A RANDOMIZED PHASE II STUDY OF CONCOMITANT TRASTUZUMAB, BEVACIZUMAB WITH PACLITAXEL VERSUS TRASTUZUMAB AND BEVACIZUMAB FOLLOWED BY THE COMBINATION OF TRASTUZUMAB, BEVACIZUMAB AND PACLITAXEL AT PROGRESSION AS FIRST-LINE TREATMENT OF PATIENTS WITH METASTATIC BREAST CANCER WITH HER2-NEU OVEREXPRESSION

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Primary objective: To establish whether concomitant therapy of trastuzumab, bevacizumab with paclitaxel (regimen A) and/or trastuzumab and bevacizumab followed by the combination of trastuzumab, bevacizumab, and paclitaxel at progression (regimen B...

Ethical review	Approved WMO
Status	Pending
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON33918

Source
ToetsingOnline

Brief title
HAT-study

Condition

- Metastases
- Breast disorders

Synonym
metastatic breast cancer/ disseminated breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: BOOG Study Center B.V.
Source(s) of monetary or material Support: BOOG;KWF (misschien) en farmaceut,Hoffmann-La Roche

Intervention

Keyword: Bevacizumab, Breast cancer, HER2/neu positive, trastuzumab

Outcome measures

Primary outcome

Progression-free survival rate at 1 year (PFR-1yr)

Secondary outcome

To evaluate:

o Median progression-free survival

o Median overall survival (OS)

o Best Overall Response (OR)

o Duration of Response (DR)

To determine the safety and tolerability of both regimens

Study description

Background summary

The current standard therapy for Her2 positive metastatic breast cancer patients is the combination of trastuzumab and a taxane. There are several reasons why adding bevacizumab to this standard might improve outcomes. In a randomized study the combination of bevacizumab and paclitaxel yielded better outcomes than paclitaxel alone. Furthermore, bevacizumab and trastuzumab interact synergistically in preclinical models.

However, starting systemic treatment with trastuzumab and bevacizumab may offer benefits over initiating treatment with the combination of these agents and a taxane. Trastuzumab and bevacizumab is an active therapy against HER2-overexpressing metastatic breast cancer in view of the anti-tumor activity of trastuzumab given as single agent and the proven synergistic interaction of trastuzumab and VEGF inhibition. As a result, this combination may yield durable progression-free periods thereby delaying initiation of taxane-containing treatments with its well-characterised toxicities.

This study aims to establish if concomitant therapy of trastuzumab, bevacizumab with paclitaxel (regimen A) and/or trastuzumab and bevacizumab followed by the combination of trastuzumab, bevacizumab and paclitaxel at progression (regimen B) is worthwhile to be further explored.

Study objective

Primary objective: To establish whether concomitant therapy of trastuzumab, bevacizumab with paclitaxel (regimen A) and/or trastuzumab and bevacizumab followed by the combination of trastuzumab, bevacizumab, and paclitaxel at progression (regimen B) deserves to be further studied as treatment of patients with locally advanced or metastatic HER2 positive breast cancer who have not been previously treated for their metastatic disease, both ER/PgR negative or positive.

Study design

Two arm randomized (1:1), open-label, multicentre phase II study.

Intervention

Regimen A:

Trastuzumab 8 mg/kg loading dose 90-minute intravenous infusion followed by 6 mg/kg 30-minute intravenous infusion every 3 weeks until progression +

Bevacizumab 15 mg/kg i.v. in 90 min on day 1 every 3 weeks until progression +

Paclitaxel 90 mg/m2; day 1, 8, 15 every 4 weeks for 6 cycles

Regimen B:
Trastuzumab 8 mg/kg loading dose 90-minute intravenous infusion followed by 6 mg/kg 30-minute intravenous infusion every 3 weeks until progression +

Bevacizumab 15 mg/kg i.v. in 90 min on day 1 every 3 weeks until progression

And at progression followed by:
Trastuzumab 6 mg/kg and bevacizumab 15 mg/kg every 3 weeks until further progression +

Paclitaxel 90 mg/m2 at days 1, 8 and 15 of a 4-week cycle for 6 cycles.
The first administration of paclitaxel should be started on a day together with trastuzumab and bevacizumab.

The loading dose of trastuzumab has to be administered 24 hours prior to bevacizumab and/or paclitaxel administration. For all subsequent cycles all drugs can be given on the same day if so according to schedule.

For the treatment arm A trastuzumab has to be administered first followed by administration of bevacizumab and paclitaxel.

The subject*s actual weight at screening should be used to calculate the trastuzumab and bevacizumab dose. If the weight changes by > 10% during the course of the study, the trastuzumab and bevacizumab dose should be recalculated.

Paclitaxel will be administered as a 1 hour infusion.

Study burden and risks

Risk: side effects may occur following treatment with (the combinbation of) the study drugs. All study drugs are regsitered for this indication.

Frequency of patient visits and treatment cycles is not different form standard treatment, the same is true for assesments

For patient can be requested to participate in side studies to get in sight in the working mechanism of bevacizumab. Therefore on day 1 of cycle 2 two extra blood samples of 7 mL each will be collected. Collecting of blood will be combined with routine blood sampling.
Patient will be asked an extra informed consent for this.

