CLINICAL STUDY REPORT_Synopsis

Sofia: Phase II study of neoadjuvant epirubicin, cyclophosphamide (EC) + sorafenib followed by paclitaxel (P) + sorafenib in women with previously untreated primary breast cancer

Trial Registration No.: NCT 00548899
EudraCT No: 2007-000124-41

Investigational Products:	**Sorafenib**
Indication:	**Primary breast cancer**
Study Protocol:	**GBG 45 – Protocol version 6.0, 16.01.2010**
(Amendment no. 4)	
Phase:	**II**
Report Version:	**Version 1**

First Patient Enrolled: November 02, 2007

Last Patient Completing Therapy (Cohort2) : November 03, 2009
(surgery at beginning of December, 2009)

Study paused

Last Patient Completing Therapy (Cohort3): July 08, 2011 (surgery at 18.July 2011),

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Date of this report: November 5, 2013.

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 and may not be disclosed to parties not associated with the clinical investigation or used for any purpose without prior written consent of GBG

SYNOPSIS

Name of Sponsor: GBG Forschungs GmbH	Individual Study Table Referring to the Dossier	*(For National Authority Use only)*
Name of finished product: Nexavar®	Volume: not applicable	
Name of active ingredient: Sorafenib	Page:	

Title of Study:

Phase II study of neoadjuvant epirubicin, cyclophosphamide (EC) + sorafenib followed by paclitaxel (P) + sorafenib in women with previously untreated primary breast cancer

Investigators:

Prof. Dr. Sibylle Loibl, Coordinating Investigator

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

Study Centers:

The study was conducted at 10 centers in Germany.

Publication (reference):

Loibl S, Conrad B, Warm M, Schwedler K, Gerber H, Schrader I, Eidtmann H, Linder M, Mehta K, von Minckwitz G SOFIA: Phase II study of neoadjuvant epirubicin, cyclophosphamide (EC) + sorafenib (S) followed by paclitaxel (Pw) + sorafenib (S) in women with previously untreated primary breast cancer (BC) (GBG 45). EBCC 2010

Sibylle Loibl, Dennis Rokitta , Bettina Conrad , Nadia Harbeck, Wüllner Michaela, Mathias Warm5 , Kathrin Schwedler, Bernd Gerber, Iris Schrader, Holger Eidtmann, Keyur Mehta1, Uwe Fuhr, Gunter von Minckwitz , Sorafenib in the treatment of early breast cancer. Results of the neoadjuvant phase II study –SOFIA, Manuscript submitted

Studied Period (years):

Date of the first patient enrolled: November 02, 2007

Last Patient Completing Therapy (Cohort2): November 03, 2009 (surgery at beginning of December, 2009),

Last patient Completing Therapy (Cohort3): July 08, 2011 (surgery at 18.July 2011), 12 weeks paclitaxel followed by 4 cycles EC (cohort 3)

Phase of Development: Phase II

Objectives:

Primary Objective with Amendment4: to establish the most feasible regimen of EC-P (P-EC) with sorafenib

Prior Primary Objectives, now secondary Objective:

To determine the rate of histopathological complete remission at the time of surgery

Secondary Objectives:

- Safety of preoperative regimen
- Disease free and overall survival
- Determine clinical response rate
- Histopathological axillary nodal status after neoadjuvant therapy
- Correlate baseline and change in tumor and serum genetic, gene expression and proteomic patterns with clinical and pathological response

Methodology:

It is an open-label, single arm, multicenter, phase II study. All eligible patients received sorafenib following an escalation scheme starting with 200 mg daily up to a maximum dose of 800 mg daily.

Number of patients (planned and analyzed):

It was planned to enroll 62 patients in total. Up to now 24 patients were enrolled and treated, all of them were included for efficacy and safety analyses. Further 12 patients (Cohort3) were enrolled with Amendment 4

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Diagnosis and Main Criteria for Inclusion:

Female patients aged ≥ 18 years with unilateral or bilateral primary carcinoma of the breast, confirmed histologically by core biopsy; tumor lesion in the breast with a palpable size of ≥ 2 cm and being measurable in two-dimensions preferably by sonography; for inflammatory disease the extent of inflammation was used as measurable lesion; stages of disease in which adjuvant chemotherapy would be considered; multifocal or multicentric breast cancer measured using the largest lesion; women of childbearing potential had to have a negative serum pregnancy test performed within 7 days prior to the start of treatment; Her-2 status negative; Karnofsky Performance status index ≥ 80%; normal cardiac function confirmed by ECG and cardiac ultrasound (LVEF or shortening fraction) within 3 months prior to registration, LVEF ≥55%; normal laboratory values with 14 days prior to registration, i.e., normal blood counts, hemoglobin, INR and PTT, liver enzymes, total bilirubin, and creatinine clearance; 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 (if positive, bone X-ray was mandatory), and other tests as indicated. All patients gave written informed consent for all procedures applied.

