1. Title page

Title:	A Multinational Double-Blind, Randomized Phase 2b Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo when Administered in Combination with Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer (Study 12740)
Test drug:	BAY 43-9006/sorafenib/Nexavar®
Indication:	Locally Advanced or Metastatic Breast Cancer
Sponsor's name and address:	SOLTI (Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos) Sant Llorenç, 23 - 1º 08202 Sabadell Spain
Study number:	SOLTI 0701
EudraCT number:	2007-00290-32
Phase:	IIb
Study dates:	07 Aug 2007 to 30 Jun 2010 (first patient's first visit to OS data cut-off date)
Investigator(s):	José Baselga, M.D. Chairman and Professor of Medicine Vall d'Hebron University Hospital Medical Oncology Service P Vall d'Hebron 119-129 Barcelona 08035
GCP compliance statement:	See Sections 5.2 and 9.6 of the report.
Date:	
Signatures:	*I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.*

Name Medical Expert	Date	**Name** Biostatistician	Date

Jose Baselga, M.D.	Date	**Name**	Date
Study Chair		Study Manager	

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2. Study synopsis

Title of the study:	A Multinational Double-Blind, Randomized Phase 2b Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo when Administered in Combination with Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer (Study 12740)
Study center(s):	There were 24 centers from 3 countries: Brazil (10 centers), France (4 centers), and Spain (10 centers)
Publications (references):	Not applicable to this report.
Period of study:	07 Aug 2007 to 30 Jun 2010 (first patient's first visit to OS data cutoff date)
Phase:	IIb
Objectives:	Primary objective: • To compare PFS in patients treated with sorafenib and capecitabine versus patients treated with placebo and capecitabine for locally advanced or metastatic breast cancer Secondary objectives: • To compare the objective response rate, duration of response, time to progression (TTP) and overall survival (OS) of patients treated with sorafenib and capecitabine versus placebo and capecitabine • To compare the safety and tolerability of patients treated with sorafenib and capecitabine versus placebo and capecitabine Exploratory objectives: • To compare change from baseline in Functional Assessment of Cancer Therapy–Breast Cancer (FACT-B), Version 4, score in patients treated with sorafenib and capecitabine versus patients treated with placebo and capecitabine • To validate the HF-QoL, and if validated, to compare the effect of sorafenib and capecitabine versus placebo and capecitabine using HF-QoL Amendment 3 treatment-continuation objectives: • To allow for patients receiving active treatment (sorafenib and/or capecitabine) to have the opportunity to continue to receive study treatment until disease progression occurs or the patient discontinues from the study for any reason. No data were collected and no specific analysis was performed using data from the treatment continuation period.

	Amendment 3 modified the protocol to allow patients who were receiving treatment with sorafenib and/or capecitabine at the time that the overall survival (OS) results were unblinded, and the sites and the patients were unblinded, to continue to receive study treatment until disease progression occurred or the patients discontinued from the study for any reason. This period of the study was referred to as the "treatment-continuation" period. Only SAE safety data was collected during this period, and no pre-specified analyses were performed.
Methodology (design of study):	This was a multinational double-blind, multicenter, randomized, Phase 2b study in 229 patients (≥18 years of age) with locally advanced or metastatic breast cancer who had failed prior therapy with taxanes and an anthracycline-containing regimen or for whom further anthracycline therapy was not indicated. The study consisted of a screening period, a treatment period, a follow-up period, and a treatment-continuation period.
Number of patients:	A total of 273 patients were screened: 44 patients failed screening and 229 patients were enrolled and randomized (114 to placebo and 115 to sorafenib). Five (5) patients did not receive study treatment: 2 patients randomized to the placebo group and 3 patients randomized to the sorafenib group. Thus, 224 patients began double-blind treatment (112 in each treatment group). The population valid for intent-to-treat (ITT) analyses comprises the 229 randomized patients (114 in the placebo + capecitabine group and 115 in the sorafenib + capecitabine group). The population valid for the safety analyses comprises the 224 treated patients (112 patients in each of the groups, placebo + capecitabine and sorafenib + capecitabine). Of the 229 patients in the ITT population, 228 patients (99.6%) were women, and 196 patients (85.6%) were Caucasian. Mean age at enrollment was 55.2 years (range 29 to 80 years). The treatment groups appeared well balanced with regard to the demographic characteristics.
Diagnosis and main criteria for inclusion:	1. Histologically or cytologically confirmed adenocarcinoma of the breast. 2. Measurable or evaluable locally advanced or metastatic disease. (Locally advanced disease must not have been amenable to resection with curative intent.) All scans used to document measurable or evaluable disease must have been done within 4 weeks prior to randomization. 3. Age ≥18 years. 4. Patients who failed taxane* or an anthracycline-containing

chemotherapy regimen or for whom anthracycline therapy is not indicated.

* Patients who had failed taxane and an anthracycline-containing chemotherapy regimen, OR had received an alternative therapy when anthracycline therapy was not indicated. A memo was provided to the sites in December 2007 (at the time point when 10 patients had been enrolled in the study) with the intent of clarifying this Inclusion Criterion (#4); all patients met the Inclusion Criterion.

5. No more than one prior chemotherapy for locally advanced or metastatic breast cancer.
6. Patients must have discontinued previous chemotherapy at least 3 weeks prior to randomization.
7. Prior hormonal therapy for locally advanced or metastatic disease was allowed.
8. Prior radiation therapy was allowed but must have been completed at least 3 weeks prior to randomization. Previously radiated area(s) must not have been the only site of disease.
9. ECOG Performance Status of 0 or 1 (See Appendix A).
10. Adequate bone marrow, liver, and renal function as assessed by the following:
    - Hemoglobin ≥9.0 g/dl
    - Absolute neutrophil count (ANC) ≥1,500/mm^3
    - Platelet count ≥100,000/mm^3
    - Total bilirubin ≤2.0 times the upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN (≤5 x ULN for patients with liver involvement)
    - International Normalized Ratio for Prothrombin Time (PT-INR) ≤1.5 and activated partial thromboplastin time (aPTT) within normal limits
    - Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin could be allowed to participate. For patients on warfarin, the INR was to be measured prior to initiation of sorafenib/placebo and monitored at least weekly, or as defined by the local standard of care, until INR was stable.
    - Creatinine ≤2.0 times the ULN
11. Women of childbearing potential must have had a negative serum pregnancy test performed within 7 days prior to randomization and must have agreed to use adequate contraception prior to randomization and for the duration of study participation.

	12. Patients must have been able and willing to sign a written informed consent. A signed informed consent must have been appropriately obtained prior to any study specific procedures. 13. Patients must have been able to swallow and retain oral medication. 14. Patients must have been willing and able to fill out patient-reported outcome questionnaires. In the event that the patient was unable to hold a pen or pencil, an accompanying family member/friend or a nurse coordinator may have filled in the questionnaire with the answers that the patient provided to him or her.
Test product, dose, and mode of administration, batch number:	Sorafenib 400 mg (2 x 200 mg tablets) or matching placebo (2 tablets), administered orally, twice daily (approximately every 12 hours); 1 hour before a meal or 2 hours after a meal, continuous administration. Sorafenib 200 mg tablets were manufactured by Bayer HealthCare AG. Batch numbers are presented in Section 16.1.6.
Duration of treatment:	Patients received study treatment until disease progression was documented, extraordinary medical circumstances occurred, intolerable toxicities occurred, or voluntary withdrawal of study treatment.
Reference therapy, dose, and mode of administration, batch number:	Placebo tablets matching the sorafenib 200 mg orally, 2 tablets twice daily. Placebo tablets matching sorafenib were manufactured by Bayer HealthCare AG. Batch numbers are presented in Section 16.1.6. A total of 229 patients were randomly assigned (1:1 ratio) to receive either: 1. Sorafenib, 400 mg (2 tablets) BID continuous administration and capecitabine, 1,000 mg/m^2 orally, twice daily for 14 days, followed by a 7-day rest period (without capecitabine) or 2. Placebo, 2 tablets BID continuous administration and capecitabine, 1,000 mg/m^2 orally, twice daily for 14 days, followed by a 7-day rest period (without capecitabine) Capecitabine 1,000 mg/m^2 was administered orally, twice daily, within 30 minutes after a meal, for 14 days followed by a 7 day rest period (without capecitabine). All patients received capecitabine, which is commercially available and was obtained for the study.

