A multicenter randomized phase III study to compare the combination trastuzumab and capecitabine, with or without pertuzumab, in patients with HER2-positive metastatic breast cancer that have progressed after one line of trastuzumab-based therapy in the metastatic setting (PHEREXA)

Published: 04-02-2010
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To compare progression-free survival (PFS) between the two treatment arms based on assessments by an independent review facility (IRF).

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

Summary

ID

NL-OMON41586

Source
ToetsingOnline

Brief title
Pherexa

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym

breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Covance
Source(s) of monetary or material Support: Hoffmann- la Roche

Intervention

Keyword: capecitabine, metastatic breast cancer, pertuzumab, trastuzumab

Outcome measures

Primary outcome

Primary objective

* To compare progression-free survival (PFS) between the two treatment arms

based on assessments by an independent review facility (IRF).

Secondary outcome

Secondary objectives

* To evaluate:

o Overall survival (OS)

o PFS based on tumor assessments by the Investigators

o Time to progression (TTP) based on IRF assessment

o Time to treatment failure (TTF) based on IRFassessment

o Overall objective response rate (ORR) clinical benefit rate (CBR), based on

Investigator and IRFassessments

o Duration of objective response (DR) based on IRF assessment

o Safety and tolerability of trastuzumab plus capecitabine in combination with

pertuzumab

o Correlation between biomarkers from tumor tissues and clinical outcomes

Study description

Background summary

It is now well established that continuation of HER2 therapy, specifically trastuzumab, is highly beneficial for metastatic breast cancer patients. However, it remains unknown how best to combine the different medications to maximize the benefit to the patient, minimize toxicity and increase tolerability. Please also refer to page 43 of the study protocol.

Study objective

To compare progression-free survival (PFS) between the two treatment arms based on assessments by an independent review facility (IRF).

Study design

Multicenter, randomized, open label phase II clinical trial. Patients will be randomized in a 1:1 ratio to one of the following two arms:
* Arm A: capecitabine + trastuzumab
* Arm B: capecitabine + trastuzumab + pertuzumab
Stratification factors will include prior CNS Disease (clinically present /absent), measurable vs. non-measurable disease at baseline, and response to first-line trastuzumab treatment (yes/no, with response defined as PR or CR and non-response defined as SD or PD).

Intervention

Patients will be randomized in a 1:1 ratio to one of two arms:

Arm A: trastuzumab + capecitabine
Arm B: pertuzumab + trastuzumab + capecitabine
Study drugs will be administered in 3-weekly cycles

Pertuzumab:
Patients randomized to arm B will receive pertuzumab as an IV loading dose of 840 mg for Cycle 1, and 420 mg for subsequent cycles.
Pertuzumab will be administered every 3 weeks until disease progression, unmanageable toxicity or patient request for discontinuation.

Trastuzumab:
Patients in both groups will receive trastuzumab 8 mg/kg IV loading dose

administered over 90 minutes followed by 6 mg/kg doses administered over 90 minutes every 3 weeks.

Capecitabine:
Patients in arm A will receive capecitabine 1250 mg/m² administered twice-daily (morning and evening, equivalent to 2500 mg/m2 total daily dose) for 14 days followed by 7-day rest period, repeated every 3 weeks.
Patients in arm B will receive capecitabine administered 1000 mg/m² twice-daily (morning and evening, equivalent to 2000 mg/m2 total daily dose) for 14 days followed by 7-day rest period, repeated every 3 weeks.

Study burden and risks

*Burden:Patients participating in this trial may have to undergo more MUGA, CT and/or MRI scans than in standard medical treatment. In addition, patients will be requested to undergo the procedures indicated under E4.

*Risks: The most commonly reported side effect of pertuzumab are:diarrhoea in around 50% of patients, allergic reactions such as fever, chills, hypotension (low blood pressure), shortness of breath, headache, nausea and/or vomiting in around 40% of patients, nausea and fatigue in around 20% of patients. rash in 17% of patients, vomiting and abdominal pain in around 10% of patients, lack of appetite, redness and soreness in the mouth, physical weakness and lack of strength and itching in 5 to 10% of patients.

The most commonly reported side effect of trastuzumab (Herceptin®) are: diarrhoea in around 25% of patients, allergic reactions such as fever, chills, hypotension (low blood pressure), shortness of breath, headache, nausea and/or vomiting in around 40% of patients, nausea, fatigue, vomiting and abdominal pain in more than 10% of patients.

The most commonly reported side effect of capecitabine (Xeloda®) are: hand-foot syndrome, diarrhoea, nausea and/ or vomiting, redness and soreness in the mouth, fever, decreased amount of fluid in the body, chest pain, decrease in red and white blood cells, possibly changes in liver function, hair loss, skin rashes, fatigue, weakness, loss of appetite and weight, abdominal pain, eye irritation, headache, dizziness, depression and insomnia.
Very rare, severe skin reactions (Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported in patients receiving capecitabine.

