A multicenter, single arm study of trastuzumab emtansine (T-DM1) in HER2 positive locally advanced or metastatic breast cancer patients who have received prior anti-HER2 and chemotherapy-based treatment

Published: 11-10-2012
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The primary objective of this study is to evaluate the safety and tolerability of trastuzumab emtansine.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON39697

Source
ToetsingOnline

Brief title
T-DM1 (Global Safety Study)

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, HER2 positive locally advanced or metastatic breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Roche Nederland B.V.

Intervention

Keyword: Breast cancer, HER2, Safety, Trastuzumab Emtansine

Outcome measures

Primary outcome

The primary objective of this study is to evaluate the safety and tolerability

of trastuzumab emtansine.

The safety outcome measures for this study are as follows:

• Incidence, nature and severity by National Cancer Institute (NCI) common

terminology criteria for adverse events (CTCA version 4.0 of AEs and SAEs

• Incidence of congestive heart failure (CHF)

• Left ventricular ejection fraction (LVEF) decrease over the course of the

study

• Laboratory test abnormalities

• Premature withdrawal from study and study medication

• Exposure to study medication

Secondary outcome

A secondary objective of this study is to evaluate efficacy of trastuzumab

emtansine treatment.

The efficacy outcome measures for this study are as follows:

• Progression free survival (PFS)

• Overall survival (OS)

• Overall response rate (ORR) = partial response (PR) + complete response (CR)

• Clinical benefit rate (CBR)

• Duration of response (DoR)

• Time To Response (TTR)

The pharmacoeconomics outcomes defined in Section 2.3 will be measured.

• To evaluate the resource expenditures, while on study treatment, due to hospitalizations that are not study-defined evaluations. The number of hospital visits, number of days admitted, and type of visits (emergency department versus inpatient care) will be recorded

Study description

Background summary

Breast cancer (BC) is the most common cancer in women worldwide, both in the developed and the developing world (WHO, World Health Statistics. 2011), with approximately 1.38 million new cases diagnosed in 2008. It is also the leading cause of cancer death in females, accounting for 458,400 deaths (14% of all cancer deaths) in 2008 (Jemal et al. 2011). Almost 100,000 of these BC-related deaths occurred in patients whose tumors overexpressed the human epidermal growth factor receptor 2 (HER2). Metastatic breast cancer (mBC) is incurable, with the primary goal of treatment to extend life and palliate symptoms while preserving quality of life.
The HER tyrosine kinase receptor family is comprised of four receptors: HER1, HER2, HER3, and HER4. These receptors are important mediators of cell growth, survival, and differentiation (Sundaresan et al. 1999). Activation of HER receptors leads to receptor dimerization and cell signaling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase pathway for cellular proliferation.
Overexpression of HER2 is observed in approximately 15-20% of human BCs. Several lines of scientific and clinical evidence support a direct role for HER2 overexpression in the aggressive growth and poor clinical outcomes associated with these tumors (Slamon et al. 1987). The development of trastuzumab in the 1990s provided women with HER2-overexpressing tumors with a markedly better outcome than was possible with chemotherapy alone. Increases in response rate, response duration, and progression free survival (PFS) were

associated with a 5-month survival advantage when trastuzumab was given in the first-line metastatic setting, as demonstrated in the initial Phase III trial (Slamon et al. 2001).
For patients with HER2-positive mBC, the combination of trastuzumab and a taxane is a globally accepted first-line treatment, based on the survival advantage demonstrated in two large pivotal trials (Slamon et al. 2001; Marty et al. 2005). However, virtually all patients with HER2-positive mBC develop progressive disease (PD) and require additional therapies. Importantly, such tumors continue to express high levels of HER2 (Spector et al. 2005), and neither the process of internalization nor the level of surface expression is altered when HER2 is bound by trastuzumab (Austin et al. 2004). HER2-directed combination therapy beyond progression for HER2-positive mBC is an accepted palliative treatment approach.

