



**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**

**TABEA**

**GBG 43**

**EudraCT No.: 2008-003997-17**

**A Study of the German Breast Group (GBG)**

**Protocol Synopsis (Version FINAL V2 16.02.2009)**

**Protocol Board GBG**

Dr. J. Bischoff, Magdeburg	PD Dr. S. Loibl, Neu-Isenburg
PD Dr. C. Denkert, Berlin (Pathology)	Prof. Dr. N. Maas, Kiel
Prof. Dr. N. Harbeck, München	Prof. Dr. G. von Minckwitz, Frankfurt
Dr. S. Kümmel, Essen	Prof. Dr. A. Schneeweiss, Heidelberg
Prof. Dr. H.-J. Lück, Hannover	Dr. K. Schwedler, Frankfurt
(Coordinating Investigator AMG)	Dr. L. Lübke, Hannover

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## PROTOCOL SYNOPSIS

<b>Study Title:</b>	<b>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</b>
<b>Study Name / Code:</b>	TABEA / GBG 43
<b>EudraCT Number:</b>	2008-003997-17
<b>Sponsor:</b>	GBG Forschungs GmbH, Neu-Isenburg
<b>Development Phase:</b>	Phase III
<b>Rationale:</b>	<ul style="list-style-type: none"> <li>• Paclitaxel and bevacizumab showed improved PFS compared to paclitaxel alone. Recent results of the AVADO study report a similar result for the combination of docetaxel and bevacizumab. The AVADO study furthermore confirmed the dose of 15 mg/kg BW of bevacizumab.</li> <li>• As in metastatic breast cancer (MBC) poly-chemotherapies are frequently used, regimens with bevacizumab and at least 2 cytotoxic agents should be investigated.</li> <li>• Docetaxel and capecitabine showed a benefit in PFS and survival. This combination is therefore a reasonable choice.</li> <li>• Dose of capecitabine and docetaxel should be reduced to 1800 mg/m<sup>2</sup> and 75 mg/m<sup>2</sup> to improve tolerability without compromising efficacy.</li> <li>• Paclitaxel and capecitabine is well tolerated and showed a PFS of 10.3 months.</li> <li>• Docetaxel 100 mg/m<sup>2</sup> as monotherapy in MBC not very often used b/o toxicity. 75 mg/m<sup>2</sup> much more accepted in daily practice. Better comparability with DBX, if both arms have 75mg/m<sup>2</sup> docetaxel as assumed.</li> </ul>
<b>Objectives:</b>	
<b>Primary Objective:</b>	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).
<b>Secondary Objective(s):</b>	<ul style="list-style-type: none"> <li>• To determine the objective response rate in both arms.</li> <li>• To determine the duration of response in both arms.</li> <li>• To determine the Time to Progression (TTP) in both arms.</li> <li>• To determine the clinical benefit defined as CR, PR, or stable disease ≥ 24 weeks in both arms.</li> <li>• To determine the overall survival rate 3 years after “Last Patient In”.</li> </ul>

	<ul style="list-style-type: none"> <li>• To determine PFS and TTP response rates in patient's <math>\geq</math> age 65.</li> <li>• To determine the toxicity and compliance in both arms.</li> <li>• To determine the predictive value of serum markers such as VEGF.</li> </ul>
<b>Study Design and Treatment:</b>	<p>Prospective, randomized, open label, phase III trial comparing treatment with a taxane and bevacizumab with or without capecitabine as first line therapy for patients with metastatic breast cancer.</p> <p>All patients will be treated with standard treatment consisting of a taxane and bevacizumab (TB).</p> <p>The following taxane regimes are allowed:</p> <ul style="list-style-type: none"> <li>• Docetaxel 75 mg/m<sup>2</sup> i.v. day 1 q day 22 or</li> <li>• Paclitaxel 80 mg/m<sup>2</sup> i.v. days 1, 8, 15 q22.</li> </ul> <p>The taxane is given in combination with bevacizumab 15 mg/kg i.v. day 1 q day 22 until progression, unacceptable toxicity, patient's request or withdrawal from study.</p> <p>Duration of treatment should continue until progression of disease or until occurrence of unacceptable toxicity. In case of unacceptable toxicity caused by one (or two in the TBX arm) chemotherapeutic agents or bevacizumab, treatment with the suspected compound(s) will be discontinued. Remaining study medication will be applied according schedule. If chemotherapy is stopped ahead of PD, bevacizumab should be continued until PD or unacceptable toxicity.</p> <p>Patients will be randomized to receive in addition and simultaneously to TB:</p> <ul style="list-style-type: none"> <li>• Capecitabine 1800 mg/m<sup>2</sup> daily given in two doses, d 1-14, q d 22 (TXB).</li> <li>• No capecitabine (TB).</li> </ul> <p>Randomization will be stratified according to:</p> <ul style="list-style-type: none"> <li>• Receptor status (ER and PgR negative versus other).</li> <li>• Planned treatment with docetaxel or paclitaxel.</li> <li>• Disease free interval <math>\leq</math> or <math>&gt;</math> 12 months.</li> </ul>
<b>Premedication and Supportive Therapy</b>	<ul style="list-style-type: none"> <li>• Paclitaxel + capecitabine: Antiemetic treatment: dexamethasone, 5-HT3. Antiallergic treatment: clemastin, ranitidin.</li> <li>• Docetaxel + capecitabine: Antiemetic treatment: dexamethasone, 5HT3-inhibitors.</li> <li>• During chemotherapy: G-CSF (pegfilgrastim, filgrastim) and antibiotics</li> </ul>

