2 Protocol Synopses

2.1 Protocol Synopsis English

Study Title	DESIREE-A multicenter randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer
Study Code	GBG 86
EudraCT Number	2014-005126-35
Sponsor	GBG Forschungs GmbH, Neu-Isenburg
Development Phase	Randomized, double-blind, phase II

Background and rationale	The BOLERO-2 study demonstrated an enormous benefit for patients who received everolimus in addition to exemestane in patients who progressed during/after a non steroidal aromatase inhibitor (NSAI) [1], which led to approval of everolimus in this indication. However, experience from routine use report a high rate of intolerability of this innovative treatment approach especially during the first 12 weeks of treatment. Most common side effect is mucositis/stomatitis which is considered the leading cause for treatment discontinuation not related to tumor progression. This outside clinical trial experience is contrary to findings from BOLERO-2, where the number of patients still taking full-dose (10mg) of everolimus at 4, 8, and 12 weeks is 77.8%, 75.6%, and 75.6%, respectively. These findings are in concordance with non-interventional studies. However, findings might be biased by positive pre-selection. In the non-responder part (setting III) of the neoadjuvant GeparQuinto study, everolimus was given as salvage treatment in combination with paclitaxel for patients without response to 4 cycles epirubicin/cyclophosphamide +/- bevacizumab. A dose-escalation schema was successfully used to improve tolerability of everolimus together with the cytotoxic agent.[2] [3]

Primary Objective	To compare the cumulative rate of mucositis/stomatitis grade 2-4 (WHO's oral toxicity scale (OTS)) at 12 weeks after start of treatment using a conventional and a dose-escalating schema of everolimus in combination with exemestane in patients with metastatic breast cancer and progression or relapse after non-steroidal aromatase-inhibitor treatment.
Secondary Objectives	• To compare the cumulative rate of mucositis/stomatitis grade 2-4 (WHO's oral toxicity scale (OTS); first episode per patient included in the numeration) at 24 weeks after start of treatment • To compare the cumulative rate of mucositis/stomatitis grade 1 and any grade (WHO's oral toxicity scale (OTS)) at 12 and 24 weeks after start of treatment • To compare the rate of patients on 10mg daily at 12 weeks and 24 weeks after start of everolimus treatment • To compare the clinical benefit rate (CR, PR und SD >=16 Weeks) at 24 weeks after start of everolimus treatment • To compare the safety with regard to other organ signs and symptoms • To compare the time to grade ≥2 mucositis/stomatitis • To compare the cumulative dose at 4 weeks • To compare the relative dose intensity for everolimus • To compare quality of life using the FACT-B questionnaire and the QSDQ Other objectives: • Potential biomarkers predicting safety and compliance will be determined after completion of study treatment
Study Design and Treatment	This multicenter, randomized, double-blind, phase II study aims to show improvement in the rate of mucositis/stomatitis (WHO´s OTS) grade 2-4 and other compliance endpoints at 12 weeks after start of treatment by comparing a conventional dosing approach starting with 10 mg at first dose versus a dose-escalating schema over 21 days in patients receiving everolimus in combination with exemestane for treatment of metastatic breast cancer. All patients will be treated within the approved indication of everolimus in combination with exemestane. Patients will be randomized in a 1:1 ratio to receive either

