Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer (HER2CLIMB-02)

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This study has been transitioned to CTIS with ID 2024-514733-38-00 check the CTIS register for the current data. Primary* Compare progression-free survival (PFS) by investigator assessment per Response Evaluation Criteria inSolid Tumors (RECIST) v1....

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON51919

Source
ToetsingOnline

Brief title
HER2CLIMB-02

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
breast cancer, breast carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Seagen Inc.
Source(s) of monetary or material Support: Farnaceutische industrie

Intervention

Keyword: Breast cancer, HER2, Tucatinib

Outcome measures

Primary outcome

Efficacy Assessments

Disease response per RECIST v1.1 (Eisenhauer 2009) will be assessed by both investigator assessment and BICR. Response assessments will include measurement of all known sites of unresectable LA/M disease (including at a minimum the chest, abdomen, and pelvis), preferably by high quality spiral contrast computed tomography (CT), at baseline, every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose interruptions. Positron emission tomography (PET)/CT (if high quality CT scan included), and/or MRI scan may also be done as appropriate, as well as additional imaging of any other known sites of disease (e.g., skin lesion photography for skin lesions, nuclear bone scan imaging for bone lesions).

Contrast MRI of the brain will be required on this same schedule only in those subjects with prior history of brain metastases or brain metastases found at screening. Additional contrast MRIs of the brain may also be performed in subjects without known brain metastases if there is clinical suspicion of new brain lesions.

Treatment decisions will be made based upon local assessment of radiologic scans. Response assessments for each subject will continue until a PFS event per RECIST v1.1 by investigator assessment has been documented. Follow-up for survival will continue until study closure or withdrawal of consent.

Safety Assessments

Safety assessments will include surveillance and recording of AEs, physical examination findings, and laboratory tests. Assessment of cardiac ejection fraction will be performed by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO).

Secondary outcome

Pharmacokinetic Assessments

PK assessments will be performed from Cycle 3 to Cycle 6 in all subjects to assess the steady state PK of tucatinib and DM1. In the US only, approximately 50 subjects (25 from each treatment arm) will participate in a PK sub-study with additional PK sampling on Days 1, 2, 3, and 5 in Cycle 2 to assess any effects of tucatinib on the PK of DM1.

Other Assessments - Quality of Life

Health-related QoL will be assessed at protocol-specified time points using standardized assessment tools including the European Quality of Life 5Dimension 3Level (EQ-5D-3L) instrument, the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30), National Cancer Institute's patient-reported outcomes version of the Common Terminology

Criteria for Adverse Events (NCIPRO-CTCAE) questionnaire customized to focus on adverse events (AEs) or symptoms of interest, and the Functional Assessment of Cancer Therapy - Breast (FACTB).

Study description

Background summary

Breast cancer is the most common form of cancer in women worldwide, and the second leading cause of cancer-related death in the United States (Ferlay 2013; Siegel 2018). In 2018, the estimated number of men and women who were newly diagnosed with breast cancer in the United States was 268,670 and there were 40,920 deaths overall due to the disease (Siegel 2018). Approximately 15%-20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2) (American Cancer Society 2018; Giordano 2014; Howlader 2014; Owens 2004). HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Tumors that overexpress HER2 are more aggressive and historically have been associated with poorer overall survival (OS) compared to HER2 negative cancers (Slamon 1987).
The introduction of HER2-targeted therapy using either antibody-based therapies or small molecule tyrosine kinase inhibitors (TKI) has led to significant and ongoing improvements in disease-free survival (DFS), progression-free survival (PFS), and OS in both the neoadjuvant/adjuvant and metastatic settings (Baselga 2012b; Geyer 2006; Slamon 2001; Verma 2012). Trastuzumab, a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, was the first anti-HER2 agent approved by the Food and Drug Administration (FDA) for use in the treatment of HER2+ breast cancer, and remains the backbone of treatment in the neoadjuvant, adjuvant, and metastatic settings, usually in combination with a taxane (Slamon 2001; Vogel 2002).
HER2-targeted therapies for the management of metastatic HER2+ breast cancer have led to meaningful prolongation in the median survival of these subjects; however, essentially all subjects in the metastatic setting ultimately progress (Swain 2015; Verma 2012). There have also been significant improvements in the outcomes for early stage HER2+ breast cancer, but despite these improvements, up to a quarter of all subjects treated with anti-HER2 therapy in the adjuvant setting relapse (Chan 2016; Gianni 2012; von Minckwitz 2017). In addition, treatment and prevention of brain metastases continue to be a significant unmet need for subjects with HER2+ breast cancer, with up to 50% of subjects with metastatic disease eventually developing brain metastases (Clayton 2004; Goldhirsch 2013; Pestalozzi 2013).

