A multicenter, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer

Published: 05-03-2012
Last updated: 26-04-2024

The objective of this study is to investigate the safety and efficacy of pertuzumab in combination with standard therapy, trastuzumab and a taxane.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON47342

Source
ToetsingOnline

Brief title
PERUSE

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms benign

Synonym
Adenocarcinoma, HER2-positive Metastatic Breast Cancer

Health condition

HER2-positieve gevorderde (gemetastaseerd of locaal recidiverend) borstkanker

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Breast cancer, HER2, Pertuzumab, Trastuzumab

Outcome measures

Primary outcome

To evaluate the safety and tolerability of pertuzumab in combination with

tratuzumab and a taxane.

Secondary outcome

To evaluate pertuzumab in combination with trastuzumab and a taxane with

respect to:

* Progression-free survival (PFS)

* Overall survival (OS)

* Overall response rate (ORR)

* Clinical benefit rate (CBR)

* Duration of response

* Time to response

* Quality of life (Functional Assessment of Cancer Therapy-Breast [FACT-B]

questionnaire for female patients only).

Study description

Background summary

Breast cancer is the most common cancer in women, with a global prevalence of more than 1 million patients and an annual mortality rate of approximately 450,000 deaths (American Cancer Society). While improved early detection and advances in systemic therapy for early stage disease have resulted in a small decline in breast cancer mortality since 1989, metastatic breast cancer (MBC) remains largely incurable with a median survival of approximately 24 months (National Cancer Institute, www.seer.cancer.gov). Factors associated with poor survival include age * 50 years, visceral disease, shorter disease-free interval, aneuploid tumors, tumors with a high S-phase fraction, p53 accumulation, low
bcl-2 expression, negative hormone receptor status, and positive human epidermal growth factor receptor 2 (HER2) status (Chang 2003).

Although the treatment of MBC is palliative rather than curative in intent, improvement in survival is an important treatment goal. There is a significant need for new agents with novel mechanisms of action and non-overlapping toxicity, which can be combined with established treatment for breast cancer.

Evidence suggests that dysregulation of ligands and receptors of the HER family are important in the pathogenesis of cancer. The HER tyrosine kinase receptor family is comprised of four receptors: HER1 (epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4. These receptors mediate tumor cell growth, survival, and differentiation (Sundaresan et al. 1999; Yarden and Sliwkowski 2001). HER receptors normally exist as inactive monomers. Activation of HER receptors occurs following ligand binding, leading 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. HER2 has no known ligand and, in a state of overexpression, can form active homodimers and initiate tyrosine kinase signaling without ligand stimulation. Additionally, as HER2 concentrations increase, the incidence of HER2 interactions with other receptors is also increased, resulting in a broad recruitment of a number of proteins (Jones et al. 2006). Recent data obtained using micro-array technology suggest that the HER2 receptor can bind to more than 17 different proteins and may recruit proteins that other HER receptors cannot recruit. These activities highlight the promiscuity of HER2 in its ability to bind to other HER receptors and initiate tyrosine kinase signaling through several mechanisms (Jones et al. 2006).

Approximately 18-25% of patients overexpress HER2. Overexpression of HER2 in breast cancer has been correlated with high histologic grade, increased mitotic activity, p53 mutation, negative estrogen receptor (ER) status, absence of bcl2, and absence of lobular architecture. Despite associations with other

known negative prognostic factors, HER2 overexpression has been independently associated with poorer disease-free survival and overall survival (OS) compared with tumors that do not overexpress HER2 (Pauletti et al. 2000). Approximately 65% of breast cancers are ER-positive and progesterone receptor-positive (American Cancer Society).

Study objective

The objective of this study is to investigate the safety and efficacy of pertuzumab in combination with standard therapy, trastuzumab and a taxane.

Study design

This study is an open-label, single-arm, multicenter Phase IIIb study to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane. Patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) who have not previously received systemic non-hormonal anticancer therapy in the metastatic setting are eligible to participate in the study. Approximately 1500 patients will be enrolled into the study in approximately 250-300 centers worldwide. Details of the treatment are given in Section 4.3. Patient will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, or death whichever occur first.

End of study: All patients will continue to be followed up until at least 60 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, whichever occurs first.

Intervention

Pertuzumab will be administered as an intravenous infusion on Day 1 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 of each subsequent 3 weekly cycle. Pertuzumab will be administered first.

Initial infusions of pertuzumab will be administered over 60 (± 10) minutes and patients observed for a further 60 minutes from the end of infusion for infusionassociated symptoms such as fever, chills etc. Interruption or slowing of the infusion may reduce such symptoms. If the infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes, with patients observed for a further 30 minutes.

Study burden and risks

The most common adverse events (also known as side-effects) reported as related to pertuzumab and trastuzumab are:
* Diarrhea is reported by approximately 67% of patients

* Neutropenia (a reduction in white blood cells, which are needed to fight infection) occurs in about half of patients and can be serious, especially if accompanied by fever. Anemia (a lack of red blood cells) occurs in about a quarter of patients.
* Symptoms such as nausea, fever, diarrhea, chills, shortness of breath, fatigue, rash and headache have been observed in between about 20% to 40% of patients. They were in general mild to moderate but may occur as an allergic reaction on the same day as the infusion in approximately 20% of patients and can, very rarely, be severe (anaphylaxis).
* Mucosal inflammation (inflammation of the lining of the mouth, gastrointestinal or genital tract), decreased appetite, vomiting, an abnormal sense of taste, disorders of the nails, asthenia (physical weakness and lack of strength) or aching of the muscles or joints may occur in about 20% to 30% of patients.
* Colds or chest infections and dry and/ or itchy skin (pruritus) can occur in around 15% of patients.
Less frequently, some patients developed heart failure (inadequate pumping of the heart) whilst having trastuzumab and/or pertuzumab treatment. In many cases, this was due to the fact that they had been treated with trastuzumab in combination with certain other chemotherapy drugs (called doxorubicin or epirubicin).

