# CLINICAL STUDY REPORT

## A phase III trial program exploring the integration of bevacizumab, everolimus (RAD001), and lapatinib into current neoadjuvant chemotherapy regimes for primary breast cancer.

## EudraCT no: 2006-005834-19

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| **Indication:** | Early breast cancer |
| **Phase:** | III |
| **Study Protocol:** | GBG44<br>Protocol (October 18th, 2007)<br>Amendment 1 (January 29th, 2008)<br>Amendment 2 (February 26th, 2010)<br>Amendment 3 (February 13th, 2013) |
| **Investigational Products:** | Bevacizumab (AVASTIN®)<br>Lapatinib (TYVERB®)<br>RAD001 (AFINITOR®) / (CERTICAN®)<br>Trastuzumab (HERCEPTIN®) |
| **Clinical Study Report Version:** | Version 1.1 (February 26th, 2016)<br>corrected July 6th, 2016) |
| First Patient Enrolled: | November 7th, 2007 |
| Last Patient Completed: | August 31st, 2015 |

Co-ordinating Investigator:
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Chair: Prof. Dr. Gunter von Minckwitz (Neu-Isenburg)
Co-Chairs: Dr. Ingo Bauerfeind (Landshut) / Prof. Dr. Bernd Gerber (Rostock)

Setting II:
Chair: Prof. Dr. Jens Huober (St. Gallen, CH; since 04-2012: Düsseldorf)

Co-Chairs: Prof. Dr. Peter A. Fasching (Erlangen / Los Angeles, CA, USA) / Dr. Claus A. Hanusch (München)

Setting III:

Chair: Prof. Dr. Michael Untch (Berlin)

Co-Chairs: Prof. Dr. Dr. h.c. Manfred Kaufmann (Frankfurt am Main) / Prof. Dr. Jörn Hilfrich (Hannover)

Sponsor:

GBG Forschungs GmbH

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Organisation authorised by the sponsor for the conduction in Switzerland (since August 1st, 2009):

Kantonsspital St. Gallen

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Switzerland

## 1. APPROVAL SIGNATURES

STUDY TITLE:
A phase III trial program exploring the integration of bevacizumab, everolimus (RAD001), and lapatinib into current neoadjuvant chemotherapy regimes for primary breast cancer.

STUDY NUMBER: GBG 44

I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: DATE:

08.03.2016

Prof. Dr. Gunter von Minckwitz
Co-ordinating Investigator /
President GBG Forschungs GmbH

2.3.2016

Prof. Dr. Sibylle Loibl
Executive Vice President, Head of Medicine and Research
GBG Forschungs GmbH

26.02.2016

Dr. Valentina Nekljudova
GeparQuinto Biostatistician
GBG Forschungs GmbH

26-FEB-2016

Dr. Mathias Uhlig
GeparQuinto Project Manager

## 2. SYNOPSIS

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|---|---|---|
| Name of Sponsor:<br>GBG Forschungs GmbH | | *(For National Authority Use only)* |
| Name of finished product:<br>(1) AVASTIN®<br>(3) TAXOTERE®<br>(5) TYVERB®<br>(7) AFINITOR® / CERTICAN®<br>(8) HERCEPTIN® | | |
| Name of substance:<br>(1) Bevacizumab (B)<br>(2) Cyclophosphamide (C)*<br>(3) Docetaxel (T)<br>(4) Epirubicin (E)*<br>(5) Lapatinib (L)<br>(6) Paclitaxel (P)*<br>(7) RAD001 (R)<br>(8) Trastuzumab (H)<br>*generic. | | |

**Title of Study**
A phase III trial program exploring the integration of bevacizumab, everolimus (RAD001), and lapatinib into current neoadjuvant chemotherapy regimes for primary breast cancer.

**Investigators**
Co-ordinating Investigator: Prof. Dr. Gunter von Minckwitz (GBG Forschungs GmbH)
Principal Investigators: see Chapter Study Center(s).

**Study Center(s)**

| Klinik | Abteilung | Strasse | PLZ | Ort | Titel | Vorname | Nachname |
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**Publication (references)**

von Minckwitz G, Eidtmann H, Loibl S, Blohmer JU, Costa SD, Fasching PA, Kreienberg R, Hilfrich J, Gerber B, Hanusch C, Fehm T, Strumberg D, Solbach C, Nekljudova V, Untch M.
Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial.
*Ann Oncol* 22:301-6, 2011.