Study objective

This study has been transitioned to CTIS with ID 2024-514733-38-00 check the CTIS register for the current data.

Primary
* Compare progression-free survival (PFS) by investigator assessment per Response Evaluation Criteria in
Solid Tumors (RECIST) v1.1 between treatment arms
Key Secondary
* Compare overall survival (OS) between treatment arms
* Compare PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline (PFS.BM per investigator)
between treatment arms
* Compare the objective response rate (ORR) by investigator assessment per RECIST v1.1 between treatment
Compare overall survival in subjects with brain metastases at baseline (OS.BM) between treatment arms.
arms
Other Secondary
* Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1 between treatment arms
* Evaluate PFS by BICR per RECIST v1.1 in subjects with brain metastases at baseline (PFS.BM per BICR) between treatment arms
* Evaluate the ORR by BICR per RECIST v1.1 between treatment arms
* Evaluate the duration of response (DOR) by investigator assessment per RECIST v1.1 between treatment
arms
* Evaluate the DOR by BICR per RECIST v1.1 between treatment arms
* Evaluate the clinical benefit rate (CBR; stable disease [SD] or non-complete response [CR]/non-progressive
disease [PD] for >=6 months or best response of CR or partial response [PR]) by investigator assessment per RECIST v1.1 between treatment arms
* Evaluate the CBR by BICR per RECIST v1.1 between treatment arms
* Evaluate the safety of tucatinib in combination with T-DM1
Exploratory
* Evaluate the pharmacokinetics (PK) of tucatinib and DM1 following administration of tucatinib and T-DM1
in combination
* Evaluate on-trial healthcare resource utilization (HCRU) between treatment arms
* Evaluate patient reported outcomes (PROs) and health-related quality of life (QoL) between treatment arms

Study design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+

breast cancer who have had prior treatment with a taxane and trastuzumab in any setting. Baseline disease assessments include measurement of all known sites of unresectable locally advanced/metastatic disease through radiographic imaging. Assessment for brain metastases is performed with contrast MRI of the brain for all subjects, regardless of prior history of brain metastases. Subjects will be randomized in a 1:1 manner to receive 21-day cycles of either tucatinib or placebo in combination with T- DM1. Randomization will be stratified by line of treatment for metastatic disease, HR status, presence or history of brain metastases, and ECOG performance status.
While on study treatment, subjects will be assessed for progression every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions. After completion of study treatment and after occurrence of disease progression, subjects in both arms of the study will continue to be followed for survival until study closure or withdrawal of consent.
An Independent Data Monitoring Committee (IDMC) will periodically review relevant aggregate safety data (blinded and unblinded) and will make recommendations to the sponsor. Safety will also be monitored in an ongoing, blinded basis by the sponsor throughout the study.

Intervention

Subjects will be randomized in a 1:1 manner to receive study treatment on a 21-day cycle, either:
* Control arm: Placebo given orally twice a day (PO BID); T-DM1 3.6 mg/kg given intravenously (IV) every 21 days
* Experimental arm: Tucatinib 300 mg PO BID; T-DM1 3.6 mg/kg IV every 21 days

Duration of Treatment
Study treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. In the absence of clear evidence of radiographic progression, development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs. No crossover from placebo to tucatinib will be allowed. Subjects assessed as having isolated progression in the brain per RECIST v1.1, may be eligible to continue on study treatment for clinical benefit after undergoing local therapy to CNS disease, with approval from the medical monitor.

Study burden and risks

If you participate in this research, it does not mean that your disease will be cured. But if you take part you will help the investigators to get more insight into the treatment of HER2+ breast cancer.

Taking part in the study can have these cons:

- You may experience the side effects or adverse effects, as described in Section 6.
- There may be some discomfort from the measurements during the study. For example: taking a blood sample can be a little painful. Or you could get a bruise as a result.
- Taking part in the study will cost you extra time.
- You have to comply with the study agreements.

What are the cons of research that uses radiation?
For a CT scan, MUGA and ECGs we use X-rays. For this study you will get around 162 mSv of radiation in total. For comparison: the standard radiation that everyone in the Netherlands gets anyway, is about ~2.5 mSv per year. It is not dangerous if you have to have an examination or treatment with radiation for a medical reason.
• If you have other checks with radiation, you should discuss with the investigator if it is wise for you to participate.
• The radiation we use during the study may cause damage to your health. But this is a small risk. We do, however, advise you not to take part in a medical study with radiation again in the near future.
It is possible that an accidental discovery is made during a CT scan, MUGA or ECGs that is not directly related to the research, but does concern your health or that of your family members. If this happens, your own doctor or specialist will discuss with you what needs to happen next. The cost of this will fall under your own insurance policy

Contacts

Public
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Bothell WA 98021
US
Scientific
Seagen Inc.