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

During 4 cycles (21 days per cycle) of epirubin and cyclophosphamide (EC) treatment, sorafenib was given orally on days 2-19 each cycle starting with 800 mg daily dose in the first group of patients (cohort 1). After a protocol amendment, it was given at an escalation dose of 200 (EC1), 400 (EC2), 600 (EC3), and 800 (EC4) mg/day (cohort 2). Dosage of sorafenib was only increased in the next EC cycle, if no skin toxicity occurred. If ≥ grade 1 toxicity developed, the dose reduction or interruption had to be applied.

Following the EC cycles, sorafenib was given concomitantly to weekly paclitaxel treatment during weeks 1-11 at the same dose level as given during the last EC cycle. Sorafenib was stopped at the end of the week 11, i.e. one day before the 12th application of paclitaxel.

Duration of Treatment:

A total of 23 weeks of sorafenib in combination with 12 weeks of EC (4 cycles) and 11 weeks of paclitaxel (the 12th week paclitaxel without sorafenib). (Cohort 1+2). Cohort3 has the same duration, however current studies assume even better results with the reversed scheme of firstly given P followed by EC.

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

This is a single arm study. Neoadjuvant chemotherapy was given as co-medication, i.e. 4 cycles of EC (epirubicin 90 mg/m², i.v. on day 1; cyclophosphamide 600 mg/m², i.v., on day 1) followed by 12 weeks of weekly paclitaxel (80 mg/m², i.v.).

Criteria for Evaluation:

Efficacy:

Primary Objective with Amendment 4: to establish the most feasible regimen of EC-P (P-EC) with sorafenib

Previous Primary Objective, Secondary primary objective with Amendment 4

The primary endpoint is pathological complete response (pCR breast) according to histopathological analyses of tissue samples after neoadjuvant chemotherapy and sorafenib therapy at the time of surgery; pCR was defined as no invasive tumor residual detectable in all removed breast tissue, ypT0/Tis, ypN0, or regressions grade III (residual noninvasive tumor) and IV (no tumor detectable).

Other endpoints included clinical Response Rate, histopathological axillary nodal status after neoadjuvant therapy (ypN0 and ypN+), and disease free and overall survival.

Safety:

The National Cancer Institute Common Terminology Criteria (NCI-CTC v3.0) and the corresponding grading system were used to grade adverse events for recording in the CRF. For all adverse events not classified by

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the NCI-CTC, a COSTART grading classification (FDA 1989) was to be performed (severity as 1: mild, 2: moderate, 3: severe, 4: life threatening, and 5: death). The overall proportion of patients experiencing any toxicity of grade 3 or 4 was determined. Adverse events duration and their relationship to study medication were presented.

Statistical Methods:

Descriptive statistics were given on the number of patients in whom treatment had to be reduced, delayed or permanently stopped.

The pCR rate, histological regression grades, and clinical response were evaluated in cohort 1 (12 patients starting sorafenib at 800 mg daily dose plus EC) and cohort 2 (12 patients starting sorafenib at 200 mg daily dose and escalated up to 800 mg daily dose at 4th EC cycle).

The Kaplan-Meier product limit method was used to estimate the DFS and Overall Survival (applies to the secondary objective). Cox's proportional hazards models were used to assess for DFS and OS for the major prognostic factors. These factors included clinical baseline parameters (especially pre-treatment), pathological markers and molecular markers. Such adjusted analyses were considered secondary to the main analysis.

For the analysis of safety and toxicity, the number of occurrences and the highest grade of severity of all documented adverse events and laboratory parameters in an individual patient were assessed. All safety parameters were analyzed and presented in terms of listings and summary tables based on the safety population.