Gerber B, Eidtmann H, Rezai M, Fasching P. A, Tesch H, Eggemann H, Schrader I, Kittel K, Hanusch C. A, Kreienberg R, Solbach C, Jackisch C, Kunz G, Blohmer J.U, Huober J.B, Hauschild M, Loibl S, Nekljudova V, Untch M, von Minckwitz G.
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**Studied Period (years):** 8

Date of the first patient enrolled: November 7th, 2007
Date of the last patient completed: August 31st, 2015

**Phase of Development**

Phase III

**Objectives**

*Primary Objectives*

To compare the pCR rates of neoadjuvant treatment of epirubicin / cyclophosphamide followed by docetaxel (EC-T) with or without bevacizumab (EC-T vs. ECB-TB) in patients with Her-2 negative primary breast cancer (Setting I).

To compare the pCR rates of neoadjuvant treatment with weekly paclitaxel with or without Everolimus (RAD001) (Pw vs. PwR) in patients with Her-2 negative primary breast cancer showing no sonographic response to 4 cycles of EC +/-B (Setting II).

To compare the pCR rates of neoadjuvant treatment with epirubicin / cyclophosphamide followed by docetaxel with either trastuzumab or lapatinib (ECH-TH vs. ECL-TL) in patients with Her-2 positive primary breast cancer (Setting III).

*Secondary Objectives*

To assess the toxicity of and compliance to all six treatments.

To determine the response rates of the breast tumor and axillary nodes by physical examination and imaging tests (sonography, mammography, or MRI) after treatment in all arms.

To determine the rates of pCR breast**,** pCR invasive**,** pCR invasive and nodes.

To determine the breast conservation rate after each treatment.

To determine the (loco-regional and distant) disease-free and overall survival after each treatment. In Her-2 positive disease, the cerebral disease-free survival will be determined separately.

To assess treatment efficacies in subgroups defined according to tumor stage (T2-3 vs. T4), receptor status (ER and / or PgR positive vs. ER and PgR negative) and response by best appropriate imaging method to the first four cycles of treatment (complete vs. partial vs. no change).

To examine and compare pre-specified molecular markers such as Ki-67, phospho-mTOR, YB-1, COX-2, HuR, phospho-p70 S6K, p65 NF kappa B, PTEN, PI3-K, Akt, SOX-10 (a marker for stem cell like breast cancers) on core biopsy before and after end of chemotherapy.
Since amendment 2: To examine and compare pre-specified molecular markers from the GeparQuattro Herceptin resistance project, Neo-PREDICT, and other ongoing translational research projects.

**Methodology**

Randomised, open, multicenter study in parallel groups.

**Number of patients (planned and analyzed)**

Planned: 2547 (Setting I: 1932 / Setting II: 566 / Setting III: 615)

Enrolled: 2600 (Setting I: 1948 / Setting II: 371 / Fill-In Setting II*: 32 / Setting III: 620)

Randomised: 2600

*Setting I*

Epirubicin-Cyclophosphamide-Docetaxel: 974

Epirubicin-Cyclophosphamide-Docetaxel + Bevacizumab: 974

*Setting II*

Paclitaxel weekly: 201 (thereof Fill-in Setting II: 15)

Paclitaxel weekly + RAD001: 202 (thereof Fill-in Setting II*: 17)

*Setting III*

Epirubicin-Cyclophosphamide-Docetaxel + Trastuzumab: 309

Epirubicin-Cyclophosphamide-Docetaxel + Lapatinib: 311

*Additional recruitment of 180 patients (planned) with tretament of four cycles Epirubicin-Cyclophosphamide outside of study before Randomisation in Setting II (Amendment 2).