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Bothell WA 98021
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Histologically confirmed HER2+ breast carcinoma, as determined by sponsor-designated central laboratory testing on tumor tissue submitted prior to randomization (see Section 7.1.1), from either:
a. Archival tissue (most recent tumor tissue sample preferred)
b. If archival tissue is not available, then a newly-obtained baseline biopsy of an
accessible tumor lesion that has not been previously irradiated is required
2. History of prior treatment with a taxane and trastuzumab in any setting, separately or in
combination. Prior pertuzumab therapy is allowed, but not required.
3. Have progression of unresectable LA/M breast cancer after last systemic therapy (as
confirmed by investigator), or be intolerant of last systemic therapy
4. Measureable or non-measurable disease assessable by RECIST v1.1
5. HR (estrogen receptor [ER]/ progesterone receptor [PR]) status must be known prior to
randomization
6. Age >=18 years at time of consent or >= the age of majority in the geographic location
7. ECOG performance status score of 0 or 1 (see APPENDIX B for conversion of performance status using Karnofsky scale, if applicable)
8. Life expectancy >=6 months, in the opinion of the investigator
9. Adequate hepatic function as defined by the following:
a. Total bilirubin <= 1.5 X upper limit of normal (ULN), except for subjects with known
Gilbert*s disease, who may enroll if the conjugated bilirubin is <=1.5 X ULN
b. Transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase
[AST/SGOT] and alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT]) <= 2.5 X ULN (<= 5 X ULN if liver metastases are present)
10. Adequate baseline hematologic parameters as defined by:
a. Absolute neutrophil count >=1.5 X 103/µL
b. Platelet count >=100 X 103/µL

c. Hemoglobin >=9 g/dL
d. In subjects transfused before study entry, transfusion must be >=14 days prior to start
of therapy to establish adequate hematologic parameters independent from transfusion support
11. Estimated glomerular filtration rate (GFR) >=50 mL/min/1.73 m2 using the Modification
of Diet in Renal Disease (MDRD) study equation (see Section 7.8.4).
12. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated
partial thromboplastin time (aPTT) <= 1.5 X ULN, unless on medication known to alter INR and PTT/aPTT.
13. Left ventricular ejection fraction (LVEF) >=50% as assessed by echocardiogram (ECHO)
or multi-gated acquisition scan (MUGA) documented within 4 weeks prior to first dose of study treatment (see Section 6.2.2 for exceptions)
14. For subjects of childbearing potential, as defined in Section 4.3, the following
stipulations apply:
a. Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to the first dose of study treatment. A subject with a false positive result and documented verification that the subject is not pregnant is eligible for participation.
b. Must agree not to try to become pregnant during the study and for at least 7 months
after the final dose of study drug administration
c. Must agree not to breastfeed or donate ova, starting at time of informed consent and
continuing through 7 months after the final dose of study drug administration
d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly
effective methods of birth control (as defined in Appendix K) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration.

15. For subjects who can father children, the following stipulations apply:
a. Must agree not to donate sperm starting at time of informed consent and continuing
throughout the study period and for at least 7 months after the final study drug administration
b. If sexually active with a person of childbearing potential in a way that could lead to
pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix K) starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

c. If sexually active with a person who is pregnant or breastfeeding, must consistently
use 1 of 2 highly effective methods of birth control (as defined in Appendix K) starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration
16. The subject must provide written informed consent
17. Subject must be willing and able to comply with study procedures
18. CNS Inclusion - Based on screening contrast brain magnetic resonance imaging (MRI),
subjects must have at least one of the following:
a. No evidence of brain metastases
b. Untreated brain metastases not needing immediate local therapy. For subjects with
untreated CNS lesions >2.0 cm in diameter on screening contrast brain MRI, approval from the medical monitor is required prior to enrollment.
c. Previously treated brain metastases
i. Brain metastases previously treated with local therapy may either be stable since
treatment or may have progressed since prior local CNS therapy, provided that there is no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator
ii. Subjects treated with CNS local therapy for newly identified lesions or previously
treated and progressing lesions found on
contrast brain MRI performed during screening for this study may be eligible to enroll if all of the following criteria are met:
* Time since SRS is >=7 days prior to first dose of study treatment, time since whole-brain radiation therapy (WBRT) is >=14 days prior to first dose of study treatment, or time since surgical resection is >=28 days
* Other sites of evaluable disease are present
iii. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