Criteria of evaluation:	Efficacy: Efficacy was evaluated based on PFS, TTP, OS, objective response rate and duration of response. • PFS was measured from the date of randomization to the date of first observed disease progression (radiological or clinical, whichever was earlier) or the date of death due to any cause (if before progression). • TTP was calculated as the time (days) from date of randomization to date of first observed disease progression (radiological or clinical, whichever was earlier). • Survival (OS) was measured from the date of randomization to death due to any cause. • Duration of response (DOR) was measured from the first documentation of complete or partial response (whichever status was recorded first) until the first date that recurrent or progressive disease or death was objectively documented, taking as reference the smallest measurements recorded since treatment started. Safety: During the treatment period, safety assessments included evaluations of adverse events, laboratory parameters, and vital signs (pulse, body temperature, and blood pressure were measured). All reported adverse events were coded using MedDRA dictionary. The adverse event grade of selected laboratory parameters was determined using the NCI-CTCAE, Version 3.0. Amendment 3 Treatment-Continuation Period: During the treatment-continuation period, safety assessments were conducted per the treating physician's standard practice. Routine Adverse Events were no longer collected. SAEs were reported to Onyx Drug Safety using paper forms.
Statistical methods:	All primary statistical summaries of the baseline and efficacy data and primary analyses of the efficacy data for the study were conducted using the intent-to-treat (ITT) population. The ITT population was defined as all patients who were randomized to study treatment. The per-protocol population for PFS was defined as the patients in the ITT population who did not have any major protocol deviations. The per-protocol population for OS was defined as the patients who received at least one dose of study drug (safety population) and did not have any major protocol deviations. All primary statistical summaries and primary analyses of the safety data were conducted using the safety population, defined as all patients who were randomized and receive any study treatment. Descriptive statistics, including 95% confidence intervals, were

	used to summarize study endpoints. P-values were calculated for descriptive purpose only. The primary analysis of all time-to-event endpoints (PFS, TTP, OS and duration of response) was a Cox regression with treatment group and the actual value of the randomization stratification factor as the covariates in the model using the ITT population. The relative risk for sorafenib to placebo was estimated by the hazard ratio of the Cox regression with 95% confidence interval. The distribution of each time to-event endpoint was estimated by the Kaplan-Meier method for each treatment group. Median times were estimated from the Kaplan-Meier estimates with 95% confidence intervals. The primary analysis of categorical endpoints (best overall response) was a Pearson Chi-square test.
Summary and conclusions:	
Summary of efficacy: The treatment groups differed significantly in favor of sorafenib + capecitabine (*P*=0.006) in terms of the primary efficacy variable of PFS based on the ITT population. The median PFS was 126 days (95% CI, 93, 168) for the placebo + capecitabine group and 194 days (95% CI, 161, 237) for the sorafenib + capecitabine group and the hazard ratio (HR) was 0.576 (95% CI, 0.410, 0.809), representing a significant (42.4%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. The treatment groups also differed significantly in terms of the analysis of PFS based on the per protocol population (*P*=0.005). With regard to the subgroup analysis of PFS, the HRs showed a consistent trend favoring the sorafenib + capecitabine group, with the strongest trends occurring in the subgroup analyses of patients that had no prior chemotherapy for metastatic setting (*P*=0.0022; HR 0.498), patients with visceral disease (*P*=0.0008, HR 0.532), and hormone receptor status of ER+ or PgR+ (*P*=0.0071; HR 0.615). In the exploratory subgroup analyses of PFS, the HRs showed a consistent trend favoring the sorafenib + capecitabine group, with the strongest trends occurring in the exploratory subgroups of age ≥ 40 years (*P*=0.0007; HR 0.569), patients with measurable disease (*P*=0.0007; HR 0.558), and patients with negative progesterone receptors (*P*=0.0015; HR 0.490). Prior use of anthracycline appeared to favor the sorafenib + capecitabine group (*P*=0.0013; HR 0.594), but no prior use of anthracycline also appeared favorable (*P*=0.0403; HR 0.263). The post-hoc exploratory analysis of PFS in patients who received taxane and anthracycline prior to the study also appeared to favor the sorafenib + capecitabine group (*P*=0.0075). The sensitivity analyses of PFS consistently showed a trend favoring the sorafenib + capecitabine group, including the analysis of PFS by primary analysis (*P*=0.0006; HR 0.576 [95% CI, 0.410, 0.809]), analysis of PFS by un-stratified analysis (*P*=0.0004; HR 0.573), analysis of PFS with new anticancer therapy or surgery (NPT)	

considered as a PFS event (*P*=0.0005; HR 0.599), and analysis of PFS with NPT neither considered as a PFS event nor used to censor PFS (*P*=0.0015; HR 0.614).

The two treatment groups differed significantly in favor of sorafenib + capecitabine (*P*=0.0005) in terms of the secondary efficacy variable of time to progression (TTP) based on the ITT population.

The analysis of overall response rate showed a trend in favor of sorafenib + capecitabine (38.3% [95% CI, 29.4%, 47.8%], *P*=0.1229), but less of a trend was seen in the analysis of objective response rate (25.2% [95% CI, 17.6%, 34.2%], *P*=0.2914). The analysis of best response showed CR in 1 (0.9%) placebo + capecitabine patient and 2 (1.7%) sorafenib + capecitabine patients, and PR in 34 (29.8%) placebo + capecitabine patients and 42 (36.5%) sorafenib + capecitabine patients.

A slight trend in favor of sorafenib + capecitabine was seen in the analysis of duration of response rate, with a median duration of response of 124 days for the placebo + capecitabine group, and 188 days for the sorafenib + capecitabine group (*P*=0.0477; HR 0.846 [(95% CI, 0.635, 1.127]). For patients with measurable disease, the median duration of response was the same: 124 days for the placebo + capecitabine group, and 188 days for the sorafenib + capecitabine group (*P*=0.0336; HR 0.799 [95% CI, 0.579, 1.102]).

A slight trend in favor of sorafenib + capecitabine was seen in the analysis of duration of objective response rate with a median duration of objective response of 127 days for the placebo + capecitabine group, and 232 days for the sorafenib + capecitabine group (*P*=0.0533; HR 0.877 [95% CI, 0.665, 1.158]). For patients with measurable disease, the median duration of objective response was 127 days for the placebo + capecitabine group, and 232 days for the sorafenib + capecitabine group (*P*=0.0417; HR 0.843 [95% CI, 0.619, 1.147]).