SUMMARY

Efficacy Results:

A total of 10 patients had a pCR (ypT0/is) (27.8% [95%CI 13.1%-42.3%]). If nodal involvement was considered for pCR definition, 9 patients (25.0%) had no invasive residuals in the breast and no involved lymph nodes (ypT0/Tis, ypN0) and 8 patients (22.2%) had no invasive and no non-invasive residuals in breast and nodes (ypT0/ypN0). Overall, 15 patients had triple negative breast cancer (TNBC) 6 of whom achieved a pCR (40.0% [95% CI 15.2%-64.8%]). From the total of 36 patients, 14 (38.9%) were treated with mastectomy.

After a median follow-up of 3.9 years (range 3.1-4.5 years) five relapses and 2 deaths have been observed.

Maximum Tolerable Dose (MTD):

In cohort 1, seven of 12 patients completed the study and six of them received sorafenib at a reduced dose; 5 patients discontinued sorafenib prematurely, 3 due to adverse events, 1 due to progression and 1 on patient's request. In cohort 1 the maximum tolerated dose of sorafenib was 400mg per day. Only one patient could be treated with 800mg sorafenib daily. In cohort 2 and 3, all 12 patients completed the study. In the 2nd cohort the sorafenib dose could be escalated to 800mg in six of the 12 patients, to 600mg in four patients and to 200mg daily in two patients. In the 3rd cohort, one patient was escalated to 800mg, three to 600mg, six to 400mg and two remained on 200mg sorafenib daily. The median cumulative dose per patient was 44.5g in cohort 1, 77.4g in cohort 2 and 55.2g in cohort 3, which corresponds to 37%, 65% and 46% relative to the maximum pre-planned cumulative dose of 800mg.In cohort 1, seven of 12 patients completed the study and six of them received sorafenib at a reduced dose; 5 patients discontinued sorafenib prematurely, 3 due to adverse events, 1 due to progression and 1 on patient's request. In cohort 1 the maximum tolerated dose of sorafenib was 400mg per day. Only one patient could be treated with 800mg sorafenib daily. In cohort 2 and 3, all 12 patients completed the study. In the 2nd cohort the sorafenib dose could be escalated to 800mg in six of the 12 patients, to 600mg in four patients and to 200mg daily in two patients. In the 3rd cohort, one patient was escalated to 800mg, three to 600mg, six to 400mg and two remained on 200mg sorafenib daily. The median cumulative dose per patient was 44.5g in cohort 1, 77.4g in cohort 2 and 55.2g in cohort 3, which corresponds to 37%, 65% and 46% relative to the maximum pre-planned cumulative dose of 800mg.

Safety Results:

No on study death occurred. One SAE, pulmonary embolism, was reported and assessed as not related to

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study drug. All patients had mild anemia (grade 1-2). All but one patient had grade 3-4 neutropenia; 20 (83.3%) patients had grade 3-4 leucopenia; and 15 (62.5%) had grade 3-4 lymphocytopenia. No grade 3-4 thrombocytopenia was reported. No grade 3-4 biochemical toxicity was reported, except one patient with grade 3-4 ALAT. The frequency of these laboratory toxicities was similar in cohorts 1 and 2.

All patients experienced skin disorders, mostly hand and food syndrome (HFS) (17 patients, 71%) and skin rash (12 patients, 50%). In cohort 1, more patients in cohort 1 experienced HFS (n=11) and skin rash (n=8) than in cohort 2 (6 and 4 patients, respectively). Grade 3-4 toxicities of HFS (n=3), skin rash (2), and single cases of allergic reaction, erythema, and mucositis were reported in cohort 1; while there was no grade 3-4 non-hematological toxicities in cohort 2.

The main toxicities were neutropenia grade 3-4 in all patients and hand-foot syndrome any grade in 33/36 patients which was severe in 6 patients (table 3). Sensory neuropathy grade 1-2 was reported in 26 patients. Nausea and vomiting grade 1-2 were observed in 32 and 12 patients, respectively. One patient had severe nausea. No patient died while on treatment.Sorafenib EC-P weekly is feasible if the starting dose is 200mg and escalated every 3 weeks based on patients´ individual toxicities.

No unexpected adverse events were reported.