Exclusion criteria

1. Prior treatment with tucatinib, afatinib, trastuzumab deruxtecan (DS-8201a), or
any other investigational anti-HER2, anti-EGFR, or HER2 TKI agent. Prior treatment with lapatinib or neratinib within 12 months of starting study treatment (except in cases where they were given for <=21 days and discontinued for reasons other than disease progression or severe toxicity). Prior treatment with pyrotinib for recurrent or mBC (except in cases where pyrotinib was given for <=21 days and discontinued for reasons other than disease progression or severe toxicity)
2. Prior treatment with T-DM1 in any treatment setting

3. History of allergic reactions to trastuzumab or compounds chemically or biologically
similar to tucatinib, except for Grade 1 or 2 infusion related reactions to trastuzumab that were successfully managed, or known allergy to any of the excipients in the study drugs
4. Treatment with any systemic anti-cancer therapy (including hormonal therapy), non-CNS
radiation (palliative or therapeutic), experimental agent or participation in another interventional clinical trial <=3 weeks prior to first dose of study treatment. An exception for the washout of hormonal therapies is gonadotropin releasing hormone agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications.
5. Any toxicity related to prior cancer therapies that has not resolved to <= Grade 1, with the
following exceptions:
* Alopecia;
* Neuropathy, which must have resolved to <= Grade 2;
* Congestive heart failure (CHF), which must have been <= Grade 1 in severity at the
time of occurrence, and must have resolved completely
6. Clinically significant cardiopulmonary disease such as:
* Ventricular arrhythmia requiring therapy
* Symptomatic hypertension or uncontrolled asymptomatic hypertension as determined
by the investigator
* Any history of symptomatic CHF, symptomatic left ventricular systolic dysfunction or symptomatic decrease in
ejection fraction
* Severe dyspnea at rest (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy
* >= Grade 2 QTc prolongation on screening electrocardiogram (ECG)
7. Known myocardial infarction or unstable angina within 6 months prior to first dose of
study treatment
8. Known carrier of Hepatitis B or Hepatitis C or has other known chronic liver disease
9. Subjects known to be positive for human immunodeficiency virus (HIV) if they meet any
of the following criteria:
* CD4+ T-cell count of <350 cells/uL
* Detectable HIV viral load
* History of an opportunistic infection within the past 12 months
* On stable antiretroviral therapy for <4 weeks
10. Subjects who are pregnant, breastfeeding, or planning to become pregnant from time of
informed consent until 7 months following the last dose of study drug

11. Unable to swallow pills or has significant gastrointestinal disease which would preclude
the adequate oral absorption of medications
12. Use of a strong cytochrome P450 (CYP) 3A4 or CYP2C8 inhibitor within 1 week, or use of a strong
CYP3A4 or CYP2C8 inducer within 5 days prior to the first dose of study treatment (see Appendix C and Appendix D). CYP3A4 or CYP2C8 inducers and inhibitors are also prohibited as concomitant medications within 1 week of discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates (Appendix E:) should be avoided 1 week before enrollment and during study treatment.
13. Unable to undergo contrast MRI of the brain
14. Other medical, social, or psychosocial factors that, in the opinion of the investigator,
could impact safety or compliance with study procedures
15. Systemic therapy for another malignancy within 2 years of the start of study treatment
16. CNS Exclusion - Based on screening brain MRI, subjects must not have any of the
following:
a. Any untreated brain lesions >2.0 cm in size, unless approved by the medical monitor
b. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases
at a total daily dose of >2 mg of dexamethasone (or equivalent). However, subjects on a chronic stable dose of <=2 mg total daily of dexamethasone (or equivalent) may be eligible with approval of the medical monitor.
c. Any brain lesion thought to require immediate local therapy, including (but not
limited to) a lesion in an anatomic site where increase in size or possible treatment- related edema may pose risk to the subject (e.g., brain stem lesions). Subjects 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 18c (ii).
d. Known or concurrent leptomeningeal disease as documented by the investigator
e. Poorly controlled (>1/week) generalized or complex partial seizures, or manifest
neurologic progression due to brain metastases notwithstanding CNS-directed therapy

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-07-2021
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	trastuzumab emtansine
Generic name:	T-DM1
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	tukysa
Generic name:	Tucatinib

Ethics review

Approved WMO Date:	02-12-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-03-2021
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	13-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	02-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-514733-38-00
EudraCT	EUCTR2019-005017-39-NL
ClinicalTrials.gov	NCT03975647
CCMO	NL75506.031.20