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

Disease-Specific:
1.Pathologically confirmed breast cancer and documented metastatic disease.
2.HER2-positive (FISH/CISH-positive or IHC 3+*) MBC confirmed by a Sponsor-designated central laboratory. Availability of a FFPE tumor tissue sample from primary tumor for eligibility testing (HER2-status) is mandatory (minimum 6 slides). Additional tumor tissue material for biomarker assessment is requested (if available).
3.Disease progression during or following a trastuzumab-based treatment for first-line metastatic breast cancer.
4.Trastuzumab must have been part of the last prior treatment regimen.
5.Prior treatment with a taxane-containing regimen.;General:
6.Female patients, age *18 years.
7.LVEF * 50% at baseline (assessed within 42 days prior to randomization) as determined by either 2D echocardiogram (ECHO) or MUGA (ECHO is the preferred method). If the patient is randomized, the same method of LVEF assessment, ECHO or MUGA, must be used throughout the study, and to the extent possible, be obtained at the same institution.
8.Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
9.For women of childbearing potential agreement to use highly effective form of contraception (patient and/or partner, e.g., surgical sterilization, or true abstinence) or two

effective forms of contraception, a reliable barrier method, condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and an intrauterine device (IUD) or intrauterine system (IUS) and to continue its use for the duration of study treatment and for at least 7 months after the last dose of study treatment. Periodic abstinence (e.g., calendar ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Postmenopausal is defined as * 12 months of amenorrhea.
10.Written and signed informed consent (approved by the Independent Ethics Committee) obtained prior to beginning any protocol-specific procedures.

Exclusion criteria

Cancer-Related:
1.Prior therapy with pertuzumab or capecitabine.
2.Concurrent immunotherapy or anticancer hormonal therapy.
3.Existing acute reversible effects of prior treatment. This generally means at least 3 weeks should have elapsed since prior chemotherapy and at least 4 weeks since prior (radical) radiotherapy or major surgery.
4.History of another malignancy which could affect compliance with the protocol or interpretation of results. Patients treated with curative intent and disease-free for at least 5 years are generally eligible, as are patients treated curatively for carcinoma in situ of the cervix or non melanomatous skin cancer.
5.CNS metastases which are not well controlled. Eligible patients must be asymptomatic, can not be receiving steroids, and must be enrolled at least 1 month after the end of the radiotherapy treatment. Note: CT or MRI scan of the brain is mandatory (within 4 weeks prior to randomization) in case of clinical suspicion of CNS metastases.
6.History of exposure to at least one of the following cumulative doses of anthracyclines:
*doxorubicin or liposomal doxorubicin > 360 mg/m2
*epirubicin > 720 mg/m2
*mitoxantrone > 120 mg/m2
*idarubicin > 90 mg/m2
*Other (e.g. liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m2 of doxorubicin)
*If more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin.
Hematological, Biochemical and Organ Function:
7.Current uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mmHg) or unstable angina.
8.History of CHF of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (except for atrial fibrillation and/or paroxysmal supraventricular tachycardia).
9.History of myocardial infarction within 6 months of randomization.
10.History of LVEF decline to below 50% during or after prior trastuzumab therapy or other cardiac toxicity during previous trastuzumab treatment that necessitated discontinuation of trastuzumab.

11.Current dyspnoea at rest requiring supportive oxygen therapy or with significant pleural effusions.
General Exclusion Criteria
12.Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization:
*absolute neutrophil count (ANC) < 1.5 x 109/L
*platelet count < 100 x 109/L
*hemoglobin < 9 g/dL
*serum (total) bilirubin > 1.5 x the upper limit of normal (ULN) (unless the patient has documented Gilbert*s syndrome)
*AST/SGOT or ALT/SGPT >2.5 x ULN (> 5 x ULN in patients with liver metastases)
*Alkaline phosphatase levels > 2.5 times the ULN at screening/baseline (> 5 x ULN in patients with liver metastases, or > 10 x ULN in patients with bone metastases)
*Moderate or severe renal impairment [creatinine clearance equal to or below 50ml/min (calculated according to Cockroft and Gault, see Appendix 2)], or serum creatinine > upper limit of normal (ULN)
*International normalized ratio (INR) and activated partial thromboplastin time (aPTT) >1.5 x ULN (unless on therapeutic coagulation)
13.Current severe, uncontrolled systemic disease (e.g. clinical significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
14.Evidence of any other disease, metabolic or psychological dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, or that may affect patient compliance with study routines, or place the patient at high risk from treatment complications.
15.Patients with insulin-dependent diabetes.
16.Major surgical procedure or significant traumatic injury within 28 days prior to study treatment start or anticipation of the need for major surgery during the course of study treatment with full recovery.
17.Pregnant or lactating females.
18.Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational drug within 30 days prior to study screening.
19.Current known infection with HIV, HBV, or HCV.
20.Active infection requiring antibiotics within 14 days of randomization.
21.Current chronic daily treatment with corticosteroids (dose of >10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).
22.Known hypersensitivity to any of the study drugs or excipients. History of severe and unexpected reactions to fluoropyrimidine therapy.
23.Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or ulcerative colitis.
24.Psychiatric disability judged by the Investigator to be interfering with compliance for oral drug intake.
25.Known deficiency or family history of deficiency of dihydropyrimidine dehydrogenase.
26.Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine.
27.Life expectancy <12 weeks.
28.Inaccessible for treatment and/or follow-up or unwilling to comply with the requirements

of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2011
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin
Generic name:	Trastuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	Pertuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	Capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-02-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2008-006801-17-NL
CCMO	NL29687.029.10