CONCLUSIONS:

- This is the first study evaluating sorafenib in a neoadjuvant setting in patients with primary breast cancer. At surgery 29% patients achieved a pCR.
- The individual dose escalation of sorafenib (200 – 800 mg daily) offers an excellent tool to reduce treatment discontinuation and skin related toxicities (mainly hand foot syndrome) and increases the maximum tolerable dose and the cumulative dose of sorafenib given.
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Date of the Report:

November 05, 2013

Investigational Center/Site

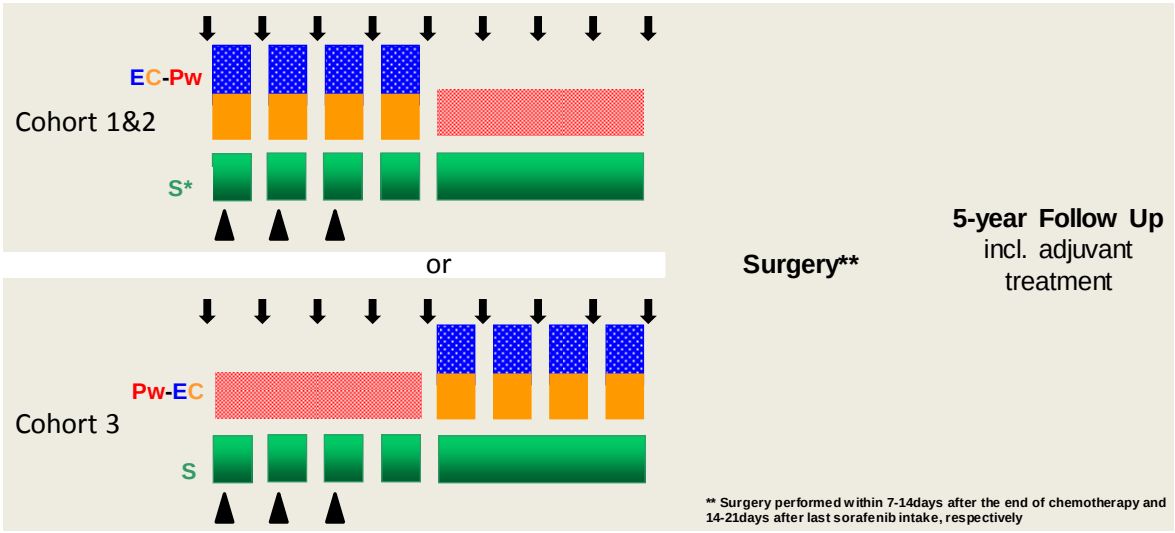
The study was conducted at 10 centers in Germany as follows:

- Rotkreuzklinikum München, Frauenklinik, Taxisstr. 3, 80637 München
- Klinikum Südstadt, Universitätsfrauenklinik, Südring 81, 18059 Rostock
- Klinikum der J. W. Goethe Universität, Zentrum der Frauenheilkunde und Geburtshilfe, Theodor-Stern-Kai 7, 60590 Frankfurt
- Universitätsklinikum, Frauenklinik, Prittwitzstrasse 43, 89075 Ulm
- Henriettenstiftung, Frauenklinik, Schwemannstr. 17 ,30559 Hannover
- Universitätsklinikum Schleswig-Holstein, Klinik für Gynäkologie und Geburtshilfe SGO Kiel, Arnold-Heller-Str. 3, aus 24,24105 Kiel
- Klinikum Offenbach, Klinik für Gynäkologie und Geburtshilfe, Starkenburgring 66, 63069 Offenbach a.M.
- Elisabeth Krankenhaus, Brustzentrum, Weinbergstrasse 7, 34117 Kassel
- Unifrauenklinik Köln, Studienzentrum Gynäkologie, Kerpener Strasse 62, 50924 Köln
- St. Gertrauden Krankenhaus, Brustzentrum, Paretzerstr. 12, 10713 Berlin