Analysed patients (efficacy and safety) total study: 2540

Analysed patients (efficacy and safety) Setting I: 1925

Analysed patients (efficacy and safety) Setting III: 615

**Diagnosis and Main Criteria for Inclusion**

1. Written informed consent for all study procedures including an additional core biopsy after the first four cycles of EC +/-B must be obtained and documented according to local regulatory requirements prior to beginning specific protocol procedures.
2. Patient has consented to the biomaterial collection and the paraffin-embedded tumor tissue block of diagnostic core has been sent to central biomaterial banks*.
   * Implemented by Amendment 2 (until Amendment 1: Paraffin tumor tissue block and two serum samples centrally made available (except when the patient does not agree to central biomaterial collection).
3. Complete baseline documentation must be sent to GBG Forschungs GmbH.
4. Unilateral or bilateral primary carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration is not sufficient. Incisional biopsy is not allowed. In case of bilateral cancer, the investigator has to decide prospectively which side will be evaluated for the primary endpoint.
5. Tumor lesion in the breast with a palpable size of ≥ 2 cm or a sonographical size of ≥ 1 cm in maximum diameter. The lesion has to be measurable in two dimensions, preferably by sonography. In case

of inflammatory disease, the extent of inflammation can be used as measurable lesion.

6. Patients should be in a stage of disease in which adjuvant chemotherapy would be considered. Therefore the following tumor stages are eligible* :
   - locally advanced tumors with cT3 or cT4 or
   - Estrogen (ER) and progesterone (PgR) receptor negative tumors or
   - ER or PgR positive tumors which are cN+ (for cT2) or $pN_{SLN}$+ (for cT1).

   * During the Run-In Phase only patients with cT4 or cT3 cN+ disease are eligible.

   In patients with multifocal or multicentric breast cancer, the largest lesion should be measured.
7. Known HER-2/*neu* status detected on core biopsy. HER-2/*neu* positive is defined as HercepTest IHC 3+ or FISH+ *.

   * Implemented by Amendment 2 (until Amendment 1: Known HER-2/neu status detected on core biopsy. HER-2/neu positive is defined as HercepTest IHC 3+ or central FISH+).
8. Age ≥ 18 years.
9. Karnofsky Performance status index ≥ 80%.
10. Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF or shortening fraction) within 3 months prior to randomization. Results must be above the normal limit of the institution and above 55%.
11. Laboratory requirements:

    a) Hematology

    - Absolute neutrophil count (ANC) ≥ 2.0 x $10^9$ / L and
    - Platelets ≥ 100 x $10^9$ / L and
    - Hemoglobin ≥ 10 g/dL (≥ 6.2 mmol/L)

    b) Hepatic function

    - Total bilirubin < 1x UNL and
    - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5x UNL and
    - Alkaline phosphatase ≤ 5x UNL.

    Patients with ASAT and / or ALAT > 1.5x UNL and associated with alkaline phosphatase > 2.5x UNL are not eligible for the study.

    c) Renal function

    Creatinine ≤ 175 µmol/L (2 mg/dL) < 1.5x UNL
    (or the calculated creatinine clearance should be ≥ 30 mL/min).

    d) Proteinuria

    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.
12. Negative pregnancy test (urine or serum) within 14 days prior to randomization for all women of childbearing potential.
13. Complete staging work-up within 3 months prior to randomization. All patients must have bilateral mammography, breast ultrasound (≤ 21 days), breast MRI (optional), chest X-ray (PA and lateral), abdominal ultrasound or CT scan or MRI, and bone scan done. In case of positive bone scan, bone X-ray is mandatory. Other tests may be performed as clinically indicated.
14. 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 at a cooperating center.

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

(1) Bevacizumab
15 mg/kg BW i.v.

(2) Cyclophosphamide
600 mg/m$^2$ BSA i.v.

(3) Docetaxel
75 mg/m$^2$ BSA i.v., since Amendment 1: 100 mg/m$^2$ BSA i.v.

(4) Epirubicin
90 mg/m$^2$ BSA i.v.

(5) Lapatinib
1250 mg orally, since Amendment 2: 1000 mg orally.

(6) Paclitaxel
80 mg/m$^2$ BSA i.v.

(7) RAD001
5 mg orally with dose escalation during the first 13 days:
Day 1: 2.5 mg; Day 2: skipped; Day 3: 2.5 mg; Day 4: skipped; Day 5: 2.5 mg; Day 6: 2.5 mg; Day 7: 2.5 mg; Day 8: 2.5 mg; Day 9: 5 mg; Day 10: 2.5 mg; Day 11: 5 mg; Day 12: 2.5 mg, Day 13 and thereafter every day: 5 mg.

