CLINICAL STUDY REPORT SYNOPSIS

A randomized phase III study to determine the efficacy of a taxane and bevacizumab with or without capecitabine as first line chemotherapy in patients with metastatic breast cancer

EudraCT no: 2008-003997-17

Indication:	Metastatic breast cancer
Phase:	III
Study Protocol:	GBG 43 Protocol (Version V2, February 16th, 2009) Amendment 1 (July 01st, 2012)
Investigational Product:	Bevacizumab (AVASTIN®) Capecitabine (XELODA®) Paclitaxel Docetaxel
Clinical Study Report Version:	Version 1 (November 26th, 2013)
First Patient Enrolled:	September 09th, 2009
Last Patient Completed:	October 05th, 2012

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SYNOPSIS

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Title of Study:

A randomized phase III study to determine the efficacy of a taxane and bevacizumab with or without capecitabine as first line chemotherapy in patients with metastatic breast cancer.

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Co-ordinating Investigator: Prof. Dr. Hans-Joachim Lück (Gynäkologische-onkologische Praxis Prof. Dr. Lück)
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- Kreiskrankenhaus Starnberg GmbH, Frauenklinik, Starnberg (PI: Anthuber)
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Publication (references):

Lück HJ, Lübbe K, Bischoff J, et al. A randomized phase III study to determine the efficacy of capecitabine in addition to a taxane and bevacizumab as first line therapy in patients with metastatic breast cancer. J Clin Oncol 31, 2013 (suppl; abstr 1082)

Studied Period (years): 37 months

Date of the first patient enrolled: September 09th, 2009.
Date of last patient enrolled: October 02nd, 2012 (patient no. 268, the 234th randomized patient).
Date of the last patient completed: October 05th, 2012 (date of the early termination of the study).

Phase of Development:

Phase III

Objectives:

Primary Objective

To determine the Progression Free Survival (PFS) in patients with metastatic breast cancer after treatment with taxane plus bevacizumab with (TXB) or without capecitabine (TB).

Secondary Objectives

To determine the objective response rate in both arms.
To determine the duration of response in both arms.
To determine the Time to Progression (TTP) in both arms.
To determine the clinical benefit defined as CR, PR, or stable disease ≥ 24 weeks in both arms.
To determine the overall survival rate 3 years after "Last Patient In".
To determine PFS and TTP response rates in patient's ≥ age 65.

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To determine the toxicity and compliance in both arms.
To determine the predictive value of serum markers such as VEGF.

Methodology:

Randomized, open, multicenter study.

Number of patients (planned and analyzed):

Planned: 432.
Enrolled and randomized: 234.
Analysed patients (efficacy and safety): 227 in safety and 187 in efficacy analysis.

Diagnosis and Main Criteria for Inclusion:

Patients were eligible for study participation only if they comply with the following inclusion and exclusion criteria:

1. Age ≥18 years.
2. Female and Male patients.
3. Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements.
4. Complete baseline documentation sent to GBG Forschungs GmbH.
5. ECOG performance status 0-2.
6. Histological confirmed carcinoma of the breast with no over expression of HER2.
7. Locally advanced or metastatic stage of disease not suitable for surgery or radiotherapy alone.
8. Patients must have either measurable or non-measurable target lesions according to RECIST criteria. Complete staging work-up within 4 weeks prior to registration. All patients must have chest X-ray (PA and lateral), abdominal ultrasound or CT scan or MRI, and bone scan. In case of positive bone scan, bone X-ray is mandatory. Other tests may be performed as clinically indicated.
9. The following previous systemic treatment are eligible:
   - (neo)adjuvant chemotherapy. However if (neo)adjuvant chemotherapy was anthracycline based, the maximum cumulative dose of prior anthracycline therapy must not exceed 360 mg/m^2 for doxorubicin and 720 mg/m^2 for epirubicin. If taxanes or capecitabine were part of (neo)adjuvant treatment, a treatment-free interval of > 6 months is requested.
   - adjuvant endocrine therapy.
   - palliative endocrine treatments.
   - treatment with bisphosphonates.
   - treatment with immunotherapies.
10. Patients have to be fully recovered from previous radiotherapy. At least one measurable lesion must be completely outside the radiation field or there must be pathologic proof of progressive disease.
11. Absolute neutrophil count ≥ 2000 cells/µl, platelet count ≥100,000 cells/µl.
12. Bilirubin ≤ 1,5 x the upper limit of normal for the institution (ULN); elevation of transaminases and alkaline phosphatase <2.5 x ULN or < 5 x ULN for patients with liver metastases.

