Phase II randomized trial of combination therapy of paclitaxel and bevacizumab versus paclitaxel, capecitabine and bevacizumab as first-line treatment for locally recurrent or metastatic breast cancer patients with HER2/neu negative tumor

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20125

Source
NTR

Brief title
ATX

Health condition

Locally recurrent or metastatic breast cancer patients with HER2/neu negative tumor

Sponsors and support

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Source(s) of monetary or material Support: BOOG , Roche NL

Intervention

Outcome measures

Primary outcome

Primary objective:

To investigate Progression Free Survival (PFS) in patients randomized to:

- bevacizumab 10 mg/kg q2wk + paclitaxel 90 mg/m2 on days 1, 8 and 15 of a 4-week cycle

versus

- bevacizumab 15 mg/kg day 1 + paclitaxel 90 mg/m2 on days 1 and 8 + capecitabine 825 mg/m2 orally twice daily on days 1-14 of a 3-week cycle

Secondary outcome

Secondary objectives:

To determine:

- Overall RR, duration of response and overall survival

- Safety

Study description

Background summary

Based on the distinct mechanisms of action, the well-documented activity of the combination

of paclitaxel and capecitabine, the known anti-angiogenic activity of paclitaxel, the significant activity of bevacizumab and weekly paclitaxel, and the need to advance the field of available therapies for patients with locally recurrent and metastatic breast cancer, evaluating a chemotherapy regimen that includes the addition of bevacizumab is an appropriate investigation to conduct at this time.
Bevacizumab is in the Netherlands registered for the indication treatment of metastatic breast cancer.

Therefore, based on the data that the weekly schedule of paclitaxel is active and tolerable in combination with capecitabine as compared to the 3-weekly schedule and that chemotherapy in combination with anti-angiogenic therapy should preferably be given more frequently in smaller doses, we have chosen for the weekly paclitaxel schedule in this protocol. The administration schedule for the reference arm is paclitaxel 90 mg/m2 i.v. days 1, 8, 15 and bevacizumab 10 mg/kg days 1 and 15, both in a 4-week cycle; paclitaxel for a maximum of 6 cycles. The experimental arm consists of paclitaxel 90 mg/m2 i.v. days 1 and 8, bevacizumab 15 mg/kg i.v. day 1 and capecitabine 825 mg/m2 p.o. twice daily on days 1-14, all three drugs in a 3-week cycle; paclitaxel for a maximum of 8 cycles.

Study objective

The primary objective is to reproduce the estimation of a PFS of a median of 13 months for bevacizumab + weekly taxol (arm A) and a median of 16 months for bevacizumab + weekly taxol plus capecitabine (arm B). The secondary objective is to reproduce the estimation of a response rate of 30% for bevacizumab + weekly taxol and 50% for bevacizumab + weekly taxol plus capecitabine.
It is estimated that, after respectively 6, 12 and 24 months the progression-free survival (PFS) in arm A will be 72.6%, 52.7% and 27.8%, assuming an exponential distribution. In arm B, where the median is expected to be 14 months, these figures will be respectively 77.1%, 59.5% and 35.4%.

Study design

PFS/Overall Response Rate/Duration of Response:

• Tumor assessment (based on RECIST criteria) of target and non-target lesions using CT- or MRI-scans, X-rays (MRI for bone lesions) will be performed at baseline, then every 12 weeks until the end of study treatment, and every 12 weeks thereafter. For bone lesions the baseline bone scan will be repeated after 24 weeks, and then every 36 weeks thereafter. In patients with increased tumor markers: assessment of tumor marker(s) at baseline, then every 4-6 weeks until the end of study treatment, and then every 6 weeks thereafter.

• Clinical examination will be performed before each cycle.

Overall Survival: From randomization till date of death or last follow-up

Intervention

Arm A (cycles of 28 days):

• Bevacizumab: 10 mg/kg i.v. on day 1 and day 15

• Paclitaxel: 90 mg/m2 i.v. on days 1, 8 and 15

Arm B (cycles of 21 days):

• Bevacizumab: 15 mg/kg i.v. on day 1

• Paclitaxel: 90 mg/m2 i.v. on days 1 and day 8

• Capecitabine: 825 mg/m2 orally twice daily on days 1-14

Paclitaxel will be given for a maximum of 6 cycles (arm A) and 8 cycles (arm B), or shorter in case of disease progression, unmanageable toxicity, withdrawal of patient's consent.

Capecitabine and bevacizumab will be given until disease progression, unmanageable toxicity, withdrawal of patient's consent.

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Eligibility criteria

Inclusion criteria

1. Patients with histologically or cytologically confirmed, HER2/neu-negative, pre- or postmenopausal adenocarcinoma of the breast with measurable or non-measurable locally recurrent or metastatic disease, who are candidates for chemotherapy. Locally recurrent disease must not be amenable to resection and/or radiotherapy with curative intent.

2. Documented ER/PR status

3. HER2/neu-negative disease as determined by immunohistochemistry or FISH/CISH

4. Prior adjuvant chemotherapy is allowed provided that the last dose of chemotherapy was not within 6 months (not within 12 months if taxane-based) prior to randomization.

