CLINICAL STUDY REPORT

A multicenter non-randomized phase II study to evaluate nab-paclitaxel in metastatic breast cancer patients failing a solvent based taxane as (neo-)adjuvant treatment.

EudraCT no: 2011-000075-13

Indication:	Metastatic breast cancer
Phase:	II
Study Protocol:	GBG 65 Protocol (Version 3, February 21st, 2011) Protocol (Version 4, February 10th, 2012) Amendment 1
Investigational Product:	nab-Paclitaxel (ABRAXANE®)
Clinical Study Report Version:	Version 1 (December 4th, 2013)
First Patient Enrolled:	November 10th, 2011
Last Patient Completed:	September 20th, 2012

Co-ordinating Investigator:
PD Dr. Marcus Schmidt
Universitätsfrauenklinik Mainz
D-55131 Mainz, Langenbeckstraße 1
Germany

Protocol Board (GBG Subboard Palliative)
Dr. Jana Barinoff (Frankfurt)
Dr. Dirk Bauerschlag (Aachen)
PD Dr. Joachim Bischoff (Magdeburg)
PD Dr. Daniel Herr (Wiesbaden)
Prof. Dr. Sibylle Loibl (Neu-Isenburg)
Dr. Kristina Lübbe (Hannover)
Prof. Dr. Hans-Joachim Lück (Hannover)

Prof. Dr. Nicolai Maass (Aachen)
Prof. Dr. Gunter von Minckwitz (Neu-Isenburg)
Prof. Dr. Volkmar Müller (Hamburg)
Prof. Dr. Christoph Mundhenke (Kiel)
PD Dr. Marcus Schmidt (Mainz)
Dr. Kathrin Schwedler (Luzern, CH)
PD Dr. Marc Thill (Frankfurt)

Sponsor:
GBG Forschungs GmbH
D-63263 Neu-Isenburg, Martin-Behaim-Straße 12
Germany

1. APPROVAL SIGNATURES

STUDY TITLE:

A multicenter non-randomized phase II study to evaluate nab-paclitaxel in metastatic breast cancer patients failing a solvent based taxane as (neo-)adjuvant treatment.

STUDY NUMBER: GBG 65

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:
PD Dr. Marcus Schmidt Co-ordinating Investigator	6/12/2013
Prof. Dr. Gunter von Minckwitz Managing Director GBG Forschungs GmbH	05.12.2013
Prof. Dr. Sibylle Loibl Head of Medicine and Research GBG Forschungs GmbH	5.12.13
Dr. Valentina Nekljudova Study Biostatistician GBG Forschungs GmbH	5.12.2013
Horst Mochnatzki Trial Manager GBG Forschungs GmbH	05.12.2013
Dr. Mathias Uhlig Trial Co-Manager GBG Forschungs GmbH	05.12.2013

2. SYNOPSIS

Name of Sponsor: GBG Forschungs GmbH		*(For National Authority Use only)*
Name of finished product: (1) ABRAXANE®		
Name of substance: (1) nab-Paclitaxel		

Title of Study:

A multicenter non-randomized phase II study to evaluate nab-paclitaxel in metastatic breast cancer patients failing a solvent based taxane as (neo-)adjuvant treatment.

Investigators:

Co-ordinating Investigator: PD Dr. Marcus Schmidt (Uiniversitätsfrauenklinik Mainz)
Principal Investigators: see Section 6.1.

Study Center(s):

See Section 0.1.

Publication (references):

Not applicable.

Studied Period (years): 10 months

Date of the first patient enrolled: November 10th, 2011.
Date of last patient enrolled: September 20th, 2012 (patient no. 5).
Date of the last patient completed: September 20th, 2013 (one year after recruitment of the last patient).

Phase of Development:

Phase II

Objectives:

Primary Objective
To determine overall response rate (ORR) and to exclude that it is 20% or lower.

Secondary Objectives

To determine compliance and toxicity of the therapy.

To determine clinical benefit rate (CBR) in patients with measurable disease.

To determine duration of response.

To determine progression-free survival (PFS).

To determine overall survival.

To assess biomarkers, e.g. SPARC expression in the tissue of the primary or metastatic tumor.

Methodology:

Non-randomized, open, multicenter study.

Number of patients (planned and analyzed):

Planned: 66.
Enrolled and registrated: 5.
Analysed patients (efficacy and safety): 5.