Analysis of ECOG performance status at the end of study treatment showed an improvement (-1 point) for slightly more patients in the placebo + capecitabine group (7 [6.1%]) versus the sorafenib + capecitabine group (4 [3.5%]). A 1-point increase (deterioration) from baseline in ECOG performance status was noted for slightly more patients in the placebo + capecitabine group (26 [22.8%]) versus the sorafenib + capecitabine group (21 [18.3%]). A 2-point increase from baseline ECOG PS was noted for similar numbers of patients in the placebo + capecitabine group (4 [3.5%]) and the in the sorafenib + capecitabine group (5 [4.3%]). A 3-point increase from baseline ECOG PS was noted for fewer patients (1 [0.9%]) in the placebo + capecitabine group versus the sorafenib + capecitabine group (6 [5.3%]).

The two treatment groups did not differ significantly in terms of OS based on the ITT population (*P*=0.2075) or for the per protocol population (*P*=0.3029).

A slight reduction in hazard for OS for the sorafenib + capecitabine group, with no significant difference between the treatment groups, was apparent in the OS subgroup analyses of hormone receptor status, visceral disease, region (regional location of the patient), and prior use of taxane and anthracycline. However, a trend in favor of sorafenib + capecitabine was observed in the subgroup analysis of patients that received no prior chemotherapy in metastatic setting (P=0.0567; HR 0.666), versus patients that

received prior chemotherapy in metastatic setting (P=0.3868; HR 1.076).

This slight reduction in hazard for OS for the sorafenib + capecitabine group, with no significant difference between the treatment groups, also extended the exploratory analyses of age, prior use of taxane, estrogen receptors, progesterone receptors, and months from adjuvant treatment to recurrence or metastatic diagnosis. Conversely, a slight trend in favor of sorafenib + capecitabine was observed in the exploratory analyses of country (country location of the patient), prior use of anthracycline, measurable disease, and number of metastatic sites, as follows: A trend was observed for patients in France (*P*=0.0770; HR 0.543), versus patients in Brazil (*P*=0.4227; HR 0.953) versus patients in Spain (*P*=0.3984; HR 0.916). A trend was observed for no prior use of anthracycline (*P*=0.0613; HR 0.301) versus prior use of anthracycline (P=0.3359; HR 0.924). A slight trend was observed for patients with measurable disease (*P*=0.1139; HR 0.789) versus patients with no measurable disease (*P*=0.2654; HR 1.319). A trend was observed for number of metastatic sites ≥ 3 (*P*=0.0381; HR 0.596) versus number of metastatic sites < 3 (P=0.4399; HR 0.966).

Summary of safety:

Exposure to study drug was slightly lower for sorafenib/placebo than for capecitabine between the 2 treatment groups:

For the PFS data set, the median duration of treatment for sorafenib/placebo was 18 weeks for the placebo + capecitabine group versus 22 weeks for the sorafenib + capecitabine group; the median duration of treatment for capecitabine was 6 cycles for the placebo + capecitabine group versus 7 cycles for the sorafenib + capecitabine group.

For the OS data set, the median duration of treatment for sorafenib/placebo was 19 weeks for the placebo + capecitabine group versus 26 weeks for the sorafenib + capecitabine group; the median duration of treatment for capecitabine was 6 cycles for the placebo + capecitabine group versus 9 cycles for the sorafenib + capecitabine group.

The percentage of patients with dose reductions and dose interruptions was lower in the placebo + capecitabine group versus the sorafenib + capecitabine group. Most of the dose reductions and interruptions in both treatment groups were due to AEs.

For the PFS Data set: Dose reductions of placebo were noted for 11.4% of placebo + capecitabine patients and of sorafenib for 47.8% of sorafenib + capecitabine patients. Dose reductions of capecitabine were noted for 31.6% of placebo + capecitabine patients and for 78.3% of sorafenib + capecitabine patients. Dose interruptions of placebo were noted for 41.2% of placebo + capecitabine patients and of sorafenib for 73.9% of sorafenib + capecitabine patients. Dose interruptions of capecitabine were noted for 40.4% placebo + capecitabine patients and for 75.7% sorafenib + capecitabine patients.

For the OS Data set: Dose reductions of placebo were noted for 14.0% of placebo + capecitabine patients and dose reductions of sorafenib for 53.0% of sorafenib + capecitabine patients. Dose reductions of capecitabine were noted for 33.3% of

placebo + capecitabine patients and for 78.3% of sorafenib + capecitabine patients. Dose interruptions of placebo were noted for 42.1% of placebo + capecitabine patients and of sorafenib for 74.8% of sorafenib + capecitabine patients. Dose interruptions of capecitabine were noted for 41.2% of placebo + capecitabine patients and for 76.5% of sorafenib + capecitabine patients

The AE profile was relatively similar between the treatment groups in this study. AEs were reported as follows for the PFS and OS data sets:

For the PFS Data set: A total of 106 (94.6%) patients in the placebo + capecitabine group and 111 (99.1%) patients in the sorafenib + capecitabine group reported 1 or more AEs. Drug-related AEs were reported for 97 (86.6%) placebo + capecitabine patients and 108 (96.4%) sorafenib + capecitabine patients.

For the OS Data set: A total of 109 (97.3%) patients in the placebo + capecitabine group and 112 (100%) patients in the sorafenib + capecitabine group reported 1 or more AEs. Drug-related AEs were reported for 100 (89.3%) placebo + capecitabine patients and 109 (97.3%) sorafenib + capecitabine patients.

Grade 3 or higher AEs occurred in fewer patients in the placebo + capecitabine group versus the sorafenib + capecitabine group.

Grade 3 drug-related AEs occurred in fewer patients in the placebo + capecitabine group versus the sorafenib + capecitabine group in both data sets. For the PFS data set, grade 3 drug-related AEs were reported by 25 (22.3%) placebo + capecitabine patients and 62 (55.4%) sorafenib + capecitabine patients. For the OS set, grade 3 drug-related AEs were reported by 28 (25.0%) placebo + capecitabine patients versus 63 (56.3%) sorafenib + capecitabine patients.

Grade 4 drug-related AEs occurred in the same number of patients (1 [0.9%]) in both treatment groups and in both data sets.

Grade 5 drug-related AEs were reported by 2 (1.8%) placebo + capecitabine patient and 0 (0%) sorafenib + capecitabine patients in the PFS and OS data sets.

AEs leading to discontinuation of any study treatment occurred in a fewer patients in the placebo + capecitabine group versus the sorafenib + capecitabine group in both data sets. For the PFS data set, 9 (8.0%) patients in the placebo + capecitabine group and 15 (13.4%) patients in the sorafenib + capecitabine group reported AEs leading to discontinuation of any study treatment. For the OS data set, 11 (9.8%) patients in the placebo + capecitabine group and 22 (19.6%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of any study treatment.

The SAE profile was also relatively similar between the treatment groups in this study. For the PFS data set, SAEs were reported by 30 (26.8%) patients in the placebo + capecitabine group and 36 (32.1%) patients in the sorafenib + capecitabine group, and for the OS data set, SAEs were reported by 31 (27.7 %) patients in the placebo + capecitabine group and 40 (35.7%) patients in the sorafenib + capecitabine group.

Drug-related SAEs occurred in fewer patients in the placebo + capecitabine group (11 patients [9.8%]) versus the sorafenib + capecitabine group (20 patients [17.9%]).

There were no apparent differences between the treatment groups in terms of the total number of subjects who died, the number of deaths within 30 days of the end of treatment, and the cause of death.

