A phase II prospective imaging study evaluating the utility of pre-treatment zirconium-89 labelled trastuzumab PET/CT and an early FDG-PET/CT response to identify patients with advanced HER-2 positive breast cancer unlikely to benefit from a novel anti-HER2 therapy: T-DM1

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

Summary

ID

NL-OMON43903

Source
ToetsingOnline

Brief title
ZEPHIR

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
HER2 positive breast cancer; Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Institut Jules Bordet
Source(s) of monetary or material Support: Hoffmann-La Roche,Jules Bordet Institute Brussel

Intervention

Keyword: advanced HER2 positive breast cancer, FDG-PET/CT, T-DM1, zirconium-89 labelled trastuzumab PET/CT

Outcome measures

Primary outcome

The primary endpoint for this study is the negative predictive value (NPV) of

the 89Zr-trastuzumab PET/CT, defined as the proportion of lesions with a

negative imaging test result which will be classified as non responding lesions

(stable or progressive) after 3 cycles of T-DM1.

Secondary outcome

The secondary endpoint is the negative predictive value of the early FDG

PET/CT, defined as the proportion of lesions without an early metabolic

response that will be classified as non responding lesions after 3 cycles of

T-DM1 according to anatomic and metabolic criteria.

Study description

Background summary

Approximately 20% to 25% of primary human breast cancers are HER2*positive and

are associated with aggressive growth and poor clinical outcome. Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of HER2, is associated with substantial activity and improved survival when combined to chemotherapy (mostly taxane) in the metastatic and adjuvant setting. The tyrosine kinase inhibitor lapatinib, in combination with capecitabine, is indicated for patients with advanced or metastatic HER2* positive breast cancer after prior trastuzumab, anthracycline, and taxane treatment.Unfortunately, all patients with metastatic disease ultimately progress on HER2*directed therapies. Trastuzumab*DM1 (T*DM1) is a novel anti* HER2 antibody*drug conjugate (ADC) that combines the HER2*targeting properties of trastuzumab with intracellular delivery of DM1, a highly potent derivative of the antimicrotubule agent maytansine. TDM1 is currently in development, with phase I and II studies already conducted. Those studies defined 3,6mg/kg every 3 weeks as optimal dose, showed a favourable safety profile and response rates correlated to the HER2 expression levels.

For the HER2 targeted therapy TDM-1 it is essential to safely and accurately predict the presence or absence of HER2, especially since
HER2 status of a tumor can vary during the course of the disease and even in the same patient between distinct tumor lesions. Instead of repeated biopsies, molecular imaging using HER2 PET might be able to identify HER2 status over time on whole body image. By perfoming and FDG and an HER2 PET/CT before TDM-1 treatment, HER2 negative tumors not expected to respond to therapy can be determined. Also by performing an early FDG-PET the early metabolic response can be determined, thereby detecting HER2 positive non responding lesions. This technique in the future can be exceptionally usefull to guide anti-HER2 therapy.

Study objective

The primary objective (on lesion-based analysis) is to show that pre-treatment 89Zr-trastuzumab PET/CT is able to select lesions not responding morphologically from treatment with T-DM1 (applying RECIST 1.0 criteria)

Secondary Objectives and endpoints on a lesion-based analysis
Early FDG-PET/CT
The objective is to show that early FDG PET/CT (performed after one cycle of T-DM1 just before the second cycle) is able to select lesions not responding from treatment with T-DM1 according to metabolic and morphological response criteria post 3 cycles of T-DM1.
The secondary endpoint is the negative predictive value of the early FDG PET/CT, defined as the proportion of lesions without an early metabolic response that will be classified as non responding lesions after 3 cycles of T-DM1 according to anatomic and metabolic criteria.

89Zr-trastuzumab PET/CT
The objective is to show that 89Zr-trastuzumab PET/CT is able to select lesions

not responding from treatment with T-DM1 according to metabolic response criteria post 3 cycles of T-DM1
The secondary endpoint is the negative predictive value of the 89Zr-trastuzumab PET/CT, defined as the proportion of lesions with a negative HER2 imaging test result that will be classified as non responding lesions after 3 cycles of T-DM1 according to metabolic criteria.
This secondary endpoint will allow the evaluation of the correlation between HER2 expression quantitatively defined on 89Zr-trastuzumab PET/CT and the metabolic response observed on FDG PET/CT.