	• everolimus 10 mg/day, week 1-3: 4x2.5 mg/day (blinded); week 4-24: 10mg/day (open according to label) or • an escalating dose of everolimus as follows: week 1: 1x2.5 mg verum + 3x placebo/day; week 2: 2x2.5 mg verum + 2x placebo/day; week 3: 3x2,5 mg verum + 1x placebo/day; week 4-24: 10 mg/day (open according to label) Treatment will be given until 24 weeks of treatment are completed, disease progression, unacceptable toxicity of the study drug, or withdrawal of consent of the patient.
Inclusion Criteria	Patients will be eligible for study participation only if they comply with the following inclusion criteria: 1. 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. 2. Complete baseline documentation must be submitted via the web-based data collection system MedCODES® to the GBG Forschungs GmbH. 3. Histological confirmed hormone receptor-positive (HR+ [ER and/or PgR status]), HER2-negative carcinoma of the breast. ER/PR positive is defined as >1% stained cells and HER2-positive is defined as IHC 3+ or in-situ hybridization (ISH) ratio >2.0. 4. Postmenopausal women 5. Locally advanced or metastatic stage of disease not amenable to curative treatment by surgery or radiotherapy alone. 6. No indication for chemotherapy (e.g. symptomatic visceral metastasis) 7. Patients have a complete staging work-up within 4 weeks prior to registration including standard routine procedures like chest and abdominal CT scan or MRI, and bone scan (except for bone scan 8 weeks). Further tests have to be performed as clinically indicated. 8. Disease progression following prior therapy with non steroidal aromatase inhibitors (NSAI), defined as:

	a. Recurrence while on, or following completion of an adjuvant treatment with Letrozole or Anastrozole, or b. Progression while on or following completion of Letrozole or Anastrozole treatment for ABC/MBC. Note: Non-steroidal aromatase inhibitors (i.e. Letrozole or Anastrozole) do not have to be the last treatment prior to enrollment. Other prior anticancer therapy, e.g. Tamoxifen, Fulvestrant, Exemestane, is also allowed. Patients must have recovered to grade 1 or better from any adverse events (except alopecia and nail changes) related to previous therapy prior to enrollment. 9. At least 4 weeks since radiotherapy, with full recovery. The measurable disease must be completely outside the radiation field or there must be pathologic proof of newly progressive disease. 10. Age ≥ 18 years 11. ECOG performance status 0-2 12. Laboratory requirements: • Absolute neutrophil count ≥1500 cells/μl, • Hemoglobin ≥9.0 g/dL (hemoglobin <9.0 g/dL is acceptable if it is corrected by growth factor or transfusion), • Platelet count ≥100,000 cells/μl, • Bilirubin ≤1.5x the upper limit of normal for the institution (ULN), • Elevation of transaminases and alkaline phosphatase <3x ULN or <5x ULN for patients with liver metastases, • BUN (blood urea nitrogen) ≤ULN, • Fasting plasma glucose (FPG) ≤160 mg/dL or ≤8.9 mmol/L, • Fasting serum cholesterol ≤ 300 mg/dl or 7.75 mmol/L (LDL cholesterol <190mg/dl) and fasting triglyceride ≤2.5xULN (<300mg/dl). In case one or both of these thresholds are exceeded the patient can only be included after initiation of a statin therapy and when above mentioned values have been achieved, • Creatinine ≤2.0 x ULN or creatinine-clearance >40 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. 13. 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 center.
Exclusion Criteria	Patients fulfilling at least one of the following exclusion criteria must not be included in the study: 1. No documented progression or recurrence on previous non-steroidal aromatase-inhibitor treatment. 2. Known hypersensitivity reaction to the compounds or incorporated substances. 3. Concurrent immunotherapy or hormonal therapy (contraceptive and/or replacement therapy). Bisphosphonates or denosumab may be continued or started before randomization. 4. Life expectancy of less than 3 months. 5. Parenchymal brain metastases, unless adequately controlled by surgery and/or radiotherapy. 6. Any ongoing toxicity from prior anti-cancer therapy that is grade 2-4 and/or that is progressing in severity, except alopecia. 7. Known or suspected congestive heart failure (>NYHA I) and/or coronary heart disease, angina pectoris requiring anti-anginal medication, previous history of myocardial infarction ≤ 6months, evidence of transmural infarction on ECG, un- or poorly controlled arterial hypertension (i.e. BP >150/100 mmHg under treatment with two antihypertensive drugs), rhythm abnormalities requiring permanent treatment, clinically significant valvular heart disease. 8. Currently active infection. 9. History of other malignancies within the last 5 years which significantly affect the diagnosis, assessment or prognosis of metastatic breast cancer. 10. Malabsorption syndrome or insufficient gastrointestinal function, preexisting diagnosis of ulcerative colitis.