Death of 1 patient in the placebo + capecitabine group was considered related to treatment: patient 16-320-1010 died 3 days after the termination of placebo + capecitabine due to a cardiac arrest (CTC Grade 5). Death of 1 patient in the placebo + capecitabine group was considered a "toxicity due to study treatment with at least one AE with the outcome of death": patient 24-300-1011 died approximately 2 months after the termination of placebo + capecitabine due to septic shock, and had experienced Grade 4 thrombocytopenia that was considered related to study treatment on two separate occasions, both within 30 days of discontinuation of study treatment.

The AEs of special interest include neutrophils/granulocytes, leukocytes, platelets, hemoglobin, febrile neutropenia, sensory neuropathy, fatigue, diarrhea, nausea, mucositis, thrombus/embolism, hemorrhage/bleeding, hypertension, hand-foot skin reaction, rash/desquamation, dermatology-other, and pruritus, all of which may be associated with sorafenib use.

The AEs which occurred with notably higher frequency in the sorafenib + capecitabine group included the AEs palmar-plantar erythrodysaesthesia syndrome, also frequently called hand foot skin reaction (89.3% versus 62.5% in placebo), alopecia (28.6% versus 4.5% in placebo), rash (22.3% versus 8.0% in placebo), diarrhoea (52.7% versus 29.5% in placebo), vomiting (20.5% versus 16.1 % in placebo), constipation (22.3% versus 8.0% in placebo), neutropenia (10.7% versus 3.6% in placebo), and anaemia (8.0% versus 5.4% in placebo).

Grade 3 palmar-plantar erythrodysaesthesia syndrome (Also known as hand foot skin reaction [HFSR]) was reported by 13.4% of placebo + capcitabine patients and 46.4% of sorafinib + capecitabine patients. No HFSR events were Grade 4 or 5. Grade 3 neutropenia was reported by 1.8% of placebo + capecitabine patients and 3.6% of sorafenib + capecitabine patients, and Grade 4 neutropenia was reported by 0.9% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients (OS data set). Grade 3 anaemia was reported by 0.9% of placebo + capecitabine patients and 1.8% of sorafenib + capecitabine patients, and Grade 4 anaemia was not reported in any patient (OS data set).

The incidence of thrombocytopenia was low overall, and a higher incidence of thrombocytopenia occurred in the placebo + capecitabine group than in the sorafenib + capecitabine group (5.4% versus 2.7%, respectively, OS data set). Grade 3 thrombocytopenia was reported by 2.7% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients, and Grade 4 thrombocytopenia was reported by 0.9% of placebo + capecitabine patients and 0% sorafenib + capecitabine patients (OS data set).

Infections occurred with similar frequency in the placebo + capecitabine group (26.8%) and the sorafenib + capecitabine group (25.9%) (OS data set). Fatigue occurred in 12.5% of placebo + capecitabine patients and in 15.2% of sorafenib + capecitabine patients. Grade 3 fatigue was reported by 0.9% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients (OS data set). Nausea was experienced with similar frequency the placebo + capecitabine group (32.1%) and the sorafenib + capecitabine group (28.6%) (OS

data set).

Hypertension was noted as an AE in 11.6% of placebo + capecitabine patients and in 17.9% of sorafenib + capecitabine patients (OS data set). Hypertension was noted as Grade 3 in 1.8% of placebo + capecitabine patients and in 0.9% of sorafenib + capecitabine patients, and was noted as an SAE in 0.9% of placebo + capecitabine patients and in 0% of sorafenib + capecitabine patients.

There were no laboratory tests for which the treatment groups differed by more than 3% regarding the incidence of Grade 3, 4 toxicity.

Most AEs were tolerable and manageable, and did not result in increased hospitalization.

Summary of pharmacokinetics:

- Capecitabine and 5-FU plasma concentrations were observed to be higher at 1 hour and 4 hours postdose when capecitabine was co-administered with sorafenib as compared to placebo.
- At 8 hours postdose, there were measurable concentrations of capecitabine for the majority of patients in the sorafenib treated group, however, plasma concentrations were mostly below the limit of quantitation for the placebo group. This is indicative of a sustained exposure to the drug in the sorafenib treated group.
- Plasma 5-FU concentrations were not quantifiable in either treatment group at 8 hours postdose.
- The increase in plasma capecitabine and 5-FU concentrations at the 1 and 4 hours postdose observed in this Phase 2b study are consistent with results observed in previous studies (REFMAL-122 and Bayer-10955).

Conclusions:

The efficacy and safety data presented in this report support the further evaluation sorafenib given in combination with capecitabine to treat locally advanced or metastatic breast carcinoma in patients previously treated with a taxane and anthracycline or for whom an anthracycline was not indicated. A significant improvement in the PFS was demonstrated for patients treated with the combination of sorafenib and capecitabine compared to those treated with capecitabine alone. This finding was further corroborated by most of the planned and exploratory subgroup analyses, the per protocol analysis and sensitivity analyses. The improvement in TTP was statistically significant, but the increases in the overall response rate and the objective response rate were slight and not statistically significant. The combined administration of sorafenib and capecitabine in this trial was tolerable with clinically manageable toxicities despite the overlapping toxicity profile of the sorafenib and capecitabine. The incidence of AEs leading to drug discontinuation was less than 15% in each of the arms. Thus the safety and efficacy of the sorafinib plus capecitabine combination appears to provide an improvement in the treatment for these breast cancer patients.

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AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
BID	*bis in die* (twice daily)
BUN	blood urea nitrogen
BSA	body surface area
cm	centimeters
Cmax	maximum concentration
CNS	central nervous system
CR	complete response (by modified RECIST criteria)
CRF	case report form
CROs	Contract research organizations
CSR	Clinical study report
CT Scan	computed tomography scan
CTC	Common terminology criteria
CTCAE	Common terminology criteria for adverse events
dl	deciliter
DLT	dose limiting toxicity
DMC	Data monitoring committee
DOR	duration of overall response
ECG	electrocardiogram
ECOG	Eastern cooperative oncology group
ECOG-PS	Eastern cooperative oncology group - performance status
EDC	electronic data capture
EMEA	European Medicines Agency
ER	Estrogen receptor
FACT-B	Functional assessment of cancer therapy - Breast cancer
FACT-B QoL	Functional assessment of cancer therapy - Breast cancer quality of life questionnaire
FDA	Food and drug administration
FISH	fluorescence *in situ* hybridization
g	gram
GCP	Good clinical practice
G-CSF	granulocyte colony-stimulating factor
g/mole	grams per mole (where 1 mole equals Avogadro's Number which is: 6.22 x 10^23)

HCG	human chorionic gonadotropin
HER-2	human epidermal growth factor receptor 2
HF-QoL	Hand-foot reaction and quality of life questionnaire
HFSR	hand-foot skin reaction
HGB	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
HR-QoL	Health Related Quality of Life
IB	Investigator Brochure
ICH	International conference on harmonisation
IEC	Independent ethics committee
INR	International Normalized Ratio
IRB	Institutional review board
ITT	intent to treat
LD	longest diameter (of lesions measurements)
m	meter
m^2	meter squared
mg	milligram
mg/m^2	milligram per meter squared
mm	millimeter
MedDRA	Medical dictionary for regulatory activities
MRI	magnetic resonance image
NCI	National cancer institute
NCI-CTCAE	National cancer institute common terminology criteria for adverse events
NPT	new anticancer therapy or surgery
NYHA	New York health association
OS	overall survival
ORR	overall response rate
PE	physical exam
PD	progressive disease (by modified RECIST criteria)
PDGFR-β	platelet-derived growth factor receptor-beta
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PO	*per os* (orally)
PR	partial response (by modified RECIST criteria)
PRO	patient reported outcome
PT	prothrombin time
PT-INR	International normalized ratio for prothrombin time
PTT	prolonged partial thromboplastin time
QD	once per day
QOD	every other day
QoL	Quality of Life
RBC	red blood cells

