A Randomized, 4-Arm, Placebo-Controlled Phase 2 Trial of AMG 386 in Combination with Bevacizumab and Paclitaxel or AMG386 plus Paclitaxel as First-Line Therapy in Subjects with Her2-Negative, Metastatic or Locally Recurrent Breast Cancer.

Published: 04-09-2007
Last updated: 11-05-2024

To estimate the treatment effect as measured by progression free survival(PFS) of subjects receiving AMG 386 (at 2 doses) in combination with paclitaxel + bevacizumabrelative to paclitaxel + bevacizumab + placebo.

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

Summary

ID

NL-OMON37293

Source
ToetsingOnline

Brief title
Phase 2 AMG386 study as first-line therapy in breast cancer patients

Condition

- Other condition

Synonym
metastatic breastcancer

Health condition

(borst)kanker

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: efficacy, fase II, first-line therapy in breast cancer, safety

Outcome measures

Primary outcome

Progression-free survival (PFS).

Secondary outcome

-Objective response (OR): the incidence of either a confirmed complete response

(CR) or partial response (PR) per modified RECIST criteria (responder).

-Duration of response (DOR): (calculated only for those subjects with a

confirmed objective response) time from first confirmed objective response to

disease progression per the modified RECIST criteria or death

-Time to response: time from randomization to date of first objective response

for confirmed responders

-Overall survival: time from randomization date to date of death from any cause

-Time to progression (TTP): time from randomization to date of disease

progression per the modified RECIST criteria

-Incidence of AEs and significant laboratory changes

-AMG 386 pharmacokinetic parameters

-Incidence of the occurrence of anti-AMG 386 antibody formation

Exploratory:

-Baseline values of and changes from baseline in pharmacodynamic markers as assessed by blood levels of angiogenic cytokines (eg VEGF, bFGF, PIGF,Ang-1, Ang-2), tumor apoptosis and other markers

-Baseline values of and changes from baseline in immunologic, biochemical, pharmacogenetic, and angiogenic markers in tumor biopsies or serum samples

Study description

Background summary

In this study, the study medication AMG 386 is evaluated for the treatment of patients with Her 2-negative metastatic or locally recurrent breast cancer. AMG 386 is a man-made medication that is designed to stop the development of blood vessels in cancer tissues. Cancer tissues rely on the development of new blood vessels, a process called angiogenesis, to obtain a supply of oxygen and nutrients to grow. AMG 386 is considered experimental (or investigational). AMG 386 is not approved by any regulatory organization (such as the Food and Drug Administration, FDA) to treat any type of cancer. AMG 386 will be evaluated in this study in combination with paclitaxel and bevacizumab. Paclitaxel is a standard agent in the treatment of metastatic breast cancer in the United States and Europe. Paclitaxel in combination with bevacizumab is indicated for the treatment of patients with metastatic breast cancer in the European Union. Bevacizumab is indicated for the treatment of patients with metastatic colorectal carcinoma, as well as metatstatic non-squamous, non-small cell lung carcinoma in the United States. About 220 patients from 70 centers will participate in this study from regions including the Unites States and Europe. Amgen Inc. a for-profit drug company, is funding this clinical study.

Study objective

To estimate the treatment effect as measured by progression free survival (PFS) of subjects receiving AMG 386 (at 2 doses) in combination with paclitaxel

+ bevacizumab
relative to paclitaxel + bevacizumab + placebo.

Study design

This is a multicentre, randomized, phase 2 study. The study consists of 3 of parts. The first part is the screening. If the patient is eligible for the study, he will go into the treatment phase and this phase lasts until the patients* cancer worsens, is unable to tolerate the investigational drug, or decides to withdraw consent. After completion of the treatment, the patient will be followed by the study staff by telephone or at routine clinic visits approximately every 3 months for up to 4 years after the last subject starts the study treatment (long term follow up).Each subject participating in this clinical research study will receive 1 of the following treatments:
Arm A: Paclitaxel 90mg/m² IV weekly (3 weeks on 1 week off) + bevacizumab 10mg/kg IV every two weeks + AMG 386 10mg/kg IV weekly.
Arm B: Paclitaxel 90mg/m² IV weekly (3 weeks on 1 week off) + bevacizumab 10mg/kg IV every two weeks + AMG 386 3mg/kg IV weekly.
Arm C: Paclitaxel 90mg/m² IV weekly (3 weeks on 1 week off) + bevacizumab 10mg/kg IV every two weeks + AMG 386 placebo weekly.
Arm D: Paclitaxel 90mg/m² IV weekly (3 weeks on 1 week off) + Open Label AMG 386 10mg/kg IV weekly. The inclusionperiod is from November 2007 till November 2008.