<p><b>Inclusion Criteria:</b></p>	<p>(ciprofloxacin) as a secondary prophylaxis.</p> <ol style="list-style-type: none"> <li>1. Age <math>\geq 18</math> years.</li> <li>2. Female and Male patients.</li> <li>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.</li> <li>4. Complete baseline documentation sent to GBG Forschungs GmbH.</li> <li>5. ECOG performance status 0-2.</li> <li>6. Histological confirmed carcinoma of the breast with no over expression of HER2.</li> <li>7. Locally advanced or metastatic stage of disease not suitable for surgery or radiotherapy alone.</li> <li>8. Patients must have either measurable or non-measurable target lesions according to RECIST criteria (phase III). 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.</li> <li>9. The following previous systemic treatment are eligible: <ul style="list-style-type: none"> <li>• (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<sup>2</sup> for doxorubicin and 720 mg/m<sup>2</sup> for epirubicin. If taxanes or capecitabine were part of (neo)adjuvant treatment, a treatment-free interval of &gt; 6 months is requested.</li> <li>• adjuvant endocrine therapy.</li> <li>• palliative endocrine treatments.</li> <li>• treatment with bisphosphonates.</li> <li>• treatment with immunotherapies.</li> </ul> </li> <li>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.</li> <li>11. Absolute neutrophil count <math>\geq 2000</math> cells/<math>\mu</math>l, platelet count <math>\geq 100,000</math> cells/<math>\mu</math>l.</li> <li>12. Bilirubin <math>\leq 1,5</math> x the upper limit of normal for the institution (ULN); elevation of transaminases and alkaline phosphatase <math>&lt; 2.5</math> x ULN or <math>&lt; 5</math> x ULN for patients with liver metastases.</li> <li>13. Creatinine <math>\leq 1,25</math> x ULN or creatinin-clearance <math>\geq 50</math> ml/min (according to Cockcroft Gault). Urine dipstick for proteinuria <math>&lt; 2+</math>. Patients discovered to have <math>\geq 2+</math> proteinuria on dipstick</li> </ol>
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	<p>urinalysis should undergo a 24 hour urine collection and must demonstrate <math>\leq 1</math> g of protein in 24 hours.</p> <p>14. Negative pregnancy test (urine or serum) within 14 days prior to registration for all women of childbearing potential.</p> <p>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.</p>
<b>Exclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1. Known hypersensitivity reaction to the compounds or incorporated substances or known dihydropyrimidine dehydrogenase deficiency.</li> <li>2. Previous chemotherapy for metastatic disease, concurrent immunotherapy or hormonal therapy (antihormonal, contraceptive and/or replacement therapy). Bisphosphonates may be continued.</li> <li>3. Life expectancy of less than 3 months.</li> <li>4. Serious intercurrent medical or psychiatric illness that may interfere with the planned treatment (including AIDS and serious active infection).</li> <li>5. Known or suspected congestive heart failure (&gt; NYHA I) and/or coronary heart disease, angina pectoris requiring antianginal medication, previous history of myocardial infarction, evidence of transmural infarction on ECG, un- or poorly controlled arterial hypertension (i.e. BP &gt; 150/100 mmHg under treatment with two antihypertensive drugs), rhythm abnormalities requiring permanent treatment, clinically significant valvular heart disease.</li> <li>6. Currently active infection.</li> <li>7. Active peptic ulcer, incomplete wound healing or unhealed bone fracture.</li> <li>8. Previous thromboembolic events, known hemorrhagic diathesis, coagulopathy with increased bleeding risk, or treatment with anticoagulants. Current or recent (within 10 days of first dose of bevacizumab) use of acetylic acid (&gt; 325mg/day) or clopidogrel (&gt; 75mg/day).</li> <li>9. Disease significantly affecting gastrointestinal function, e.g. malabsorption syndrome, resection of the stomach or small bowel, ulcerative colitis; abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months of enrolment.</li> <li>10. Major surgery within the last 28 days or anticipation of the need for major surgery during study treatment with bevacizumab. No minor surgeries including insertion of an indwelling catheter within 24 h prior to randomization.</li> <li>11. Parenchymal brain metastases, unless adequately controlled by surgery and/or radiotherapy with complete resolution of</li> </ol>

