# CLINICAL STUDY REPORT

# DUAL BLOCKAGE WITH AFATINIB AND TRASTUZUMAB AS NEOADJUVANT TREATMENT FOR PATIENTS WITH LOCALLY ADVANCED OR OPERABLE BREAST CANCER RECEIVING TAXANE-ANTHRACYCLINE CONTAINING CHEMOTHERAPY

## EudraCT no: 2011-004704-38

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| **Indication:** | Early breast cancer |
| **Phase:** | II |
| **Study Protocol:** | GBG 70<br>Protocol (December 02nd, 2011)<br>Amendment 1 (August 13th, 2012) |
| **Investigational Products:** | Afatinib, Paclitaxel, Trastuzumab |
| **Clinical Study Report Version:** | Version 1 |
| **First Patient Enrolled:** | May 31st, 2012 |
| **Last Patient Completed:** | February 19th, 2014 |
| **Data Cut-off Database:** | May 25th, 2014 |

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**Sponsor:**
GBG Forschungs GmbH
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**Date of this report:** September 25th, 2014

This study was performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements. The information contained in this document is the property of GBG Forschungs GmbH and may not be disclosed to parties not associated with the clinical investigation or used for any purpose without prior written consent of GBG Forschungs GmbH.

## 1. APPROVAL SIGNATURES

STUDY TITLE:
Dual blockage with Afatinib and Trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy.

STUDY NUMBER: GBG 70

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: 30. SEP. 2014

Dr. Claus Hanusch
Co-ordinating Investigator
Rotkreuzklinikum München

DATE: 02.10.2014

Prof. Dr. Gunter von Minckwitz
Co-Chair DAFNE /
Managing Director GBG Forschungs GmbH

DATE: 02.10.2014

Prof. Dr. Sibylle Loibl
Head of Medicine and Research
GBG Forschungs GmbH

Burchardi DATE: 02. Okt. 2014

Dr. Nicole Burchardi
Study Biostatistician
GBG Forschungs GmbH

## 2. SYNOPSIS

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| Name of substance:<br>(1) Afatinib (A)<br>(2) Cyclophosphamide (C)*<br>(3) Epirubicin (E)*<br>(4) Paclitaxel (P)*<br>(5) Trastuzumab (H)<br>*generic. | | |

**Title of Study:**

Dual blockage with Afatinib and Trastuzumab as neooadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy.

**Investigators:**

Co-ordinating Investigator: Dr. Claus Hanusch (Rotkreuzklinikum München)
Principal Investigators: see Section "Study Center(s)".

**Study Center(s):**

The study was conducted at 11 study centers in Germany.

- HELIOS Klinikum Berlin Buch, Klinik für Gynäkologie und Geburtshilfe, Berlin (PI: Mau)
- Luisenkrankenhaus Düsseldorf, Senologie, Brustzentrum, Düsseldorf (PI: Rezai)
- UFK Erlangen, Frauenklinik mit Poliklinik, Erlangen (PI: Fasching)
- UFK Greifswald, Klinik für Frauenheilkunde und Geburtshilfe, alte Frauenklinik, Greifswald (PI: Belau)
- UFK Heidelberg, Frauenklinik, Heidelberg (PI: Schneeweiss)
- Elisabeth Krankenhaus Kassel, Brustzentrum, Kassel (PI: Conrad)
- UFK Kiel, Klinik für Gynäkologie und Geburtshilfe, Kiel (PI: Schem)
- Klinikum der Otto-v.-Guericke-Universität Magdeburg, Frauenklinik, Magdeburg (PI: Neumeister)
- Rotkreuzklinikum München, Frauenklinik, München (PI: Hanusch)
- Klinikum Offenbach, Klinik für Gynäkologie und Geburtshilfe, Offenbach (PI: Jackisch)
- UFK Tübingen, Frauenklinik, Tübingen (PI: Grischke)

**Publication (references):**

Claus Hanusch, Andreas Schneeweiss, Michael Untch, Stefan Paepke, Sherko Kümmel, Christian Jackisch, Jens Huober, Jörn Hilfrich, Bernd Gerber, Holger Eidtmann, Carsten Denkert, Serban Costa, Jens Uwe Blohmer, Sibylle Loibl, Nicole Burchardi, Gunter von Minckwitz.
Dual blockade with Afatinib and Trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy (DAFNE)-GBG70 – efficacy and safety analysis. Congress of the European Society of Molecular Oncology, Madrid, 2014 (abstract ID 6671), Annals of Oncology (suppl.) 2014.