Study objective

The primary objective of this study is to evaluate the safety and tolerability of trastuzumab emtansine.

Study design

This study is a single-arm, international, multicenter Phase IIIb study to evaluate the safety and tolerability of trastuzumab emtansine.
This study will enroll patients with HER2 positive, unresectable, locally advanced or mBC who have previously received prior anti-HER2 and chemotherapy treatment and have progressed either on metastatic treatment, or within 6 months of completing adjuvant therapy.
Approximately 1000 patients will be enrolled into the study.
The study is estimated to last 4 to 5 years. Enrollment is estimated to take 2 years. The follow-up period will last 2 years after the last patient first visit. Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after last patient first visit, whichever occurs first. Patients who have not progressed at the end of the trial will be offered options to continue with trastuzumab emtansine treatment, see Section 4.2.4
The study design is presented in Figure 2. The schedule of assessments is provided in Appendix 1.
All patients will be followed-up until study closure for survival every 6 months until death, loss to follow-up or withdrawal of consent. Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments every 3-6 months until study closure.

Intervention

Trastuzumab emtansine will be administered intravenously every 3 weeks at a

dose of 3.6 mg/kg.

Study burden and risks

The following assessments are done during the study: Screening/Baseline: Informed Consent • Submission of tumor tissue to test for HER-2 positivity • Submission of tumor tissue for research purposes (other than HER-2 positivity testing) • Medical history (including demographics) • Physical exam including height (screening only) and weight • Heart function tests (ECG, ECHO or MUGA) at screening and if necessary according to judgement of physician • Scans (CT or MRI) and X-ray (at screening) • Blood tests (Screening and each treatment cycle) • Blood samples for research purposes (at screening) • Medical history • Vital signs (blood pressure, pulse, temperature) during screening and each visit •Pregnancy test during screening and once per 3 cycles • Performance status (questionnaire about ability to carry on daily activities) during screening and specific visits • General health status will be performed at any side effects that a patient has experienced • AEs / SAEs • Concomitant therapy during Study • A small amount of pain can be experienced with both the MUGA heart scan and bone scans when the tracer (a radioactive chemical which emits a type of radioactivity) is injected but otherwise the test is painless • There is a slight
risk of developing an allergic reaction to the contrast material or the tracer. The reaction can be mild (itching, rash) or severe (difficulty breathing or sudden shock). Death resulting from an allergic reaction is rare. Most reactions can be controlled using medication • The extra radiation involved in the MUGA and bone scans is very small and comparable to receiving a standard chest X-ray.

The following common side effects (>= 10% of Patients) were seen with Trastuzumab Emtansine: Dyspnea difficulty breathing while resting, Fatigue, Lack or loss of strength, Skin rash, Nose bleed, Fever, Chills, Cough, Insomnia, Nausea, vomiting, constipation, diarrhea, abdominal pain, Dry mouth, sores in mouth, Temporary abnormal liver function tests, Low numbers of platelets, Low numbers of red blood cells and hemoglobin, Neuropathy in arms and legs (tingling, pain, numbness, itching, pins and needles), Low potassium in blood, Pain in joints and muscle, Headache. The following side effects (>= 1% to <10% of Patients) were seen with Trastuzumab Emtansine: Heart disorders: ejection fraction decreased, High blood pressure, Dry eye, increased tears, blurred vision, pinkeye, Edema (arms and legs), Itchy skin, Dizziness, Altered taste sensation, Upset stomach or indigestion, Neutropenia, High levels alkaline phosphatase in blood, Reaction to infusion and hypersensitivity (allergic reaction). Rare but Serious (< 1% of Patients): Pneumonitis (inflammation of the lung), Severe liver dysfunction including localized high blood pressure in liver and development of benign nodules.
Rare cases of severe liver toxicity, including death resulting from drug-induced liver injury and worsening of brain function because the liver is no longer able to remove toxic substances, have been observed in patients