The following problems may be caused by taxanes such as docetaxel, paclitaxel, or nab-paclitaxel:
* Alopecia (hair loss) and edema (swelling) of the ankles and feet.
* Neutropenia (reduction in white blood cells) usually occurring 7 days after the infusion.
* Allergic reactions such as fever, chills, hypotension (low blood pressure), shortness of breath, headache, flushing and rashes. These reactions usually occur during the first or second infusion within minutes. They are in general mild to moderate.
* Peripheral neuropathy (numbness, tingling and pain in the fingers and toes).
* Nausea, vomiting, constipation or diarrhea.
* Pain and swelling at the injection site and the surrounding veins.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL
Scientific

Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed written informed consent approved by the relevant Institutional Review Board (IRB), or Independent Ethics Committee (IEC).;2. Male or female patients aged 18 years or over.;3. Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally recurrent disease not amenable to curative resection.;4. HER2-positive (defined as either IHC 3+ or in situ hybridization [ISH] positive) as assessed by local laboratory on primary tumor and/or metastatic site if primary tumor not available (ISH positivity is defined as a ratio of 2.0 or greater for the number of HER2 gene copies to the number of signals for CEP17, or for single probe tests, a HER2 gene count greater than 4).;5. At least one measurable lesion and/or non-measurable disease evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix 5).;6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 (Appendix 3).;7. LVEF of at least 50%.;8. Negative serum pregnancy test in women of childbearing potential (WOCBP; premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization).;9. For WOCBP and male patients with partners of CBP who are sexually active, agreement to use a highly effective, non-hormonal form of contraception (such as surgical sterilization) or two effective forms of non-hormonal contraception (such as a barrier method of contraception in conjunction with spermicidal jelly) during and for at least 7 months post-study treatment (refer to Section 4.5.2.1 for details).;10. Life expectancy of at least 12 weeks.

Exclusion criteria

1. Previous systemic non-hormonal anticancer therapy for the metastatic or locally recurrent disease. Note: Prior to study entry, up to two lines of hormonal therapy for metastatic or locally recurrent disease are permitted, one of which may be in combination with Everolimus.
2. Disease-free interval from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence within 6 months.;3. Previous approved or investigative anti-HER2 agents in any breast cancer treatment setting, except trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting.;4. Disease progression while receiving trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting.;5. History of persistent Grade 2 or higher (National Cancer Institute [NCI]-Common Toxicity Criteria [CTC], Version 4.0) hematological toxicity resulting from previous adjuvant or neoadjuvant therapy.;6. Patients with radiographic evidence of central nervous system (CNS) metastases as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) that are not well controlled (symptomatic or requiring control with continuous corticosteroid therapy (eg dexamethasone). Note: Patients with CNS metastases are permitted to participate in the study if they are stable in the 3 months prior to screening (as assessed by the investigator) after receiving local therapy (irradiation, surgery etc) but without anti-HER2 therapy.
7. Current peripheral neuropathy of Grade 3 or greater (NCI-CTC, Version 4.0).;8. History of other malignancy within the last 5 years prior to 1st study drug administration (dosing), except for carcinoma in situ of the cervix or basal cell carcinoma.;9. Serious uncontrolled concomitant disease that would contraindicate the use of any of the investigational drugs used in this study or that would put the patient at high risk for treatment-related complications.;10. Inadequate 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;*Total bilirubin greater than the upper limit of normal (ULN; unless the patient has documented Gilbert*s syndrome);*Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) >2.5 × ULN (> 5 × ULN in patients with liver metastases);*Alkaline phosphatase levels > 2.5 × the ULN (> 5 × ULN in patients with liver metastases, or >10 × ULN in patients with bone metastases);*Serum creatinine >2.0 mg/dL or 177 *mol/L;*International normalized ratio (INR) or activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) >1.5 × ULN (unless on therapeutic anti-coagulation).;11. Uncontrolled hypertension (systolic >150 m m Hg and/or;diastolic >100 mm Hg) or clinically significant (i.e. active) cardiovascular disease: cerebrovascular accident/stroke or myocardial infarction within 6 months prior to first study medication, unstable angina, congestive heart failure (CHF) of New York Heart Association (NYHA) Grade II or higher, or serious cardiac arrhythmia requiring medication.;12. Current known infection with HIV, Hepatitis B virus, or Hepatitis C virus.;13. Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy.;14. Major surgical procedure or significant traumatic injury within 14 days prior to 1st study drug administration (dosing) or anticipation of need for major surgery during the course of study treatment. Note: Should surgery be necessary during the course of the study, patients should be allowed to recover for a minimum of 14 days prior to subsequent pertuzumab and trastuzumab treatment.
15. Receipt of intravenous antibiotics for infection within 7 days prior to enrolment.;16. Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose

equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids.;17. Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies.;18. History of receiving any investigational treatment within 28 days prior to 1st study drug administration (dosing).;19. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.;20. Concurrent participation in any interventional clinical trial.

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):	01-06-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Perjeta
Generic name:	Pertuzumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	05-03-2012
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-06-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-06-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	31-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-06-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	10-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-03-2019

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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 Roche studies worden, zodra er patienten in zitten, publiek gemaakt op www.rochetrials.com. Via het protocolnummer kan de studie worden gevonden. Het EUDRACT nummer is: 2011-005334-20
EudraCT	EUCTR2011-005334-20-NL
CCMO	NL39727.060.12