Diagnosis and Main Criteria for Inclusion:

Patients will be eligible for study participation only if they comply with the following inclusion and exclusion

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criteria:

1. Written informed consent for all study procedures according to local regulatory requirements prior to beginning specific protocol procedures.
2. Complete baseline documentation must be submitted via the web-based data collection system MedCODES to the GBG Forschungs GmbH.
3. Diagnosis of locally advanced or metastatic hormone-sensitive or insensitive, HER2-negative or -positive breast cancer.
4. Relapse within ≤ 12 (≤ 24*) months after completing (last day of last cycle) (neo-)adjuvant chemotherapy.
5. Documented relapse of either a measurable or a non-measurable lesion according to the modified RECIST criteria.
6. Previous neoadjuvant or adjuvant treatment with a solvent based taxane (paclitaxel or docetaxel) irrespective of dose and duration.
7. Prior endocrine treatment for metastatic / advanced disease is allowed.
8. Complete radiological and clinical tumor assessment within 4 weeks prior to registration performed as clinically indicated.
9. Age ≥ 18 years.
10. ECOG Performance Status ≤ 2 (irrespective of restrictions due to breast cancer).
11. Laboratory requirements:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
    - Platelets ≥ 100 x 10^9/L.
    - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L).
    - Prothrombin time (PT) or international normalized ratio (INR) ≤ 1.2x ULN (upper normal limit).
    - Partial thromboplastin time (PTT) ≤ 1.2x ULN.
    - Total bilirubin < 1.5x ULN.
    - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5x ULN (concomitant elevations in serum bilirubin and ASAT/ALAT above 1.0x ULN are not permitted).**
    - Creatinine clearance ≥ 50 mL/min).
    - Urine Protein to Creatinine Ratio (UPC) < 1 (if UPC ≥ 1, then 24-hour urine protein must be < 1 g).
12. Normal cardiac function confirmed by ECG.
13. A female either of:
    - *Non-childbearing potential*, i.e. physiologically incapable of becoming pregnant because of history of hysterectomy, bilateral oophorectomy (ovariectomy), bilateral tubal ligation or postmenopausal status.
    - *Childbearing potential* with a negative pregnancy test (urine or serum) within 2 weeks prior to registration, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:
      - An intrauterine device with a documented failure rate of less than 1% per year.
      - Vasectomised partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
      - Complete abstinence from sexual intercourse for 14 days before exposure to the investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.

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- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

14. Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

* Changed with amendment 1.

** Removed with amendment 1.

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

(1) nab-Paclitaxel
125 mg/m^2 weekly in 5 of 6 weeks i.v.

Duration of Treatment:

(1) nab-Paclitaxel
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:

n.a.

Criteria for Evaluation:

Efficacy
To determine overall response rate (ORR) and to exclude that it is 20% or lower.

Safety

Toxicity
The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 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-CTCAE, a COSTART grading classification (FDA 1989) will be performed (severity as 1: mild, 2: moderate, 3: severe, 4: life-threatening, and 5: death). Heart failure will be graded according to the NYHA classification system. Analysis of adverse events will include all laboratory data (e.g. observed toxicity). No separate analysis of laboratory data is planned, but may be performed afterwards. At the first two interim safety analyses, the overall proportion of patients experiencing any toxicity of NCI grade 3 or 4 will be determined. The most extreme intensity should be used for reporting.

Compliance
Treatment compliance parameters are dose reductions, cycle delays, treatment interruptions and permanent discontinuations. The reasons for treatment modifications include aspects of efficacy (e.g. termination of treatment due to relapse), safety (e.g. dose reduction, delay or termination due to adverse event) and compliance (e.g. cycle delay or treatment discontinuation due to patient wish).

Statistical Methods:

Efficacy
The (modified) intent-to-treat analysis set consists of all patients that are registered for study participation and have received at least one dose of study medication. There will be two cohorts. A descriptive analysis of

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efficacy will be performed overall and separate for cohort I (≤ 12 months) and II (> 12 – ≤ 24 months).

Safety

The whole intent-to-treat population is included in the safety analysis. For the analysis of safety and toxicity, the highest grade of severity of all documented adverse events and laboratory parameters per individual patient will be assessed. The incidence of grade 1-4 and of grade 3-4 of each adverse event will be reported per patient for each treatment arm and overall. The proportion of patients experiencing any toxicity and the proportion of patients experiencing any toxicity of grade 3 or 4 will be determined, per treatment arm and overall, together with the 95% confidence intervals. Adverse events will also be presented by their relationship to study medication. The number and proportion (together with the 95% confidence interval) of patients whose treatment had to be reduced, delayed, interrupted or permanently stopped will be reported. Reasons for each modification of treatment will be categorized and presented in frequency tables. All safety parameters will be analyzed and presented in terms of listings and summary tables based on the safety population. In addition, the difference in toxicity and tolerability of treatment between treatment arms will be evaluated, and the significance will be tested with the Fisher exact test. The significance level is set to $\alpha = 0.05$.

SUMMARY

The TIFFANY trial was closed prematurely due to slow recruitment after 5 patients had been enrolled within 11 months due to strong recommendations from the IDMC. None of the measures to stimulate recruitment, such as training, amendment were able boost the recruitment to finalise the study.In conclusion, although in a very small sample, nab-paclitaxel 125 mg/m² weekly in 5 of 6 weeks with or without trastuzumab seems to be a feasible regimen in metastatic breast cancer patients who failed a solvent-based taxane as adjuvant or neoadjuvant treatment. However, the study failed to demonstrate that nab-paclitaxel can be used to rechallange a taxane in patients with taxane resistant primary breast cancer.

Date of the Report:

December 4th, 2013