treated with trastuzumab emtansine. Rare instances of severe toxicity and cardiac death and Rare cases of severe lung inflammation including fatal cases have been observed with trastuzumab emtansine.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. HER2-positive disease determined locally i.e., IHC 3 + and/or gene-amplified by in-situ hybridization (ISH) as per institutional practice, (however, both tests should be performed wherever possible and only one positive result is required for eligibility)
2. Histologically or cytologically confirmed invasive BC
3. Prior treatment for BC in the advanced/metastatic, unresectable locally advanced or metastatic setting must include an anti-HER2 agent and chemotherapy in combination or sequential administration (complementary hormonal therapy is allowed)

4. Documented progression of incurable, unresectable, locally advanced, or mBC, defined by the investigator: progression must occur during or after most recent treatment for locally advanced/mBC or within 6 months after completing adjuvant therapy
5. Measurable and/or non-measurable disease
6. Signed written informed consent approved by the institution*s independent Ethics Committee (EC)
7. Age >= 18 years
8. Left ventricular ejection fraction >= 50% by either ECHO or MUGA
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0,1 or 2
10. Adequate organ function
11. For women of childbearing potential and men with partners of childbearing potential agreement by the patient and/or partner to use a highly effective non-hormonal form of contraception.
12. Negative serum pregnancy test for women of childbearing potential and for all women not meeting the definition of postmenopausal, and who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential.

Exclusion criteria

1. History of treatment with trastuzumab emtansine;2. Prior enrolment into a clinical study containing trastuzumab emtansine regardless of having received trastuzumab emtansine or not;3. Peripheral neuropathy of Grade >= 3 per NCI CTCAE Version 4.0;4. History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage 1 uterine cancer, synchronous or previously diagnosed HER2-positive breast cancer, or cancers with a similar curative outcome as those mentioned above;5. History of receiving any anti-cancer drug/biologic or investigational treatment within 21 days prior to first study treatment except hormone therapy, which can be given up to 7 days prior to first study treatment; recovery of treatment-related toxicity consistent with other eligibility criteria;6. History of exposure to the following cumulative doses of anthracyclines:;• Doxorubicin or liposomal doxorubicin > 500 mg/m2;• Epirubicin > 900 mg/m2;• Mitoxantrone >120 mg/m2;• If another anthracycline, or more than one anthracycline, has been used, the cumulative dose must not exceed the equivalent of 500 mg/m2 doxorubicin.;7. History of radiation therapy within 14 days of first study treatment. The patient must have recovered from any resulting acute toxicity (to Grade <= 1) prior to first study treatment.;8. Metastatic CNS disease only;9. Brain metastases which are symptomatic. NOTE: A 14 days window after end of radiotherapy must be observed. Patient must not be receiving steroids to control symptoms.;10. History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment;11. History of symptomatic congestive heart failure (CHF; New York Heart Association [NYHA] Classes II*IV) or serious cardiac arrhythmia requiring treatment;12. History of myocardial infarction or unstable angina within 6 months of first study treatment;13. Current dyspnea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy;14. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular,

pulmonary, or metabolic disease);15. Pregnancy or lactation;16. Currently known active infection with HIV, hepatitis B virus, or hepatitis C virus;17. History of intolerance (such as Grade 3*4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins or any component of the product. ;18. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol throughout

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-02-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	kadcyla
Generic name:	trastuzumab emtansine (T-DM1)

Ethics review

Approved WMO

Date:	11-10-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	02-11-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-12-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-01-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-04-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-10-2013
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-02-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-07-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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
Other	Alle studies worden, zodra er patienten in zitten, publiek gemaakt op www.rochetrials.com. Via het protocolnummer kan de studie gevonden worden. Het EUDRACT nummer is: 2012-001628-37
EudraCT	EUCTR2012-001628-37-NL
CCMO	NL42030.031.12