Intervention

Subjects will receive intravenous paclitaxel/ bevacizumab (Arms A, B, and C) or paclitaxel (Arm D) in addition to either blinded AMG 386 or placebo until they develop disease progression per modified RECIST criteria, clinical progression, unacceptable toxicity, withdraw consent, or death.

Study burden and risks

Estimated median length of subject treatment is 11 months for subjects on paclitaxel/ bevacizumab plus AMG 386 placebo (Arm C), 17 months for subjects on paclitaxel/ bevacizumab plus AMG 386 (Arms A and B) and 11 months for paclitaxel plus AMG 386 (Arm D). Safety follow up assessments for each individual subject will be conducted 30 (+7) days after discontinuation of all study drug (AMG 386 or placebo, paclitaxel and bevacizumab). Subjects need to visit the clinic weekly during the treatment phase, study visits with the subject receiving studymedication will last 4-6 hours.

Long term follow up: All subjects who discontinue study drug for disease progression, clinical progression or unacceptable toxicity will be contacted by clinic visit or telephone every 3 months through 48 months from the last subject*s date of randomization. Subjects who discontinue without developing

progressive disease per modified RECIST criteria and have not withdrawn full consent to participate in this study will continue to be followed for disease progression with the radiological assessments until disease progression or commencement of new therapy. Imaging will be done once after 8 weeks and every 8 weeks if the subject has not been in the study for 2 years. If the subject has been on study for 2 years, radiological imaging will be performed every 4 months during long term follow up period.

Contacts

Public
Amgen

Minervum 7061
4800DH Breda
NL
Scientific
Amgen

Minervum 7061
4800DH Breda
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must have histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease. Locally recurrent disease must not be amenable to resection with curative intent.

• Measurable or non-measurable disease per modified RECIST guidelines (see Appendix G).
• Complete radiology and tumor measurement within 28 days prior to randomization:
o Chest: CT / MRI scan with intravenous contrast if the contrast is not medically contraindicated
o Abdomen: CT / MRI scan with intravenous contrast if the contrast is not medically contraindicated
o Pelvis: CT / MRI scan with intravenous contrast if the contrast is not medically contraindicated
o Head/ Brain: CT / MRI scan
o Bone: Whole body Bone Scintigraphy
Demographic
• Female 18 years of age or older at the time the written informed consent is obtained
• Subjects of child-bearing potential and sexually active must use an accepted and effective non-hormonal method of contraception (ie, double barrier method [eg, condom plus diaphragm]) from signing the informed consent through 6 months following last administration of study drug
General
• Able to tolerate intravenous infusions
• ECOG of 0 or 1 (within 14 days prior to randomization)
Laboratory
Adequate organ and hematological function as evidenced by the following laboratory studies within 28 days prior to randomization:
• Hematological function, as follows:
* Absolute neutrophil count (ANC) >= 1.5 x 109/L
* Platelet count >= 100 x 109/L and <= 850 x 109/L
* Hemoglobin >= 9 g/dL
* PTT or aPTT and INR <= 1.0 x ULN, per institutional laboratory range
• Renal function, as follows:
* Calculated creatinine clearance > 40 cc/min according to the Cockcroft-Gault formula
GFR (mL/min) = (140-age) x actual body weight (kg) (x 0.85 for females)
72 x serum creatinine (mg/dL)
* Urinary protein quantitative value of <= 30 mg in urinalysis or <= 1+ on dipstick, unless quantitative protein is <= 1000 mg in a 24 hour urine sample
• Hepatic function, as follows:
* Total bilirubin <= 2.0 x ULN, per institutional laboratory range
* SGOT (AST) and SGPT (ALT) <= 2.5 x ULN, per institutional laboratory range (<= 5 x ULN if liver metastases are
present)
* Cardiac function, as follows:
* Normal sinus rhythm (no significant ECG changes)
* Left ventricular ejection fraction >= LLN, as determined by echocardiogram or MUGA scan, according to institutional standards within 14 days prior to randomization