RCC	renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RPIC	randomization and product inventory control system
SAE	serious adverse event
SAP	statistical analysis plan
SOE	strength of evidence
SD	stable disease (by modified RECIST crieria)
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SOE	Strength of Evidence
SOLTI	Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos
TTP	time to progression
µl	Microliter
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptors
VEGFR-1	vascular endothelial growth factor receptor-1
VEGFR-2	vascular endothelial growth factor receptor-2
VEGFR-3	vascular endothelial growth factor receptor-3
WBC	white blood cells
WHO-DD	World health organization drug dictionary
5-FU	5-Fluorouracil

Study period definitions

Screening period	The "screening period" was the period of time before study entry, while screening procedures were ongoing. Study entry was defined as the time of randomization and Cycle 1, Study Day 1.
Double-blind treatment period	The "double-blind treatment period" began with the first dose of study treatment, and continued until the patient withdrew from treatment for any reason.
Follow-up period	Patients entered the "follow-up period" upon documentation of disease progression, extraordinary medical circumstances, intolerable toxicities, or voluntary withdrawal of study treatment. The follow-up period consisted of periodic assessments (approximately every 4 months +/-2 week) for survival until the planned number of overall survival (OS) events was reached.
Treatment continuation period (Amendment 3)	Patients could continue to receive study treatment in the "treatment-continuation" period (until disease progression occurred or a patient discontinued by patient or physician request) if they were receiving treatment with sorafenib and/or capecitabine at the time that the OS results were unblinded, and the sites and the patients were unblinded.

5. Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol and the first two amendments were reviewed by the appropriate Independent Ethics Committees (IECs) for all sites. The third amendment was reviewed by the appropriate IECs for the 5 sites with active patients in Brazil (see Appendix 16.1.3 for details).

Each investigator was required to submit a copy of the protocol to an IEC or to an Institutional Review Board (IRB) for the institution before the study start. On the approval/advice sheet, the trial (title, protocol number, and version), the documents studied (protocol, informed consent material, advertisement when applicable), and the date of the review were clearly stated. Approval documents for all participating centers were forwarded to the Sponsor, in accordance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) guidelines and local laws and regulations. Drug supplies were not released and the trial was not started until notification of this written approval/advice was received by the Sponsor. Where necessary, extensions, amendments, or renewals of IEC/IRB approval were obtained and also forwarded to the Sponsor. The IEC/IRB was required, upon request, to supply the Sponsor with a list of committee members involved in the vote and a statement to confirm that the committee operates in accordance with GCP guidelines and applicable laws and regulations. A list of all IECs and IRBs consulted is provided in Appendix 16.1.3.

5.2 Ethical conduct of the study

All clinical work conducted in this study was subject to rules of Good Clinical Practice (GCP). These practices include the following areas: IRB/IEC procedures, informed consent, protocol adherence, administrative documents, drug supply accountability, data collection, patient records (source documents), adverse event (AE) recording and reporting, inspection and audit preparation, and records retention. They were based on current guidelines of the ICH for GCP, SOLTI's (Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos) Standard Operating Procedures, the Declaration of Helsinki, and on all applicable laws and regulations. The investigators were made aware that government regulatory agencies and SOLTI representatives could inspect the documents and patient records at any time.

5.3 Patient information and consent

Before any study procedure (including screening) was performed and before a patient was enrolled in the study, an investigator or a staff member explained the investigational nature and the purpose of the study to the patient. The explanation was sufficiently detailed to allow the patient to make an informed decision about participating in the study. If the patient understood the requirements of the study and agreed to participate, he/she signed the informed consent form.

The sites were responsible for writing the patient informed consent forms and for obtaining IRB/IEC approval. Monitors confirmed that the site's IRB/IEC approved the informed consent form and that each patient signed it before any study procedure was started or study drug was dispensed. A sample informed consent form is provided in Appendix 16.1.3.

6. Investigators and study administrative structure

This multinational study was conducted at 24 centers, 23 centers screened patients, and 23 centers enrolled and randomized at least 1 patient in 3 countries: Spain, France and Brazil. A complete list of investigators and study sites is presented in Section 16.1.

The Study Sponsor was SOLTI (Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos), Sant Llorenç, 23 - 1º, 08202 Sabadell, Spain. Key personnel (SOLTI and Onyx) are listed in Table 1 and Table 2.

Various Contract Research Organizations (CROs) were used during this study.

The Coordinating Investigator was: José Baselga, M.D., Chairman and Professor of Medicine, Vall d'Hebron University Hospital, Medical Oncology Service, P Vall d'Hebron 119-129, Barcelona 08035. Key CRO personnel are listed in Table 3.

Table 1: Key SOLTI Personnel

Role	Name	Address
Project Manager	Isabel Esono	SOLTI, Sant Llorenç, 23-planta baixa 08202 Sabadell
Clinical Operations Manager	Elena Serra	SOLTI, Sant Llorenç, 23-planta baixa 08202 Sabadell
Clinical Leader, Oncology	Dr Josefa Morales	SOLTI, Sant Llorenç, 23-planta baixa 08202 Sabadell

Table 2: Key Onyx Research Organization Personnel

Role	Name	Institution or Company Address
Study Manager	Margaret O Donoghue	Onyx European Contractor
	Harinder Chera	Onyx Pharmaceuticals, Inc.
Medical Expert	Shell Li, MD	Onyx Pharmaceuticals, Inc
Statistician	Sunhee Ro, Ph.D.	Onyx Pharmaceuticals, Inc
Data Manager	Regina Norelli	Onyx Pharmaceuticals, Inc

Table 3: Key Contract Research Organization Personnel

Role	Name	Institution or Company Address
Project Managers	Christelle Grall Ladan Duvillieu Gilles Pierrefiche Hind Abdelouahab Sandra Martins	Nuvisan-Oncology (formerly AAI Oncology), 18-20, rue Pasteur, 94278 Le Kremlin-Bicêtre Cedex. France
Clinical Operations Director	Denise de la Reza Renata Berardocco	IBPC/Oncopartners, Rua Cincinato Braga 37 conj 81/82, 01333-011 - São Paulo - SP - Brasil
EDC and IVRS Provider	MedNet Solutions, LLC	Minnetonka, MN

No biomarkers or biopsy samples were collected.

An outside bioanalytical laboratory provided pharmacokinetic (PK) sample collection, processing, storage and shipping instructions. The analytical assay was a validated method.

Patients used their local laboratories for clinical laboratory tests.

A Data Monitoring Committee (DMC) was instituted for this study to ensure its ongoing safety. The committee included 3 members, including an independent statistician and 2 oncologists. A safety review meeting was held after the 20th patient completed Cycle 2 of study treatment (see Appendix 16.1.9.2). The study was not paused for this initial safety review. In addition, the DMC met on a regular basis every 3-4 months to review the cumulative safety data from the study. The DMC operated independently of the Sponsor and participating Investigators.