Combination of 89Zr-trastuzumab PET/CT and Early FDG-PET/CT
The objective is to show that a lesion with no/faint uptake on 89Zr-trastuzumab PET/CT and not responding metabolically on the early FDG-PET/CT will not respond according to metabolic and morphological criteria after 3 cycles of T-DM1.

Exploratory/confirmatory Objectives of the clinical imaging study
- Confirm the antitumor activity of T-DM1 in metastatic HER2 positive breast cancer.
- Confirm on a patient-based analysis in 105 patients whether the combination of HER2 PET/CT and early FDG metabolic response assessment can indeed predict with high NPV and PPV whether the patients will benefit or not from T-DM1 (benefit being defined as being responder using RECIST 1.1 assessment and FDG assessment).
- Explore if the early FDG PET performed in a timely manner (eg within 7 days before start of therapy) is also associated with a high NPV.
- Confirm the predictive value of HER2 PET/CT positive combined to early metabolic response on time to treatment failure : indeed, we found, on the series of the 60 first included patients, a median time to treatment failure of 13.3 months for patients with most or all lesions HER2+ and early responders (n=25, 18 events, group 1) compared to a median of 2.8 months for patients with most or all lesions HER2- and being non responders on early FDG-PET (n=13, 13 events, group 2).
- Compare, on a lesion basis, the anatomopathological HER2 status (performed on the primary tumor or metastasis) with the 89Zr-Trastuzumab PET/CT imaging results.
- Explore if the biodistribution of the tracer (in case myocardial uptake) can predict changes in Left Ventricular Ejection Fraction (LVEF) or cardiac toxicity.
- Detect any potential antitumor activity of T-DM1 on asymptomatic brain lesions detected by HER2 PET/CT.
- Demonstrate that standardization of 89Zr-Trastuzumab PET/CT is feasible in a multicentric trial using a Molecular Imaging Core Lab (ORILaB).

Study design

This is a multicenter, non randomised phase II single agent study with an

extensive imaging component designed to evaluate the utility of a pre*treatment 89Zr labelled trastuzumab PET/CT combined with an early FDG PET/CT response as a way to identify patients with locally recurrent and/or metastatic HER2 positive breast cancer unlikely to respond from a novel anti*HER2 therapy: T* DM1. A total of 105 patients will be enrolled in 5 university hospital sites in Belgium and the Netherlands.

Following the determination of eligibility a patients will undergo FDG PET/CT and 89Zr*trastuzumab PET/CT (4 days after tracer injection) followed by intravenous T*DM1 administration (3.6mg/kg) over 30*90 minutes on Day 1 of cycle 1 every 3 weeks. Before the second cycle of T*DM1, an early FDG PET/CT will be performed in order to assess the early metabolic response. After 3 cycles of T*DM1, response assessment will be done according to morphological criteria (RECIST 1.0 and 1.1) and FDG PET/CT response criteria (PERCIST and EORTC criteria).

Intervention

Following the determination of eligibility and screening (including ECG, LVEF evaluation and biopsy of one tumor lesion), patients will undergo FDG PET/CT and 89Zr*trastuzumab PET/CT (4 days after tracer injection) followed by intravenous T*DM1 administration (3.6mg/kg) over 30*90 minutes on Day 1 of cycle 1 every 3 weeks. Before the second cycle of T*DM1, an early FDG PET/CT will be performed in order to assess the early metabolic response. After 3 cycles of T*DM1, response assessment will be done according to RECIST 1.1 and FDG PET/CT response criteria (EORTC criteria).

Study burden and risks

For this study patients should visit the clinic 3-4 times for screening (including the first FDG PET/CT, biopsy, ECG, MUGA/echocardiography), followed by 2 visits for the HER2 PET/CT (1x tracer injection and 1x for the actual scan), after which T-DM1 treatment (3,6 mg/kg once every 3 weeks) can start. After the first en third T-DM1 cycle FDG PET/CTs will be performed. Thereafter patients can continue the T-DM1 treatment until progression or unacceptable toxicity. HER2 PET/CT implements a radiation burden of about 20 mSv. Also the biopsy is associated with risk on bleeding and infection. Furthermore patients may experience side effects of the new drug.No standard treatment for patients in this setting exists and this trial gives these patients access to the new targeted drug T-DM1. By participating in this study, our knowledge about the use of immunoPET, which may guide patient treatment in the future, will be further improved.