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13. Creatinine ≤ 1,25 x ULN or creatinin-clearance ≥ 50 ml/min (according to Cockcroft Gault). Urine dipstick for proteinuria <2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis should undergo a 24 hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.
14. Negative pregnancy test (urine or serum) within 14 days prior to registration for all women of childbearing potential.
15. Patients must be available and compliant for treatment and follow-up. Patients registered on this trial must be treated and followed up at the participating or a cooperating site.

Test Products, Dose and Mode of Administration, Batch Number:

(1) Bevacizumab
15 mg/kg body weight i.v. on day 1 q day 22

(2) Capecitabine
1800 mg/m^2 on day 1-14 q day 22

(3) Paclitaxel or (4) Docetaxel* (decision of the investigator)

Paclitaxel: 80 mg/m^2 on day 1, 8, 15 q day 22

Docetaxel: 75 mg/m^2 on day 1 q day 22

* *Removed with amendment 1*

Duration of Treatment:

(1) Bevacizumab
Until progression, detection of a new lesion, unacceptable toxicities or patient´s request or non-compliance.

(2) Capecitabine
Until progression, detection of a new lesion, unacceptable toxicities or patient´s request or non-compliance.

(3) Paclitaxel
Until progression, detection of a new lesion, unacceptable toxicities or patient´s request or non-compliance.

(4) Docetaxel
Until progression, detection of a new lesion, unacceptable toxicities or patient´s request or non-compliance.

Reference Therapy, Dose and Mode of Administration, Batch Number:

(1) Bevacizumab
15 mg/kg body weight i.v. on day 1 q day 22

(3) Paclitaxel or (4) Docetaxel* (decision of the investigator)

Paclitaxel: 80 mg/m^2 on day 1, 8, 15 q day 22

Docetaxel: 75 mg/m^2 on day 1 q day 22

* *Removed with amendment 1*

Criteria for Evaluation:

Efficacy (primary)

The primary objective of the study was to determine the progression free survival (PFS) in patients with

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metastatic breast cancer treatment after taxane/bevacizumab with or without capecitabine. Progression-free survival was defined as time in months from the randomization until disease progression or death due to any cause has occurred. Patients with no progression reported has been censored on the date of the last contact ("last tumor assessment", "last follow up date" or "last date in drug log") or at the date of the premature study termination, whichever was earlier. Patients who discontinued therapy due to reasons other than progression and received chemotherapy/radiotherapy afterwards has been censored at the date of the chemotherapy/radiotherapy start.

Efficacy (secondary)

1. Objective response rate: consists of complete and partial response according to RECIST criteria (phase III). RECIST guidelines allows for phase III trials with objective response not being the primary endpoint to restrict the number of target lesions or to abstain from a confirmation of response 4 weeks later. The prerequisite in this trial for a response evaluation is a measurement of up to a maximum of 5 target lesions in total, representative of all involved organs. No confirmation of response is required 4 weeks later. Missing data on response evaluation will be set to no response.
2. Duration of response: time from when the response was first noted until the date of documented progression, death or withdrawal (whichever occurs first).
3. To determine the time to progression (TTP) in both arms – was omitted according to SAP due to premature study end.
4. Clinical Benefit: Clinical benefit consists of complete response (CR), partial responses (PR) and stable disease lasting ≥ 24 weeks.
5. Overall Survival rate at 3 years after "Last Patient In": There were no 3 years follow up in the study, so no OS rate 3 after last patient in can be determined, but ovaerall survival analysis was performed with the actual follow up.
6. To determine PFS, TTP (TTP will be omitted) and objective response rates in patient's ≥ 65 years of age.
7. To determine the predictive value of serum markers such as VEGF – not covered by this report, will be analyzed later

