verified: September 2018

Keywords provided by Seattle Genetics, Inc. (Cascadian Therapeutics Inc.):
Tucatinib HER-2 Positive Breast Carcinoma
Capecitabine HER-2 Positive Locally Advanced Breast Cancer
Trastuzumab Recurrent Breast Carcinoma
Xeloda Stage IV Breast Cancer
Herceptin Metastatic Breast Cancer
Breast Cancer Breast Carcinoma
ARRY-380 Metastatic Malignant Neoplasm in the Brain
ONT-380 Brain Metastases in Breast Cancer
HER2 Positive Breast Carcinoma Asymptomatic Brain Metastases in Breast Cancer
HER2 Positive Locally Advanced Breast Cancer Low Symptomatic Brain Metastases in Breast Cancer
HER-2 Positive Breast Cancer

Additional relevant MeSH terms:
Breast Neoplasms Trastuzumab
Neoplasms by Site Antimetabolites, Antineoplastic
Neoplasms Antimetabolites
Breast Diseases Molecular Mechanisms of Pharmacological Action
Skin Diseases Antineoplastic Agents
Capecitabine