7. Introduction

This multinational double-blind, randomized Phase 2b study was designed to evaluate the efficacy and safety of sorafenib compared to placebo and capecitabine in patients with locally advanced or metastatic breast cancer. The primary objective of the study was to compare progression-free survival (PFS) in patients treated with sorafenib and capecitabine, versus patients treated with placebo and capecitabine, for measurable or evaluable locally advanced or metastatic breast cancer (that was not amenable to resection with curative intent). Patients included in the study had failed taxane and an anthracycline-containing chemotherapy regimen, or had received an alternative therapy when anthracycline therapy was not indicated. Patients had received no more than one prior chemotherapy for locally advanced or metastatic breast cancer. Prior hormonal therapy was allowed. Prior radiation therapy was allowed, but was required to be discontinued 3 weeks prior to randomization. The protocol was sponsored by SOLTI and was not a company-sponsored trial.

The incidence of breast cancer is overwhelming, with more than 1,000,000 new cases and approximately 373,000 deaths each year [Guarneri 2004]. Locally advanced or metastatic breast cancer is a significant medical problem. While less than 5% of breast cancer patients have metastases at the time of initial diagnosis, approximately 25–40% of develop distant metastases during the course of their disease. In 1999, approximately 45,000 women died of metastatic breast cancer, and this statistic has not changed appreciably in decades [Olin 2000]. Median survival of metastatic breast cancer patients ranges from 2 to 4 years; the life expectancy is more prolonged for patients with limited metastatic disease (e.g., lymph nodes, skin, isolated lung metastases) or bone disease only, while patients with multiple visceral lesions or central nervous system (CNS) metastases have a median survival ranging from 4 to 13 months [Guarneri 2004].

The vast majority of women with metastatic breast cancer will not be cured, and therefore, aims of treatment must be tailored to individual patients' needs: from survival prolongation to symptomatic control and maintenance of quality of life [Guarneri 2004, Olin 2000]. There are a number of treatment options for patients with advanced/metastatic disease, although a single standard of care does not exist. For patients with hormone responsive disease without visceral metastases, endocrine manipulation is the treatment of choice. Patients with steroid receptor–negative tumors, disease that is resistant to hormonal therapy and visceral disease, are optimal candidates for chemotherapy [Guarneri 2004]. Sequential, single-agent chemotherapy has been shown to provide comparable survival to combination chemotherapy with generally less toxicity [Gralow 2005] and is considered an effective palliative approach. First-line single-agent chemotherapeutics include the taxanes, capecitabine, gemcitabine, anthracyclines, and vinorelbine. A better understanding of the molecular pathways involved in breast cancer pathogenesis has spurred the development and use of novel agents. The most recent advance in the treatment of metastatic breast cancer has come from the use of agents targeted to inhibit angiogenic pathways.

Sorafenib is an oral multi-kinase inhibitor that targets kinases known to be involved in tumor cell proliferation and tumor angiogenesis. These kinases include RAF kinase, vascular endothelial growth factor receptor-1 (VEGFR-1), vascular endothelial growth factor receptor-

2 (VEGFR-2), vascular endothelial growth factor receptor-3 (VEGFR-3), platelet-derived growth factor receptor-beta (PDGFR-β), c-KIT, and Flt-3.

Angiogenesis plays a critical role in the development, transformation, and metastasis of breast cancer. Preclinical experiments suggest that angiogenesis precedes transformation of mammary hyperplasia to malignancy. Tumor cells transfected with angiogenic stimulatory peptides have shown increased growth, invasiveness, and metastasis; whereas, tumor cells transfected with inhibitors of angiogenesis have exhibited decreased growth and metastasis [Schneider 2005]. Development of a malignant solid tumor requires the up-regulation of growth factors that induce angiogenesis for development of the tumor blood supply. This is known as the "angiogenic switch" and occurs very early in tumorigenesis [Hanahan 1996]. In human breast cancer, including some carcinoma in situ lesions, the up-regulation of vascular endothelial growth factor (VEGF) and increase in microvessel density occurs at an early stage [Brown 1995, Guidi 1994]. The up-regulation of VEGF is not correlated with estrogen receptor status, lymph node metastasis, or tumor size [Relf 1997]. Recently, clinical evidence has emerged supporting the role of angiogenesis in the pathogenesis of advanced/metastatic breast cancer. In a large National Cancer Institute (NCI) Cooperative Group trial (E2100) led by Kathy Miller and colleagues, bevacizumab in combination with weekly paclitaxel nearly doubled median PFS compared to paclitaxel alone (11 versus 6 months) in women who had not previously received chemotherapy for locally recurrent or metastatic breast cancer [Miller(1) 2005]. A previous Phase 3 trial of bevacizumab in combination with capecitabine doubled response rates, but failed to prolong PFS compared to capecitabine alone in women with advanced/metastatic breast cancer who received 1-2 prior therapies. The authors of the study hypothesized that patients in the capecitabine trial may have had disease too advanced for inhibition of a single factor or pathway to produce a sustained clinical benefit [Miller(2) 2005]. The capecitabine trial suggests that the optimal time to intervene with an antiangiogenic agent may be earlier in the course of disease. Interpreting trials of antiangiogenic agents may require a paradigm shift. Unlike cytotoxic agents that are aimed at tumor kill and shrinkage, anti-angiogenics appear to stabilize disease processes, potentially diminishing the usefulness of response rates as a surrogate measure of clinical benefit [Schneider 2005].

Once daily oral dosing of sorafenib demonstrated broad-spectrum anti-tumor activity in colon, breast, and non-small-cell lung cancer xenograft models. In these models, significant inhibition of neovascularization was also shown [Wilhelm 2004]. Preclinical in vivo experiments have demonstrated that sorafenib can be safely combined with a variety of cytotoxic drugs including paclitaxel, irinotecan, gemcitabine, 5-fluorouracil and cisplatin with no significant increase in toxicity. Combining agents with different mechanisms of action is known to enhance anti-cancer activity. In vitro studies show that sorafenib causes redistribution of cells into S and M phases of the cell cycle, which may make them more sensitive to the activity of chemotherapy agents that target these cell cycle phases. Preclinical (in vitro) experiments indicate that the combination of sorafenib with a variety of chemotherapeutic agents including paclitaxel, cisplatin, gemcitabine, and 5-fluorouracil results in additive cytotoxic activity [Sorafenib Investigator Brochure 2005].

Given the modest effects of single-agent anti-angiogenics on improving PFS in patients with metastatic breast cancer, more definitive efficacy investigations have focused on the

combination of chemotherapy with these novel agents. A large trial was conducted by the Eastern Cooperative Oncology Group (ECOG) evaluating the combination of weekly paclitaxel combined with bevacizumab compared to paclitaxel alone. The trial enrolled 715 patients with locally recurrent or metastatic breast cancer. The combination significantly prolonged PFS compared to chemotherapy alone (11 months versus 6 months; $p < 0.0001$). There was no significant difference in overall survival (OS) at the last reported analysis [Miller(3) 2005].

8. Study objectives

Primary objective

The primary objective of the study was to compare Progression Free Survival (PFS) in patients treated with sorafenib and capecitabine versus patients treated with placebo and capecitabine for locally advanced or metastatic breast cancer.

Secondary objectives

- To compare the overall response rate (ORR), duration of response, time to progression (TTP), and Overall Survival (OS) of patients treated with sorafenib and capecitabine versus placebo and capecitabine.
- To compare the safety and tolerability of patients treated with sorafenib and capecitabine versus placebo and capecitabine.