Safety

Toxicity

The National Cancer Institute Common Terminology Criteria version 3.0 (NCI-CTCv3) and the corresponding grading system has been used to grade adverse events for recording in the CRF. For all adverse events not classified by the NCI-CTC, a COSTART grading classification (FDA 1989) has been performed (severity as 1: mild, 2: moderate, 3: severe, and 4: life threatening). At the interim look, the overall proportion of patients experiencing any toxicity of NCI grade III or IV was determined. The proportion of patients experiencing any toxicity of NCI grade III or IV was displayed for each category and for compiled categories, if applicable. Moreover, adverse events was presented per patient and per cycle. The most extreme intensity was used for reporting.

Compliance

Compliance refers to dose modification through dose reduction, dose interruption or dose delays as well as permanent treatment discontinuation due to the reasons other than progression. Descriptive statistics were

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given on the number of patients in whom the study medication has been reduced, delayed or permanently stopped.

Statistical Methods:

The statistical analysis of the present study was performed in accordance with the principles stated in the Consensus Guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonization (ICH).

Sample Size Calculation:

The PFS of 1st-line chemotherapy with taxanes and bevacizumab was considered to be approximately 10 months based on the paclitaxel +/- bevacizumab registration trial and the presented results of the docetaxel and bevacizumab-containing AVADO trial. The addition of capecitabine to docetaxel alone had improved TTP from 4.2 to 6.1 months (O'Shaugnessy, 2002). Taking this prolongation into account, the expected PFS was assumed to be 13.3 months with TBX.

Based on these assumptions a total of 386 events had to have occured. The recruitment was planned to take 3 years with an additional follow up of 3 years. The significance level α was set to 0.05 and β to 0.2 which corresponds to a power of 80%. Expecting an exponential drop out rate of 5%, 432 patients were required to be included in the trial.

Statistics:

Randomization was stratified according to participating sites, age, receptor status, planned taxane treatment and disease free interval.

One interim efficacy and safety analysis was planned when 25% of the required events have occurred (96 events) or after 50% of the required total recruitment (216 patients), whichever occurred first.

The Intent-to-treat analysis set consists of all patients that were randomized and had received at least one dose of study medication. However, patients who consented to participation and fulfilled all study criteria but did not receive any study medication after enrolment (drop-outs) were not included in the intent-to-treat analysis and were listed separately together with their reason (if known) for not starting study treatment.

The Kaplan-Meier product limit method was used to estimate PFS, duration of response, and OS. The log-rank test, overall and stratified by stratification factors, was used to compare the two treatment arms with respect to PFS, duration of response, and OS.

Cox's proportional hazards models were assessed for PFS, TTP, duration of response, and OS in order to adjust the treatment comparison for the major prognostic factors. These factors include but were not limited to clinical baseline parameters, pathological markers and serum markers such as VEGF. Such adjusted analyses were considered secondary to the main analysis. Any subset analyses were reported with appropriate caveat.

SUMMARY

One Bayesian interim analysis for futility was performed after 25% of events occurred combined with an interim analysis for safety. The analysis was presented to the Independent Data Monitoring Committee (IDMC). The IDMC pronounced the recommendation for a premature termination of the study according to

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the protocol (chapter 11.8.2, page 75). The protocol board decided to prematurely stop the study based on the results of this analysis and the recommendation of the IDMC, on October 2nd, 2012. Therefore the trial has been ended prematurely on October 5th, 2012. Totally 234 patients were included into the trial.

Adding capecitabine to taxane plus bevacizumab treatment cannot be recommended as first line therapy in metastatic breast cancer due to lack of efficacy and high rate of adverse events.

NEW: The efficacy analysis was done at the time-point of the interim safety analysis. Therefore the results of the efficacy analysis represents the overall evaluation of the trial.

Date of the Report:

May 2nd, 2014