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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.The patient must have histologically confirmed HER2 positive invasive carcinoma of the breast in the reference laboratory of the participating center. HER2 positive criteria to be applied are those used in the participating countries:
- Belgium: FISH amplification ratio * 2 in the reference laboratory of the participating center
- The Netherlands: IHC 3+ or FISH ratio *2 in the reference laboratory of the participating center
2.The patient must have documented progressive disease and present with at least 2 non-bone *target* metastatic lesions, unequivocally of neoplastic origin with a transaxial diameter greater than 2 cm on the screening diagnostic CT/MRI. These two lesions should not be confluent with adjacent lesions and not have been irradiated previously
3. A concurrent biopsy of a metastatic site is mandatory (with two formalin fixed paraffin embedded (FFPE) core sample and two snap frozen tumor sample) after progression has

been documented and before inclusion and the patient agrees with the procedure.
4. Primary tumor blocks (or 11 unstained slides) available for confirmatory central laboratory HER2 testing in Jules Bordet Institute. If available, a snap frozen sample of the primary tumor will also be centralized in Jules Bordet Institute.
5.Age >= 18 years
6.Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1
7.No significant cardiac history and current LVEF >= 50%
8.Adequate organ function, evidenced by the following laboratory results:
• Absolute neutrophil count > 1,500 cells/mm3
• Platelet count >100,000 cells/mm3
• Hemoglobin > 9 g/dL
• AST (SGOT) and ALT (SGPT) <2.5xULN
• Total bilirubin <= 1.5xULN unless the patient has documented Gilbert's syndrome. Patients with known Gilbert's Syndrome should have direct bilirubi within normal limits.
• Serum alkaline phosphatase <= 2.5 × ULN. Patients with bone metastases <= 5x ULN
• Serum creatinine < 2.0 mg/dL or 177 µmol/L
• International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) <1.5 x ULN (unless on therapeutic anti-coagulation excpet vitamin K antagonists which are prohibited in this study)
9.Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
10.For women of childbearing potential a pregnancy test will be done (and it must be negative) and an agreement to use a highly-effective form of contraception during all the study and at least the following 7 months will be obtained.
11.Signed written informed consent obtained prior to any study specific procedure.
12. Completion of all necessary baseline surgical, laboratory and imaging investigations prior to patient inclusion (see Section 5 and Figures 1- 2 for the schedule of assessments).

Exclusion criteria

1.Patients with bone only metastases are not eligible
2.Diffuse liver (>= 50%) involvement on imaging
3.Patients with brain metastasis as the sole site of metastatic disease and/or are symptomatic or require therapy to control symptoms
NB: Brain metastasis are allowed provided they are asymptomatic and/or controlled by previous radiotherapy. In case of recent prior brain radiotherapy, there must be evidence on MRI imaging of brain metastatic control for at least 6 weeks since the end of radiotherapy. Moreover, the patient should be at the end of corticosteroid therapy and be clinically asymptomatic.
4.Current uncontrolled hypertension despite medication intake (systolic > 150 mmHg and/or diastolic > 100 mmHg)
5.Current unstable angina
6.History of symptomatic CHF of any New York Heart Association (NYHA) criteria or ventricular arrhythmia that requires treatment

7. History of myocardial infarction within the last 6 months
8.History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment
9.Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy
10. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures)
11.History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those previously mentioned
12.Pregnant or lactating women
13.Current known uncontrolled infection with HIV, HBV, or HCV
14.Known prior severe hypersensitivity to trastuzumab
15.Patient who received lapatinib within the 15 days prior to 89Zr-trastuzumab injection
16.Patients under a prohibited concomitant therapy including vitamin K antagonists
17. Patients with a peripheral neuropathy grade 3 or higher.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2012
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin□DM1
Generic name:	Trastuzumab-DM1

Ethics review

Approved WMO Date:	06-03-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-06-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-08-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2014

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-04-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-04-2021

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2011-005437-39-NL
ClinicalTrials.gov	NCT01565200
CCMO	NL39546.042.12