**Studied Period (years):** 2

Date of the first patient enrolled: May 31st, 2012
Date of the last patient completed: February 19th, 2014

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**Phase of Development:**

Phase II

**Objectives:**

Primary Objective

To compare the pathological complete response (pCR = ypT0/is ypN0) rates of neoadjuvant treatment of afatinib in combination with weekly paclitaxel + trastuzumab followed by epirubicin/ cyclophosphamide/ trastuzumab in patients with HER2-positive primary breast cancer.

Secondary Objectives

- To determine the rates of ypT0 ypN0; ypT0; ypT0/is; ypN0; and regression grades according to Sinn.
- To determine the response rates of the breast tumor and axillary nodes by physical examination and imaging tests (sonography, mammography, or MRI) after 6 weeks of the 2 anti-HER2 agents alone and at surgery.
- To determine the breast and axilla conservation rate after treatment.
- To assess the toxicity and compliance.
- To correlate skin toxicity and diarrhoea with pCR.
- To examine and compare pre-specified molecular markers such as EGFR, HER2, HER3, HER4, TGFß, EGF, AREG, HBEGF, BTC, EPIGEN, EREG, NRG1, NRG2, neuroglycan, tomoregulin, NRG4 and NRG3K-RAS, MET, IGF1R, IRS1, PTEN, FGFR1, FGFR2, FGFR3, AXL, RET, and PDGFR; EGFR signature, Ki67, p95HER2, and PI3K mutation before start of afatinib+trastuzumab, before and after chemotherapy.

**Methodology:**

Randomised, open, multicenter study in parallel groups.

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

Planned: 65
Enrolled: 65
Randomised: 65
Analysed patients (efficacy and safety) study:

**Diagnosis and Main Criteria for Inclusion:**

1. Written informed consent for all study procedures according to local regulatory requirements prior to beginning of specific protocol procedures.
2. Complete baseline documentation must be sent to GBG Forschungs GmbH.
3. Unilateral primary carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration is not sufficient. Incisional biopsy is not allowed. Tumor lesion in the breast with a sono-

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graphical size of ≥ 2 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.

4. Operable or locally advanced or inflammatory breast cancer (cT2 - cT4a-d). In patients with multifocal or multicentric breast cancer, the largest lesion should be measured.
5. Centrally confirmed positive HER2 status detected on core biopsy. HER2-positive is defined as IHC 3+ by a validated test method or FISH/SISH ratio ≥ 2.0. Formalin-fixed, paraffin-embedded (FFPE) breast tissue from core biopsy has therefore to be sent to the Department of Pathology at the Charité, Berlin, prior to registration.
6. Centrally confirmed hormone receptor status (ER/PgR).
7. Age ≥ 18 years.
8. Karnofsky Performance status ≥ 80%.
9. Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF or shortening fraction) within 3 months prior to registration. Results must be above 55%.
10. Laboratory requirements:

    *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)

    *Hepatic function*
    - Total bilirubin ≤ 1.5x UNL and
    - ASAT (SGOT) and ALAT (SGPT) ≤ 1.5x UNL and
    - Alkaline phosphatase ≤ 2.5x UNL.

    *Renal function*
    - Creatinine ≤ 175 µmol/L (2 mg/dL) ≤ 1.5x UNL.
11. Negative pregnancy test (urine or serum) within 14 days prior to registration for all women of child-bearing potential.
12. Complete staging work-up within 3 months prior to registration. 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.
13. Patients must be available and compliant for treatment and follow-up. Patients registered on this trial must be treated at the participating or at a cooperating centre.

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

(1) Afatinib

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20 mg oral (daily).

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

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

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

(5) Trastuzumab
Loading dose 8 mg/kg body weight i.v., thereafter 6 mg/kg body weight i.v.

**Duration of Treatment:**

(1) Afatinib
17 weeks (daily; first two weeks: every second day).

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

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

(4) Paclitaxel
12 weeks (weekly).

(5) Trastuzumab
30 weeks (10 cycles 1 q 22).

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

All therapies/drugs are listed in the chapter above.

**Criteria for Evaluation:**

**Efficacy**

Primary Objective

To compare the pathological complete response (pCR = ypT0/is ypN0) rates of neoadjuvant treatment of afatinib in combination with weekly paclitaxel + trastuzumab followed by epirubicin/cyclophosphamide/ trastuzumab in patients with HER2-positive primary breast cancer.

Secondary Objectives

To determine the rates of ypT0 ypN0; ypT0; ypT0/is; ypN0; and regression grades according to Sinn.

To determine the response rates of the breast tumor and axillary nodes by physical examination and imaging tests (sonography, mammography, or MRI) after 6 weeks of the 2 anti-HER2 agents alone and at surgery.