Exploratory objectives

- To compare change from baseline in Functional Assessment of Cancer Therapy–Breast Cancer (FACT-B), Version 4 (See Protocol Appendix C) score in patients treated with sorafenib and capecitabine versus patients treated with placebo and capecitabine.
- To validate the HF-QoL (See Protocol Appendix D), and if validated, to compare the effect of sorafenib and capecitabine versus placebo and capecitabine using HF-QoL.

Amendment 3 treatment-continuation objective

- To allow for patients receiving active treatment (sorafenib and/or capecitabine) to have the opportunity to continue to receive study treatment until disease progression occurs or the patient discontinues from the study for any reason. No data will be collected and no specific analyses were performed using data from the treatment continuation period.

Amendment 3 modified the protocol to allow patients who were receiving treatment with sorafenib and/or capecitabine at the time that the OS results were unblinded, and the sites and the patients were unblinded, to continue to receive the study treatment to which they were originally randomized until disease progression occurred or the patients discontinued from the study for any reason. This period of the study was referred to as the "treatment-continuation" period. Safety assessments were conducted per the treating physician's standard practice. Only serious adverse event (SAE) safety data was collected during this period, and no analyses were planned for this dataset.

9. Investigational plan

The original protocol, Version 1.0 dated 14 Feb 2007, was amended three times. Amendment 1 (Version 2.0, 20 Jul 2007) and Amendment 2 (Version 3.0, 18 Apr 2008) were implemented at all 23 sites. Amendment 3 (Version 4.0, 15 Jul 2010), which encompassed the treatment-continuation period, was implemented at the 6 sites in Brazil with 7 active patients at the time of the Amendment. The changes implemented by the three amendments are incorporated into the appropriate sections of this study report to provide a comprehensive description of the study and its procedures. Changes are referenced by the applicable amendment only if they were implemented after patients were enrolled.

An overview of the amendments is presented in Section 9.8. The original protocol and all of its amendments are included in Section 16.1.

9.1 Overall study design and plan

This study was a multinational, multicenter, double-blind, randomized, placebo-controlled, Phase 2b study evaluating the efficacy and safety of sorafenib when administered in combination with capecitabine in patients (≥ 18 years of age) with locally advanced or metastatic breast cancer who failed prior therapy with taxanes and an anthracycline-containing regimen, or for whom anthracycline therapy was not indicated.

A total of 229 patients were randomized in a double-blinded fashion using 1:1 allocation via a web-based randomization and product inventory control system (RPIC) provided by a third-party vendor. Site of metastatic disease was used as a stratification factor and was classified as either visceral or nonvisceral. Visceral sites are the soft internal organs of the body, including lungs, heart, and the organs of the digestive, excretory, and reproductive systems.

Patients were randomized into 1 of the 2 treatment groups, either:

Group A:

- Capecitabine: 1000 mg/m^2 orally, BID for 14 days, followed by a 7-day rest period (without capecitabine)
- Sorafenib: 400 mg (2 tablets) BID continuous administration

Group B:

- Capecitabine: 1000 mg/m^2 orally, BID for 14 days, followed by a 7-day rest period (without capecitabine)
- Placebo: 2 tablets BID continuous administration

The study consisted of four periods: a screening period, a treatment period, a follow-up period, and a treatment-continuation period. See Table 11 for the Study Evaluation Flowchart.

Sorafenib and placebo were identical in appearance.

Treatment cycles were 21 days. Patients could receive cycles of capecitabine/sorafenib combination or capecitabine/placebo combination until disease progression was documented, intolerable toxicities, or voluntary withdrawal of study treatment. If the patient discontinued

treatment for any reason (except death or lost to follow-up), an End-of-Treatment assessment was performed.

Disease assessment was conducted every 6 weeks (+/- 7 days) for the first 24 weeks and every 9 weeks thereafter. Assessment of disease included clinical disease assessment (for palpable or visual lesions), contrast computed tomography scans (CT scans) or magnetic resonance images (MRIs) of the chest, abdomen, and pelvis. Patients with bone lesions identified by bone scan at baseline were further evaluated by the investigator's radiographic method of choice (i.e., CT, MRI, and/or x-ray,) provided the same radiographic method used at baseline to fully evaluate the tumor status per modified RECIST criteria (Response evaluation criteria in solid tumors) could be repeated at all subsequent tumor assessment time points. Patients with known treated brain metastases at baseline had repeated CT or MRI scans performed at the same time points as disease assessment. All other non-measurable lesions (including small lesions, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions, leptomengial disease and abdominal masses) were followed by the same method of assessment (clinical examination, CT, MRI or chest X-ray) and the same technique used to characterize each lesion at baseline and during follow-up.

Per Protocol Amendment 1 effective as of July 2007, patients completed the HF-QoL within 2 weeks of randomization and every 3 weeks for the first 24 weeks, and every 9 weeks thereafter, provided the patient had no disease progression and remained active in the trial, and again at the end-of study or withdrawal.

The treatment period began with the first dose of study combination treatment, and continued until the patient withdrew from treatment. Patients received study treatment until disease progression was documented, extraordinary medical circumstances occurred, intolerable toxicities occurred, or voluntary withdrawal of study treatment. All patients entered the follow-up period with the exception of patients who withdrew consent to participate in the study.

Amendment 3 modified the protocol to allow patients who were receiving treatment with sorafenib and/or capecitabine at the time that the OS results were unblinded, and the sites and the patients were unblinded, to continue to receive the study treatment to which they were originally randomized, until disease progression occurred or the patients discontinued from the study for any reason. This period of the study was referred to as the "treatment-continuation" phase. Assessments of survival were not performed during the treatment-continuation period, safety assessments were conducted per the treating physician's standard practice. Only SAE safety data was collected during this phase, and no pre-specified analyses were performed. SAEs were reported to Onyx Drug Safety using paper forms. At the time of discontinuation of the treatment-continuation period, patients did not enter a follow-up period, and study medication was no longer provided.

A DMC was instituted for this study to ensure its ongoing safety. The committee included an odd number of members, at least 3, including an independent statistician and oncologist. A safety review meeting was held as per separate DMC charter (see Section 16.1). The DMC performed an initial review of the safety data from this study after 20 patients had completed 2 cycles of their assigned treatment regimen. In addition, the DMC met on a regular basis every 3-4 months to review the cumulative safety data from the study.

No interim analysis of efficacy (PFS) was planned for this study. The final analysis for PFS was to be performed when approximately 120 PFS events occurred. The final analysis for OS was performed when approximately 120 deaths occurred.

9.2 Study design, including the choice of control groups

When this protocol was instituted, a database of monitored patients receiving sorafenib had been established. More than 9,000 patients had received sorafenib to date. Chronic administration is well tolerated. The recommended sorafenib dose for Phase 2 studies was 400 mg BID.

Two Phase 2 single-arm studies of sorafenib in patients with metastatic breast cancer have been completed. Both studies evaluated the safety and activity of sorafenib as monotherapy. As with other single agent anti-angiogenics, single-agent sorafenib has shown modest activity in patients with metastatic breast cancer. In both trials, the drug was shown to be generally well tolerated.