INVESTIGATIONAL PLAN

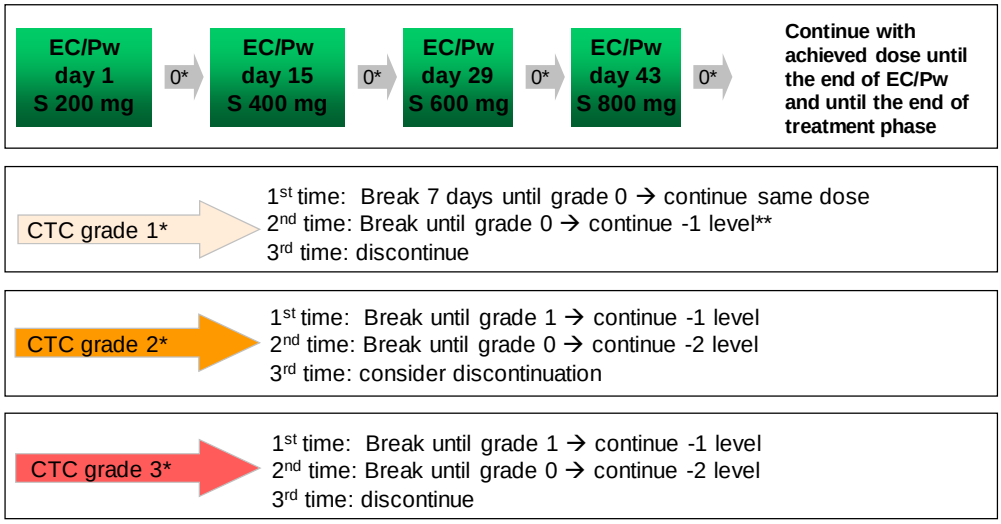
Overall Study Design and Plan Description

All patients received neoadjuvant EC (epirubicin 90mg/m² plus cyclophosphamide 600mg/m² body surface area) once every three weeks for four cycles followed or preceded by P (paclitaxel 80m/m²) every week for 12 weeks. In cohort one, patients received a fixed oral daily dose of 800mg sorafenib on day 2-19 during EC and continuously during paclitaxel. Sorafenib was stopped after 23 weeks of treatment. This would result in a cumulative dose of 119.2g sorafenib. After an amendment due to increased skin toxicities (any type) resulting in therapy discontinuations, patients in cohort two and three started with sorafenib 200mg daily and increased the dose during EC every cycle and during paclitaxel every 2 weeks if no skin toxicity occurred. In case of skin toxicity grade 1, the same dose was continued. The maximum achieved dose was maintained throughout treatment. In cohort three, patients started with paclitaxel followed by EC using the same dose escalating schedule for sorafenib. (Figure) All patients were then operated on and received adjuvant radiotherapy and endocrine treatment as standard of care if indicated.



Epirubicin: 90 mg/m² i.v.
Cyclophosphamide: 600 mg/m² i.v.
} EC cycle: once every 21days on day 1
Paclitaxel: 80 mg/m² i.v., weekly
*Sorafenib: 800mg orally (cohort 1)
*Sorafenib: Dose escalation 200-800mg during EC (cohort 2)
Sorafenib: Dose escalation 200-800mg during Pw (cohort 3)
Pharmacokinetic analyses EC/Pw cycle 1 and EC/Pw cycle 2 or 3
Sampling for translational research

Sorafenib dose escalation during EC (cohort 2) or Pw (cohort3)



* NCI-CTC Grade v.3.0 of any skin related adverse event ** Discontinue if level was 200 mg

Selection of Study Population

Inclusion Criteria

Patients had to meet all of the following criteria:

Written informed consent for all study procedures including an additional core biopsy after the first 4 cycles of EC had to be obtained and documented according to the local regulatory requirements;

Complete baseline documentation sent to GBG Forschungs GmbH;

Unilateral or bilateral primary carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration was not sufficient. Incisional biopsy was not allowed. In case of bilateral cancer the investigator had to decide prospectively the side to be evaluated for the primary endpoint;

Tumor lesion in the breast with a palpable size of ≥ 2 cm in maximum diameter. The lesion had to be measurable in two-dimensions preferably by sonography. In case of inflammatory disease the extent of inflammation was used as measurable lesion;

Patients needed to have stages of disease in which adjuvant chemotherapy was to be considered. In patients with multifocal or multicentric breast cancer, the largest lesion was measured;

Age ≥ 18 years;

Women of childbearing potential had to have a negative serum pregnancy test performed within 7 days prior start of therapy

Her-2 status negative

Karnofsky Performance status index ≥ 80%;

Normal cardiac function had to be confirmed by ECG and cardiac ultrasound (LVEF or shortening fraction) within 3 months prior to registration. Results had to be above the normal limit of the institution and above 55%;

Laboratory requirements: (within 14 days prior to registration)

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)

INR ≤ 1.5 ULN and PTT ≤ 1.5 ULN within 14 days prior to enrolment

ASAT or ALAT < 2.5 x ULN

Alkaline phosphatase ≤ 5 UNL. Patients with ASAT and/or ALAT > 1,5 x UNL associated with alkaline phosphatase > 2,5 x UNL were not eligible for the study

Total bilirubin < 1 X UNL

Creatinine ≤ 175 µmol/L (2 mg/dl), the calculated creatinine clearance ≥ 60 mL/min.