	11. Concurrent treatment with other experimental drugs; participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry. 12. Insufficiently controlled diabetes, known HIV infection or chronic hepatitis B or C and seriously impaired liver function (Child-Pugh, class A, B or C). 13. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures (including severe pulmonary conditions, AIDS and serious active infection and diabetes mellitus). 14. Male patients.
Investigational product and formulation	Refer to the everolimus SmPc for information regarding the physical and chemical properties of everolimus and a list of excipients. After the dose-adjustment phase (3weeks), the interventional part of the study is completed and the patient will continue on prescribed everolimus as part of her Standard of Care.
Non-investigational product and formulation	Exemestane will be given according to marketed formulation via normal procedures according to recommendations of the manufacturers and in adherence to the German Guidelines from AGO Breast Commission.
Primary endpoints	Incidence of first episode of mucositis WHO's OTS 2-4 any time during a 12 week period after start of everolimus
Secondary endpoints	Incidence of first episodes of mucositis/stomatitis WHO's OTS grade 2-4 any time during a 24 week period. Incidence of first episodes of mucositis/stomatitis WHO's OTS grade 1 and any grade any time during a 12 and 24 week period. Average dose of treatment during week 12 and during week 24. Clinical benefit rate (CBR) is defined as all patients with no evidence for tumor progression at 24 weeks after start of everolimus treatment. Safety by toxicity grades in general is defined by the NCI-CTCAE version 4.03, mucositis by WHO's OTS. Cumulative dose will be calculated by adding all daily doses of everolimus until end of treatment or discontinuation. Relative dose intensity for everolimus is the ratio of Actual Total Dose

	Intensity (ATDI) and Planned Total Dose Intensity (PTDI), expressed as a percentage. Quality of life will be assessed using the FACT-B questionnaire and the QSDQ.
Biomaterial	- blood sample for SNP analysis taken any time during study participation - serum and plasma sample at study start and at end of study treatment -optional collection Primary tumor and/or metastasis
Exploratory endpoints	Potential biomarkers predicting safety and compliance will be determined after completion of study treatment, like SNPs, CTC, PI3kinase marker and other biomarkers considered for breast cancer
Statistical Methods/Number of patients	156 evaluable patients (78 in each arm) are required to detect a clinically relevant difference of 20% in the mucositis/ rate (WHO's OTS grade 2-4) between treatment arms using a continuity-corrected $\chi 2$-test on a significance level alpha of 0.2 and beta of 0.9. The rate was estimated to be 40% and 20% in the control arm and the treatment arm, respectively. A modified intent-to-treat (mITT) analysis for the primary endpoint will include all randomized patients who received at least one dose of the study medication.
Number of sites	Up to 60 sites mainly from the BRAWO trial experienced with the use of Everolimus
Approximate Timelines	Enrollment period: 24 months (Q-II 2015 – Q-II 2017) Study start (FPFV): 01.04.2015 Recruitment end (LPFV): 01.04.2017 Final Analysis: 31.03.2018 Study end (LPLV): 30.10.2017

DESIREE – GBG 86
STUDY DESIGN

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Everolimus 10 mg
week 1-3: 4x2.5 mg/day (blinded)
week 4-24: 10mg/day (open)

Everolimus dose-escalated
week 1: 1x2.5 mg verum + 3 x placebo/day
week 2: 2x2.5 mg verum + 2 x placebo/day
week 3: 3x2.5 mg verum + 1 x placebo/day
week 4-24: 10 mg/day (open)

N=156

Eligibility according to current label
+ exemestane in both arms
Follow-up: EOT visit (week 25-28)

Primary Objective
Cumulative Mucositis grade 2-4 at 12 weeks

Statistical assumption:
Control arm: 40% Mucositis
Escalation arm: 20% Mucositis