**Safety**

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The National Cancer Institute Common Toxicity Criteria (NCI-CTC) and the corresponding grading system were 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) was performed (severity as 1: mild, 2: moderate, 3: severe, 4: life-threatening, and 5: death). The proportion of patients experiencing any toxicity of NCI grade 3 or 4 was displayed for each category and for compiled categories.

**Statistical Methods:**

"Intent-to-treat" (ITT) analysis was conducted for all patients. In addition, a "per-protocol" analysis was conducted. The pCR rates with their exact 90% CI were calculated based on the ITT and PP population. Not evaluable patients (e.g not having surgery) were considered as having no pCR. One interim safety analysis was conducted 12 weeks after the 15th patient has been included in the protocol. In case more than 4 patients permanently discontinued afatinib during the first 12 weeks of treatment, the protocol has to be reviewed and measures to optimise tolerability of treatment have to be taken. If this does not appear to be possible, the study has to be stopped. The sample size calculation is based on the following assumptions: Neoadjuvant anthracycline-taxane-based chemotherapy given simultaneously with trastuzumab results in a pCR rate of approx. 40%. If HER2-status was centrally reviewed, the pCR rate in this population increases to 50%. The addition of a dual anti HER2 blockade to chemotherapy increased the pCR by absolute 20%. It was therefore assumed that the pCR rate in this study will be 70%. We have expected a pCR rate of 70% and wanted to exclude a pCR rate of 55% or lower with $\alpha$=0.1 and power 1-$\beta$=80%, this required 65 evaluable patients for two-sided one group $\chi$2-test. The study would support a subsequent phase III study if a pCR rate of 55% or lower can be excluded (it is expected to be the case if the observed pCR is $\geq$ 65% since the observed pCR rate has to be $\geq$ 65% for the lower 90% confidence interval not including 55%).

Subject Accountability

The number of patients in each of the following categories were reported:

- Screened patients.
- Screen failure patients and reasons for screen failure, if available.
- Included patients.
- Included but not treated patients with reason for not starting treatment.
- Included and treated patients.
- Patients who completed the study treatment period as per protocol.
- Patients who permanently discontinued study treatment with reasons.
- Patients who had / who did not have surgery.

Demographic and Baseline Characteristics

The demographic and baseline characteristics were reported descriptively. Following demographic and baseline characteristics were displayed:

- Age at registration,
- Height, weight, BMI,

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- Karnofsky index,
- Menopausal status,
- cT, cN by palpation/sonography,
- Tumour site, tumour focality,
- SNB yes/no, if yes: positive/negative result,
- ER/PgR, HER2 (local, central - pre-specified molecular marker),
- grading, histological tumour type,
- Ki67 (pre-specified molecular marker),
- PIK3CA,
- LVEF and other cardiac medical history at baseline,
- General medical history,
- Concomitant medication.

Continuous data were summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data were summarized using the number and percentage of patients.

Efficacy

Number and percent of pCRs (for each pCR endpoint, primary and secondary) is reported with exact confidence intervals (90% CI for primary endpoint, 95% CI for secondary endpoints). 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.

Number and percent of breast and axilla conservation rates, clinical (imaging) response (CR or PR) rates is reported with 95% exact confidence intervals.

Safety

The incidence of grade 1-4 and grade 3-4 of each adverse event is reported per patient, per anti-cancer therapy (A, H, P, EC), for the whole study period and per treatment period.

The incidence of any hematological toxicity grade 1-4, grade 3-4 is reported per patient, per anti-cancer therapy (A, H, P, EC), for the whole study period and per treatment period.

The incidence of any non-hematological toxicity grade 1-4, grade 3-4 is reported per patient, per anti-cancer therapy (A, H, P, EC), for the whole study period and per treatment period.

Incidence of SAEs (split into hematological and non-hematological) is reported separately per patient, per anti-cancer therapy (A, H, P, EC), for the whole study period and per treatment period. 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 patient and per anti-cancer therapy (A, H, P, EC). The incidence of treatment interruptions is reported per patient and per chemotherapy (A, H, P, EC).

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Descriptive Statistics is given for Relative Total Dose, Relative Total Dose Intensity and for Full Dose of Relative Total Dose and Relative Total Dose Intensity, respectively.