Paraffin tumor tissue block and each one serum and one plasma sample centrally made available

Complete staging work-up within 3 months prior to registration. All patients had to 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. In case of positive bone scan, bone X-ray was mandatory. Other tests were to be performed as clinically indicated;

Patients had to be available and compliant for treatment. Patients registered on this trial had to be treated and followed up at the participating or a cooperating center.

Exclusion Criteria

Patients had to be excluded for any one of the following reasons:

Patients with low or moderate risk, who were only doubtful candidates for adjuvant chemotherapy and did not fulfill the inclusion criteria.

Evidence of distant metastasis;

Prior chemotherapy for any malignancy;

Prior radiation therapy for breast cancer;

Preexisting rhagades at hand and feet and other skin problems (e.g. psoriasis)

Pregnant or lactating patients. Patients of childbearing potential had to implement adequate non-hormonal contraceptive measures (barrier methods, intra uterine contraceptive devices, sterilization) during study treatment;

Pre-existing motor or sensory neuropathy of a severity ≥ grade 2 by CTCAE criteria;

Concurrent treatment with:

Chronic corticosteroids unless initiated > 6 months prior to study entry and at low dose (≤ 20 mg methylprednisolone or equivalent);

Sex hormones. Prior treatment had to be stopped before study entry;

Patients with increased risk of bleeding due to concurrent therapeutic or prophylactic anticoagulative treatment. Low dose of coumarines were permitted.

Other experimental drugs or any other anti-cancer therapy;

Drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (e.g. Rifabutin, Rifampicin, Clarithromycin, Ketoconazole, Itroconazole, Ritinavir, Telithromycin, Erythromycin, Verapamil, Diltazem) within the last 5 days or the expected need for these treatments during study participation.

Other serious illness or medical condition:

Previous malignant disease without being disease-free of less than 5 years (except CIS of the Cervix and non-melanomatous skin cancer)

Known or suspected congestive heart failure (≥NYHA II) and/or coronary heart disease, angina pectoris requiring antianginal medication, previous history of myocardial infarction within past six months, evidence of transmural infarction on ECG, un- or poorly controlled arterial hypertension (systolic blood pressure >150 mm Hg or > 90 mmHg diastolic blood pressure under treatment with two antihypertensive drugs), rhythm abnormalities requiring permanent treatment, clinically significant valvular heart disease

Thrombotic or embolic events including transient ischemic attacks within the past six months

Hemorrhage/bleeding event ≥ Grade 3 within 4 weeks of first dose of study drug

Evidence or history of bleeding diathesis or coagulopathy

History of significant neurological or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent

Patients with seizure disorders requiring medication such as steroids or antiepileptics

Currently active infection

History of HIV infection or chronic hepatitis B or C

Serious non healing wound, ulcer or bone fracture

Patients with prior immunosuppressive treatment

Severe pulmonary condition/illness

Disease significantly affecting gastrointestinal function, e.g. malabsorption syndrome, resection of the stomach or small bowel, ulcerative colitis;

Patients with severe liver disease

Major surgery, open biopsy or significant traumatic injury within 4 weeks of first dose of study drug

Definite contraindications for the use of corticosteroids

Inadequate general condition (not fit for anthracycline/taxane-containing chemotherapy)

Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry

Known or suspected allergy to any agent given in association with this trial

Patients previously treated with sorafenib

Male patients

Removal of Patients from Therapy or Assessment

Patients had to be withdrawn from the study for the following reasons:

At the patients' own request without giving reasons.

Clinical progression under preoperative therapy.

Unacceptable toxicity of the study medication.

Pregnancy.

Significant protocol violation.

Evidence of an uncooperative attitude.

At the discretion of the investigator if this decision was in the medical interest of the patient (following consultation with the Principal Investigator).

Presence of significant concomitant diseases or complications that did not correlate with the treatment.

Withdrawal from the study and therapeutic measures was at the discretion of the investigator. A full explanation for the discontinuation from the study was made on the appropriate case report form. All adverse reactions, regardless of severity, were followed up by the investigator until satisfactory resolution; local authorities were informed by the corresponding pharmaceutical company according to local regulations.