Exclusion criteria

Disease Related
• Inflammatory Breast Cancer
• Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 peripheral neuropathy > grade 1 at randomization
• History of arterial or venous thrombosis, including transient ischemic attack (TIA), within 1 year prior to randomization
• Adjuvant or neoadjuvant taxane treatment within 12 months of randomization. Any other adjuvant chemotherapy regimen must be discontinued at least 21 days prior to randomization
• Prior chemotherapy, vaccine, or biological therapy for locally recurrent or metastatic breast cancer (prior endocrine therapy is permitted)
• Prior radiation therapy, radiofrequency ablation, percutaneous cryotherapy, or hepatic chemoembolization on all sites of disease unless disease progression was subsequently documented 14 days prior to randomization.
• Overexpression of Her-2 (gene amplification by FISH or 3+ over expression by immunohistochemistry).
* Eligibility of subjects with 2+ immunohistochemistry must be confirmed by a negative FISH assay
• Current or prior history of central nervous system metastasis
• History of bleeding diathesis or clinically significant bleeding within 6 months prior to randomization
• Major surgical procedure within 28 days prior to randomization
• Open breast biopsy within 14 days prior to randomization
• Minor surgical procedure, placement of access device, or fine needle aspiration within 7 days of first dose
• Exclude subjects with a history of prior malignancy, except:
- Malignancy treated with curative intent and with no known active disease present for >= 3 years before enrollment and felt to be at low risk for recurrence by treating physician
- Adequately treated non-melanomatous skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
• Clinically significant cardiac disease within 12 months prior to randomization, including myocardial infarction, unstable angina, grade 2 or greater peripheral vascular disease, cerebrovascular accident, transient ischemic attack, congestive heart failure, or arrhythmias not controlled by outpatient medication
• Non-healing wound, ulcer, or fracture
• Ongoing or active infection
• Known hypersensitivity to paclitaxel or drugs using the vehicle cremophor
• Known hypersensitivity to bacterial proteins, or any of the drugs required in this study
• Known positive test for human immunodeficiency virus (HIV), hepatitis C, or hepatitis B surface antigen
• Known active or chronic hepatitis
• Uncontrolled hypertension as defined as systolic blood pressure >= 150 mm Hg and diastolic blood pressure >= 90 mm Hg. Anti-hypertensive medications are allowed if the

subject is stable on their current dose at the time of randomization
Medications
• Currently or previously treated with any VEGF or VEGFr inhibitor, including but not limited to: bevacizumab, SU11248 (sunitinib), PTK787 (vatalinib), AZD 2171, AEE-788, BAY 43-9006 (sorafenib), and AMG 706
• Concurrent or prior (within 1 week before randomization) anticoagulation therapy, excluding aspirin and anti-platelet agents. The concurrent use of low molecular weight heparin or low dose warfarin (i.e. <= 1mg daily) for prophylaxis against thrombosis is acceptable while on study
• Currently or previously treated with angiopoietin inhibitors, or inhibitors of TIE-1 or TIE-2 including, but not limited to: AMG 386, XL880, XL820
• Treatment with immune modulators such as cyclosporine and tacrolimus within 30 days prior to randomization
• Concomitant therapy with any hormonal agent such as raloxifene, tamoxifen, or other selective estrogen receptor modulators (SERMS), given for breast cancer prevention or for osteoporosis. Subjects must have discontinued these agents 14 days prior to randomization
General
• Any condition which in the investigator*s opinion makes the subject unsuitable for study participation
• Participation in other investigational device or drug trials or administration of other investigational treatments within 30 days prior to randomization
• Pregnant (ie, positive beta-human chorionic gonadotropin test) or is breast feeding
• Previously enrolled into this study
• Inability to comply with protocol and/or not available for follow-up assessments

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	11-02-2008
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	04-09-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-01-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-05-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-06-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	22-08-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-08-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-11-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-01-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-01-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-04-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-04-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-12-2009
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-01-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-03-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-03-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-10-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-12-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	26-09-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-12-2011
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

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	EUCTR2007-003384-51-NL
ClinicalTrials.gov	NCT00511459
CCMO	NL19244.068.07