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. Patients age >= 18 years
2. Able to comply with the protocol
3. ECOG PS of <= 1
4. Life expectancy of >= 12 weeks
5. Written informed consent [informed consent document to be approved by the institution*s Independent Ethics Committee (IEC)] obtained prior to any study specific screening activities.
6. Pre- or postmenopausal patients with histologically confirmed breast cancer (adenocarcinoma) with measurable or non-measurable, locally recurrent breast cancer that cannot be treated with curative intent by local treatment (surgery, radiotherapy +/- hyperthermia) or metastatic lesions, who are candidates for chemotherapy. ER/PgR and HER2 status must be documented.
7. Measurable lesions have at least one dimension (longest diameter to be recorded) as >=1 cm (10 mm) with spiral CT scan or >= 2 cm on conventional imaging methods. In case of a lung metastasis fully surrounded by air, a chest X-ray may be used instead of CT-scanning, provided the lung lesion is unidimensionally measurable and has a diameter of >= 2 cm (20

mm). Index lesions should not be in a previously irradiated area. Ultrasound is not allowed for measurements of liver metastases.
8. Patients must have HER2 protein overexpression (3+) as determined by immunohistochemistry (IHC); or amplification of HER2/c-erbB2 as determined by fluorescent in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) of the primary tumor or a metastasis.
9. Patients who received trastuzumab in the adjuvant setting are eligible as long provided they received at least 10 months of therapy with trastuzumab and >= 6 months have elapsed since last adjuvant administration of trastuzumab.
10. Patients who were treated with anthracyclines in adjuvant or neo-adjuvant setting are only eligible if they received their last dose > 6 months prior to randomization. The maximum cumulative dose must not exceed 360 mg/m2 for doxorubicin and 720 mg/m2 for epirubicin.
11. Patients who were treated with a taxane are only eligible if they received their last adjuvant or neo-adjuvant chemotherapy > 6 months prior to randomization and taxane-associated toxicity has resolved to less than grade 2.
12. Baseline Left Ventricular Ejection Fraction (LVEF) not below 50% measured by either echocardiography or MUGA.
13. The use of full-dose oral or parenteral anticoagulants is permitted as long as the patient has been on a stable level of anticoagulation for at least two weeks at the time of randomization.
14. Previous radiotherapy for treatment of metastatic breast cancer is allowed in case:
• Less than 30% of marrow-bearing bone has been irradiated
• The last fraction of radiotherapy has been administered more than 4 weeks prior to randomization
Prior adjuvant radiotherapy for breast cancer is allowed, provided it has stopped at least 6 months prior to randomization.

Exclusion criteria

1. Previous chemotherapy for metastatic or locally recurrent breast cancer. Prior hormonal therapy is allowed but must have been discontinued at least 2 weeks prior randomization.
2. Other primary tumor (including primary brain tumors) within the last 5 years prior to randomization, except for adequately treated carcinoma in situ of the cervix, squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer.
3. Evidence of spinal cord compression or current evidence of CNS metastasis. CT or MRI scan of the brain is mandatory in case of clinical suspicion of brain metastasis.
4. History or evidence upon physical/neurological examination of CNS disease (unrelated to cancer) (unless adequately treated with standard medical therapy) e.g. uncontrolled seizures.
5. Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to to study treatment start, or anticipation of the need for major surgery during the course of the study treatment.
6. Existing peripheral neuropathy > CTC Grade 2 at randomization.
7. Inadequate bone marrow function: ANC < 1.5 x 109/L, Platelet count < 100 x 109/L and Hb < 6.0 mmol/L.
8. Inadequate liver function:

• serum (total) bilirubin > ULN
• ASAT & ALAT > 2.5 x ULN (> 5 x ULN in patients with liver metastases) or ASAT/ALAT levels > 1.5 x ULN concurrent with serum alkaline phosphatase levels of > 2.5 x ULN or ASAT/ALAT > ULN concurrent with alkaline phosphatase > 6 x ULN
• INR > 1.5 in patients not receiving anticoagulans.;9. Inadequate renal function:
i. calculated or measured creatinine clearance < 30 mL/min
ii. Urine dipstick for proteinuria > 2+. Patients with >*2+ proteinuria on dipstick urinalysis at baseline should undergo 24 hours urine collection and must demonstrate *1 g of protein/24 hr.
10. Current or recent use (within 10 days of first dose of bevacizumab) of aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day).
11. Chronic daily use of corticosteroids (dose > 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).
12. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (i.e. active) cardiovascular disease: CVA/stroke (<= 6 months prior to randomization), myocardial infarction (<= 6 months prior to randomization), unstable angina, New York Heart Association (NYHA) class 2 or greater Congestive Heart Failure, or serious cardiac arrhythmia requiring medication.
13. Arterial or venous thrombosis <= 12 months prior to registration;14. History or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding.
15. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization.
16. Active infection requiring i.v. antibiotics at randomization.
17. Serious non-healing wound, peptic ulcer, or bone fracture.
18. 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 use of an investigational drug, or that may affect patient compliance with study routines, or place the patient at high risk from treatment complications.
19. Pregnant or lactating females. Serum pregnancy test to be assessed within 7 days prior to study treatment start, or within 14 days with a confirmatory urine pregnancy test within 7 days prior to study treatment start.
20. Patients of childbearing potential (women < 2 years after last menstruation) not using effective non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile). Male patients with a partner of childbearing potential should also use effective means of contraception.
21. Current or recent (within 30 days prior to starting study treatment) treatment with another investigational drug or participation in another investigational study.
22. Known hypersensitivity to any of the study drugs or excipients.
23. Hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2009
Enrollment:	84
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Herceptin
Generic name:	Trastuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-07-2008
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-04-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-10-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-03-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-04-2012
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
EudraCT	EUCTR2008-003834-12-NL
CCMO	NL23763.031.08