**SUMMARY**

Efficacy Results

Between May 2012 and July 2013, 65 patients with centrally confirmed HER2-overexpressing tumors started treatment in 10 trial centers in Germany. Fourteen patients were not included in the study because positive HER2-status was not confirmed centrally (N=9) or due to other exclusion criteria (metastatic disease or bilateral carcinoma; N=5). Median age at diagnosis was 50.0 (range: 29-73) years. The majority of patients had tumor stage T2 (76.6%), no nodal involvement (51.6%), tumor grade 3 (60%), and hormone receptors were positive in tumors of 70.8% of patients. Lymphocyte predominant breast cancer (LPBC) was present in nine patients (13.9%) and a PIK3CA mutation was found in 13 patients (21.3%).

Pathological complete response (ypT0/is ypN0) was reported in 32 of 65 patients that have started treatment (49.2%; 95% CI: 38.5%-60.1%). Twenty one (33.9%) patients had neither invasive nor non-invasive residuals in the removed breast and axillary specimens (ypT0, ypN0). No invasive residuals in the breast (ypT0/is ypN0/+) were found in 36 (55.4%) patients. Pathological tumor-free lymph nodes were documented in 54 (83.1%) patients. Patients with hormone-receptor-negative (N=19) or -positive (N=46) tumors showed pCR rates of 63.2% and 43.5%, respectively (odds ratio 0.449; P=0.153). Five (38.5%) of 13 patients with a PIK3CA mutation in the tumor and 26 (54.2%) of 48 patients with wild-type PIK3CA status showed a pCR (P=0.363). Seven (77.8%) of nine patients with LPBC and 15 (26.8%) of 56 patients without LPBC showed a pCR (P=0.0053). No association of efficacy was observed in relation to the occurrence of skin toxicity (P=0.269) or diarrhea (P=0.841).

At surgery, clinical objective response rate was 96.3%. Three (5.3%) and 21 (36.8%) of 57 evaluable patients already showed a complete or partial response after 6 weeks of trastuzumab and afatinib without chemotherapy, respectively. However, 8 (14.0%) patients showed initially clinical signs of tumor progression during this induction phase.

Breast-conserving surgery was possible in 38 (60%) patients, and 22 (35%) patients required no complete axillary dissection.

Safety Results

Nine patients (13.8%) discontinued all study treatment before surgery due to adverse events, disease progression, patient´s wish or due to investigator decision (N=1 during the anti-HER2-treatment only phase, N=5 during the paclitaxel phase and N=3 during the EC phase); additional nine (13.8%) patients discontinued at least one of the treatments; and 47 (72.3%) patients completed all 30 weeks of treatment. Dose reduction during this time was necessary in 37 (56.9%) patients due to adverse events (26 patients, 40.0%) or other reasons (N=9 during the anti-HER2-treatment only phase, N=34 during the paclitaxel phase and N=3 during the EC phase). Dose delays were reported in a total of 45 (69.2%) patients (N=5 during the anti-HER2-treatment only phase, N=37 during the paclitaxel phase and N=16 during the EC phase).

At least 85% of full dose intensity of afatinib, trastuzumab, paclitaxel, and EC was given to 37 (56.9%), 58

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(89.2%), 59 (90.8%), and 57 (91.9%) patients, respectively. The most common grade 3-4 hematological toxicities were neutropenia (53.8%) and leukopenia (32.3%) reported mainly during chemotherapy treatment. The incidences of grade 3-4 anemia and thrombocytopenia were low (4.6% or 0%, respectively). Most frequent grade 3-4 non-hematological toxicities were diarrhea (7.7%), increased creatinine (4.6%) and infection (4.6%), occurring again mostly during chemotherapy treatment. Liver toxicity was frequent throughout all treatment phases, but never reached grades 3 or 4. Of a total of 22 SAEs occurred in 16 patients; 27.3% were gastrointestinal, 18.2% hematologic, 13.6% infections, and 9.1% related to the nervous system. One patient developed symptomatic congestive heart failure, 12 patients showed decreased or abnormal left ventricular ejection fraction throughout the treatment. Nine adverse events of special interest were reported: N=6 diarrheas grade 3, N=1 rashes grade 3, and N=2 renal failures grade 3. No hepatic injury or interstitial lung disease were reported. No deaths occurred during the study.

Conclusion

Dual blockade with trastuzumab and afatinib in combination with anthracycline-taxane based chemotherapy did not meet its primary endpoint to show a pCR rate of as high as 70% to suggest superior efficacy than other currently available regimes using dual HER2-blockade in breast cancer. Even if below expectation the achieved rate of pCR is comparable to that of other anti-HER2 doublets. Diarrhea still emerges as the major toxicity associated with afatinib. Supportive treatment with loperamide is therefore necessary. No significant correlation was seen between the occurrence of skin toxicity or diarrhea and pCR.

**Date of the Report:**

September 25th, 2014