(8) Trastuzumab (preoperative)
Loading dose: 8 mg/kg BW i.v., thereafter maintenance dose: 6 mg/kg BW i.v.

**Duration of Treatment**

(1) Bevacizumab
12 weeks (4 cycles 1 q 22) with EC, if response than 12 weeks (4 cycles 1 q 22) with T.

(2) Cyclophosphamide
12 weeks (4 cycles 1 q 22).

(3) Docetaxel
12 weeks (4 cycles 1 q 22).

(4) Epirubicin
12 weeks (4 cycles 1 q 22).

(5) Lapatinib
24 weeks (daily).

(6) Paclitaxel
12 weeks (12 cycles 1 q 8).

(7) RAD001
12 weeks (daily) with dose escalation.

(8) Trastuzumab
24 weeks preoperative (8 cycles 1 q 22).

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

All reference therapies/drugs (cyclophosphamide, docetaxel, epirubicin, paclitaxel) were also part of the test therapies and are listed in the chapters above.

**Criteria for Evaluation**

*Efficacy*

To compare the pCR rates of neoadjuvant treatment of epirubicin / cyclophosphamide followed by docetaxel (EC-T) with or without bevacizumab (EC-T vs. ECB-TB) in patients with Her-2 negative primary breast cancer (Setting I).

To compare the pCR rates of neoadjuvant treatment with weekly paclitaxel with or without Everolimus (RAD001) (Pw vs. PwR) in patients with Her-2 negative primary breast cancer showing no sonographic response to 4 cycles of EC +/-B (Setting II).

To compare the pCR rates of neoadjuvant treatment with epirubicin / cyclophosphamide followed by docetaxel with either trastuzumab or lapatinib (ECH-TH vs. ECL-TL) in patients with Her-2 positive primary breast cancer (Setting III).

*Safety*

The National Cancer Institute Common Toxicity Criteria (NCI-CTC) and the corresponding grading system will be 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) will be performed (severity as 1: mild, 2: moderate, 3: severe, 4: life-threatening, and 5: death). At each interim look, the overall proportion of patients experiencing any toxicity of NCI grade 3 or 4 will be determined. The proportion of patients experiencing any toxicity of NCI grade 3 or 4

will also be displayed for each category and for compiled categories.

**Statistical Methods**

All categorical variables are summarized as number and percent of patients in each category. Continuous parameters are summarized as mean, median, minimum and maximum. All statistical tests are two-sided. Significance level is .05. No adjustment for multiple testing was done.

*Subject Accountability*

For each setting the number of patients randomized, started treatment, completed treatment and discontinued treatment prematurely (with reasons) is reported per arm. It was checked for each patient enrolled whether she violates any of the inclusion or exclusion criteria, major violations were reported. For each Her2-negative patient with no change after 4 cycles EC+-B, it was checked whether she was randomized into setting II (if not, the reasons are reported).

*Demographic and Baseline Characteristics*

The demographic and baseline characteristics are reported descriptively in each setting per treatment arm and overall. The Pearson $\chi 2$-test (for categorical parameters with more than 2 categories), Fisher exact test (for binary parameters), Mann-Whitney test (for age and tumor size) were used to assess the comparability of two randomized treatment arms in each setting.

*Efficacy*

Number and percent of pCRs (for each pCR endpoint, primary and secondary) is reported for each treatment arm together with 95% exact confidence intervals for percent. Number and percent of breast conserving surgery is reported for each treatment arm together with 95% exact confidence intervals for percent. Number and percent of patients with clinical (imaging) response (CR or PR) is reported for each treatment arm together with 95% exact confidence intervals for percent. The continuity corrected $\chi 2$-test was used to compare the pCR-rates, clinical response rates and breast conservation rates between treatment arms in each setting. The subgroup analyses were performed in a similar way and are presented in tables; Breslow-Day interaction tests were performed to assess homogeneity of odds ratios across subgroups for primary endpoint.
All multivariate models were fit as full models without variable selection, but only factors with univariate Wald p-value of 0.2 were taken into multivariate models (except for the treatment arm which was taken into multivariate model irrespectively of the univariate p-value). The results are presented in tables.