	<p>symptoms and discontinuation of all steroids.</p> <p>12. History of other malignancy within the last 5 years which could affect the diagnosis or assessment or outcome of metastatic breast cancer.</p> <p>13. Concurrent treatment with other experimental drugs; participation in another clinical trial with any investigational drug within 30 days prior to study entry.</p> <p>14. Treatment with sorivudine or derivatives e.g. brivudin.</p> <p>15. Pregnant or lactating patients. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures (barrier methods, intra uterine contraceptive devices, sterilization) during study treatment.</p> <p>16. Patients who are not able to give informed consent as defined according to AMG (§40 Abs.1 Satz3 Nr.3 Buchst. a).</p>
<b>Criteria for Evaluation:</b>	
<b>Efficacy:</b>	<p>Progression Free Survival is the primary endpoint of the trial and is defined as the time period between randomization and documented disease progression or disease-related death. Response of tumor lesions is based on investigator assessments and will be assessed according to a phase III adapted Response Evaluation Criteria in Solid Tumors (PFS endpoint modified RECIST). Missing data on response evaluation will be set to no response.</p> <p>Duration of response is defined as the time period between first notification of a response and the date of documented progression, disease-related death, or withdrawal.</p> <p>Clinical benefit is defined as complete response, partial response or disease stabilization for <math>\geq 24</math> weeks.</p> <p>Overall survival was defined as the time period between randomization and death. Patients who withdraw consent or were lost to follow-up were censored at the date of last contact.</p>
<b>Safety:</b>	<p>Toxicity will be assessed according to the National Cancer Institute Common Terminology Criteria Version 3.0 (NCI-CTC v3).</p> <p>For the assessment of compliance all treatment discontinuations, dose delays and dose modifications will be summarized.</p>
<b>Statistical Methods:</b>	<p>An intention-to-treat (ITT) analysis will be conducted for all patients. In addition, a per-protocol analysis will be conducted among the eligible patients.</p> <p>The primary objective of this study is the Progression Free Survival (PFS) of patients with metastatic breast cancer treated with taxane and bevacizumab with or without capecitabine.</p>

	<p>Randomization will be stratified according to participating sites, age, receptor status, planned taxane treatment and disease free interval.</p> <p>One interim efficacy and safety analysis is planned when 25% of the required events have occurred (96 events) or after 50% of the required total recruitment (216 patients), whichever comes first.</p>								
<b>Sample Size Determination:</b>	<p>The PFS of 1st-line chemotherapy with taxanes and bevacizumab is 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 has improved TTP from 4.2 to 6.1 months (O'Shaughnessy, 2002). Taking this prolongation into account, the expected PFS is assumed to be 13.3 months with TBX.</p> <p>Based on these assumptions a total of 386 events have to occur. The recruitment is planned to take 3 years with an additional follow up of 3 years. The significance level <math>\alpha</math> is set to 0.05 and <math>\beta</math> to 0.2 which corresponds to a power of 80%. Expecting an exponential drop out rate of 5%, thus 432 patients have to be included in the trial.</p>								
<b>Planned Number of Study Sites:</b>	80 (some outside of Germany)								
<b>Planned No. of Patients:</b>	432								
<b>Enrolment Period:</b>	Q I 2009 – Q I 2012								
<b>Follow-up Period:</b>	Q I 2012 – Q I 2015								
<b>Timeline</b>	<table> <tr> <td>First patient in:</td> <td>March 2009</td> </tr> <tr> <td>First interim analysis</td> <td>April 2010</td> </tr> <tr> <td>Last patient in</td> <td>March 2012</td> </tr> <tr> <td>Final analysis</td> <td>Juni 2015</td> </tr> </table>	First patient in:	March 2009	First interim analysis	April 2010	Last patient in	March 2012	Final analysis	Juni 2015
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