5. Prior maximum cumulative dose must not exceed 360 mg/m2 for doxorubicin and 720 mg/m2 for epirubicin

6. Female only

7. Age > 18 years and ≤ 75 years

8. ECOG PS of 0 or 1

9. Life expectancy of > 12 weeks

10. Able to comply with the protocol

11. Written informed consent (Informed Consent document to be approved by the institution’s Independent Ethics Committee [IEC]) obtained prior to any study specific screening

Exclusion criteria

* Previous treatment

• Previous chemotherapy for locally recurrent or metastatic breast cancer

• Prior hormonal therapy for locally recurrent or metastatic disease should have been discontinued at least 2 weeks before randomization.

• Patients with bone metastases only are allowed provided that they are on bisphosphonate treatment > 3 months.

- Patients who have received adjuvant radiotherapy as part of the treatment of early breast

cancer are eligible if the last fraction of radiotherapy was administered at least 6 months prior to randomization. Radiotherapy administered for the relief of metastatic bone pain is allowed prior to study entry, but

• no more than 30% of marrow-bearing bone should have been irradiated

• the last fraction of radiotherapy should not have been administered within 3 weeks prior to randomization.

- Other primary tumors within the last 5 years before inclusion, except for adequately controlled basal cell carcinoma of the skin, or carcinoma in situ of the cervix

* Neurological signs and symptoms

- Previous or current CNS metastases. A CT or MRI of the brain must be performed within 4 weeks prior to randomization if the presence of metastases at this site is suspected.

- History or evidence upon physical/neurological examination of CNS disease unrelated to cancer, unless adequately treated with standard medical therapy e.g. uncontrolled seizures.

- Pre-existing peripheral neuropathy ≥ NCI-CTC (version 3.0) grade 1 at randomization

* Hematology, coagulation and biochemistry

- Inadequate bone marrow function: ANC: < 1.5 x 109/L, platelet count < 100 x 109/L and hemoglobin < 6 mmol/L.

- Patients with INR > 1.5 x ULN and/or aPTT > 1.5 x ULN within 7 days prior to randomization

- Inadequate liver function:

• Serum (total) bilirubin above the normal limit for the institution, and or

• ASAT & ALAT > 2.5 x ULN (> 5 x ULN in patients with liver metastases) Patients are not eligible for the study if they have ASAT/ALAT levels > 1.5 x ULN concurrent with:

- serum alkaline phosphatase levels of > 2.5 x ULN at baseline
or

- ASAT/ALAT > ULN concurrent with alkaline phosphatase > 6 x ULN

- Inadequate renal function:

• Serum creatinine > 177 µmol/L or calculated creatinine clearance < 30 mL/min.

Note: In patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min) at baseline, a dose reduction to 75% of the capecitabine starting dose is recommended.

• Urine dipstick for proteinuria ≥ 2+. Patients with ≥ 2+proteinuria on dipstick analysis at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein/24 h.

* Cardiovascular problems

- Current or recent use (within 10 days of first dose of bevacizumab) of aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day). No therapeutic treatment with LMWH or oral anticoagulants. Prophylactic doses of LMWH are allowed.

- History or evidence or inherited bleeding diathesis or coagulopathy with the risk of bleeding

- History of cerebrovascular accident

- Arterial or venous thrombosis ≤ 12 months prior to registration

- 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 ≥ II congestive heart failure, or serious cardiac arrhythmia requiring medication that might interfere with protocol treatment or not controlled by medication.

- Inadequate left ventricular ejection fraction at baseline. LVEF by MUGA or ECHO must be ≥ 50% and should be performed within 4 weeks prior to randomization if cardiac failure is suspected.

* Wounds and infection

- Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of the study treatment

- Minor surgical procedures within 24 hours prior to treatment, including insertion of an indwelling catheter

- Serious non-healing wound, active peptic ulcer, or non-healing bone fracture

- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months of randomization

- Active infection requiring i.v. antibiotics at randomization

* Other

- Pregnant or lactating females. Serum pregnancy test to be assessed within 7 days prior to randomization, or within 14 days with a confirmatory urine pregnancy test within 7 days prior to study treatment start.

- Women of childbearing potential (< 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), during the study and for a period of 6 months following the last administration of treatment.

- 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 places the patient at high risk from treatment related complications.

- Psychiatric disability judged by the investigator to be interfering with compliance for oral drug intake should be excluded from the study

* Hypersensitivity, investigational agents, co-medication

- Known hypersensitivity to any of the study drugs or excipients

- Hypersensitivity to Chinese hamster ovary cell products or recombinant human or humanized antibodies

- Clinically significant malabsorption syndrome, or inability to take oral medication

- Current or recent (within 30 days of inclusion) treatment with another investigational drug or participation in another investigational study

- Chronic daily treatment with corticosteroids (dose of ≥ 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids)

- Requirement for concurrent use of the antiviral agent sorivudin (antiviral) or chemically related analogues, such as brivudine

- Patients with a known DPD deficiency

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-05-2007
Enrollment:	312
Type:	Anticipated

Ethics review

Positive opinion

Date:	17-06-2008
Application type:	First submission

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
NTR-new	NL1300
NTR-old	NTR1348
Other	EudraCT 2006-006058-83 : BOOG 2006-06
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results
N/A