*Safety*

In each setting the incidence of grade 1-4 and grade 3-4 of each adverse event is reported per cycle, per patient, per chemotherapy (EC, T, Pw), for each treatment arm and overall.
The incidence of any hematological toxicity grade 1-4, grade 3-4 is reported per cycle, per patient, per chemotherapy (EC, T, Pw), for each treatment arm and overall, together with the 95% CI.
The incidence of any non-hematological toxicity grade 1-4, grade 3-4 is reported per cycle, per patient, per chemotherapy (EC, T, Pw), for each treatment arm and overall, together with the 95% CI.
Incidence of SAEs (split into hematological and non-hematological) is reported separately per patient, per chemotherapy (EC, T, Pw), for each treatment arm and overall. SAEs also contributed to the analysis of AEs (were conservatively considered as grade 3-4 AEs).

*Compliance*

The incidence of cycle delays and dose reductions is reported per cycle, per patient, per chemotherapy (EC, T, Pw), for each treatment arm and overall.
The reasons for cycle delays and dose reductions are reported per cycle, per patient and per chemotherapy (EC, T, Pw), for each treatment arm and overall.
The incidence of treatment interruptions (for lapatinib) is reported per cycle, per patient, per chemotherapy (EC, T, Pw).
The reasons for lapatinib treatment interruptions are reported per cycle, per patient, per chemotherapy (EC, T, Pw).
The incidence of permanent chemotherapy discontinuation is reported per patient, per chemotherapy (EC, T, Pw), for each treatment arm and overall.
The reasons for permanent chemotherapy discontinuation are reported per patient, per chemotherapy (EC, T, Pw), for each treatment arm and overall.
The incidence of permanent targeted treatment discontinuation is reported per patient, per chemotherapy (EC, T, Pw) for ECB-TB, ECL-TL, ECH-TH, and PwR arms.
The reasons for permanent targeted therapy discontinuation are reported per patient, per chemotherapy (EC, T,

Pw) for ECB-TB, ECL-TL, ECH-TH, and PwR treatment arms.
The number and percentage of patients who received full dose of EC, T, Pw, and targeted treatment are reported per treatment arm and overall.
All deaths under therapy are listed together with the treatment arm, cycle number and death cause.
The duration of trastuzumab/lapatinib treatment before surgery is presented graphically in form of the Kaplan-Meier curves. Also the time until lapatinib reduction and the time until lapatinib reduction or discontinuation is presented graphically in form of the Kaplan-Meier curves.

**SUMMARY**

The addition of bevacizumab to a standard anthracycline taxane based chemotherapy increase the pCR rate for the HER2-negative patients in general with an increase in toxicity. After a median follow-up of 3.8 years DFS and OS were not different for patients receiving bevacizumab compared with patients receiving chemotherapy alone. Patients with triple negative disease as well as no other predefined subgroup show a significant benefit from the addition of bevacizumab. These results are in line with those reported from two large adjuvant studies E5103 and BEATRICE.

For the HER2-negative patients whose tumors did not respond to EC+/- Bev the addition of everolimus to paclitaxel weekly did not improve the pCR rate. No difference in DFS and OS was observed for nonearly responding patients receiving paclitaxel with or without everolimus overall as well in subgroups. If we take the added toxicity of everolimus into account and the outcome results, the risk benefit analysis is clearly negative and adding everolimus is certainly contraindicated for this subset of patients.

Given these data, the GeparQuinto study does not support the use of bevacizumab or everolimus in the neo-adjuvant setting in addition to an anthracyclines-taxane-based chemotherapy.

Trastuzumab in addition to an anthracycline taxane based therapy increased the pCR rate tremendously; however simply exchanging it for lapatinib is significantly inferior. Long-term results do not support the neoadjuvant use of lapatinib in addition to an anthracycline-taxane-based chemotherapy for patients with HER2-positive disease. Only patients with locally advanced disease seem to benefit from lapatinib and/or of a longer duration of anti-HER2 treatment (lapatinib followed by trastuzumab for a total of 1 year). Moreover a large adjuvant trial (ALTTO trial) clearly shows a worse overall survival for patients receiving adjuvant chemotherapy with lapatinib. Taking into account the increased toxicity with lapatinib compared with trastuzumab and the long-term results, lapatinib is not an option for the general HER2 positive population.

**Date of the Report:**
February 26th, 2016