In one Phase 2 trial, 17 patients who had an ECOG performance status (ECOG-PS) 0–2, received at least one prior chemotherapy regimen for metastatic breast cancer, and failed at least one adjuvant hormonal therapy (if estrogen receptor [ER]/progesterone receptor positive) were enrolled. Sorafenib was administered orally, 400 mg BID, continuously. In total, 54 patients were enrolled. Patients had received between 1 and 11 prior chemotherapy regimens and 69% had received ≥3 prior chemotherapy regimens for metastatic breast cancer. Twenty-four percent of the patients had stable disease or better at 4 months. Grade 3 AEs included rash/desquamation (6% of patients), fatigue (4%), hand-foot skin reaction (4%), nausea (2%), other pain (2%), gastritis (2%) and vomiting (2%). No Grade 4 AEs occurred.

In a second Phase 2 study, 18 patients who had an ECOG-PS 0-1, were candidates for first or second line chemotherapy for metastatic disease and had received prior anthracycline and/or taxane therapy in the neoadjuvant, adjuvant, or metastatic setting were enrolled. Unlimited prior hormonal therapy was allowed. Sorafenib was administered orally, 400 mg BID, continuously. In total, 23 patients were enrolled. Sixty-five percent of patients had visceral metastases and 44% had received prior chemotherapy for metastatic disease. Six percent of patients were alive and progression free at 6 months. Grade 3 AEs included acne (9% of patients), hand/foot skin reaction (4%), neutropenia (4%) cough (4%), wound infection (4%), and prolonged partial thromboplastin time (PTT) (4%). No Grade 4 AEs occurred.

Given the modest effects of single-agent anti-angiogenics on improving PFS in patients with metastatic breast cancer, more definitive efficacy investigations have focused on the combination of chemotherapy with these novel agents. A large trial was conducted by ECOG evaluating the combination of weekly paclitaxel combined with bevacizumab compared to paclitaxel alone. The trial enrolled 715 patients with locally recurrent or metastatic breast cancer. The combination significantly prolonged PFS compared to chemotherapy alone (11 months versus 6 months; $p < 0001$). There was no significant difference in OS at the last reported analysis [Miller(4) 2005].

Multiple Phase 2 trials have been reported showing that capecitabine, as a single agent, is an effective and safe treatment for patients with metastatic breast cancer. Most trials of capecitabine have involved patients previously treated with an anthracycline and/or a taxane for advanced disease; in a review of capecitabine monotherapy trials, median time-to-progression was 5 months (range: 3 to 12 months) and OS was 12 months (range: 10 to 15 months) in pretreated patients [Erschler 2006]. In a randomized Phase 2 trial of single-agent capecitabine versus paclitaxel, time to progression and OS were comparable [Talbot 2002]. A randomized Phase 2 trial of capecitabine versus cyclophosphamide, methotrexate, and 5-Fluorouracil (5-FU) confirmed that capecitabine is also an effective first-line therapy for patients with metastatic breast cancer [O'Shaughnessy, 2001]. The most commonly studied capecitabine regimen in Phase 2 trials was 1,250 mg/m^2 BID for 14 days followed by a 7-day rest period. Dose reductions were frequent; the dose was reduced by 25% in one-quarter to one-half of the patients in several studies.

The safety and efficacy of the combination of sorafenib with capecitabine have been tested in a single Phase 1 dose escalation trial of 35 patients with unresectable and/or metastatic solid tumors (Awada, 2006). Four cohorts were tested: sorafenib 200 mg BID with capecitabine 2,100 mg/m^2; sorafenib 400 mg BID with capecitabine 2,100 mg/m^2; sorafenib 200 mg BID for the first 2 cycles, then 400 mg BID thereafter with capecitabine 2,100 mg/m$^{2;}$ and sorafenib 400 mg BID with capecitabine 1,700 mg/m^2. In this trial, the median duration on sorafenib was 147 days (range 2-925) and 131 days (range 9-903) for capecitabine. The most frequently reported drug-related toxicities (all grades) over all cycles were hand-foot skin reactions (HFSR, 89%), diarrhea (71%), and fatigue (69%). The maximum-tolerated dose was not reached in any of the cohorts; and therefore, a Phase 2 dose recommendation could not be made from this study. Dose limiting toxicities were recorded in each of the 4 cohorts. In Cohort 1, two of the 13 patients treated experienced Grade 3 HFSR. In Cohort 2, one of the 4 patients treated had HFSR. In Cohort 3, one case of Grade 3 HFSR was recorded out of the 6 patients treated. In Cohort 4, two DLTs were recorded in the 12 patients treated, both due to HFSR. In the study, drug-drug interactions were minimal. The PK of sorafenib (200 and 400 mg BID) was not affected to a clinically relevant degree by capecitabine, and sorafenib caused only a moderate increase (30-40%) in capecitabine exposure. One heavily pretreated patient with breast cancer and skin lymphangitis (Cohort 1) and 2 patients in Cohort 4 (RCC, n=1; urothelial cancer, n=1) had tumor shrinkage.

Based on these findings, the regimen selected for the experimental arm of the present Phase 2b trial was sorafenib 400 mg oral (PO) BID with capecitabine 2,000 mg/m^2 PO daily in two divided doses (1,000 mg/m^2 BID); this dose accounted for the increase in capecitabine exposure observed in the Phase 1 trial described above by reducing the dose of capecitabine by 25% from the labeled dose. The schedule also fell within the range of doses found to be tolerable in the same trial [Awada 2006] and was consistent with doses commonly delivered in other trials of capecitabine [Ershler 2006] and in clinical practice. In order to account for the possibility that higher doses of capecitabine may have been tolerable in this combination and to insure that patients received the maximum tolerated dose of capecitabine, dose escalation was allowed for patients who experienced less than Grade 2 AEs in Cycle 1. Additionally, an interim analysis of safety was performed after the 20th patient finished his/her second cycle of therapy. Protocol amendments were made to address any significant findings from the safety interim analysis.

The present study is one of several randomized Phase 2b "screening studies". The purpose of these trials is to screen out ineffective therapies and to screen in therapies that might be effective and warrant further investigation. This means that in a Phase 2b screening trial, a lower threshold for an observed treatment effect is accepted in order to support continued investigation. Three considerations apply when designing a Phase 2b screening trial:

- Design Phase 3 study first
- Goals for Phase 2b study follow from Phase 3
  - Large enough to support proof of concept
  - Small enough to be practical as a Phase 2b study
- Primary endpoint for Phase 2b is identical to Phase 3

In determining the number of events in a Phase 2b trial, one-quarter of the events in the Phase 3 is assumed. The number of events in a Phase 3 trial is estimated by identifying the minimal difference in the treatment arms that would represent a meaningful clinical outcome or advance and determining the strength of evidence (SOE) desired. Screening trials identify outcomes that are certainly ineffective, certainly effective, and somewhere in the middle. Decisions to progress from Phase 2b to Phase 3 were based on interpretation of the results from this individual trial, as well as from other screening trials [Fleming 2004].

A randomized, double-blind design is a standard and rigorous method of comparing therapeutic regimens. Patients were randomly selected from the same study population to receive sorafenib and capecitabine, or placebo and capecitabine. A placebo-controlled trial is ethical for patients with locally advanced or metastatic breast cancer and the characteristics described in the inclusion/exclusion criteria (Section 9.3). Treatment options currently available for patients who continue to have measurable disease after prior systemic therapy are limited and are associated with potentially severe or fatal side effects. This study included periodic monitoring of safety and efficacy data to allow for early stopping in the event of intolerable toxicities. All patients received best supportive care while participating in this study.

9.3 Selection of study population

The study population was comprised of patients with histologically or cytologically confirmed adenocarcinoma of the breast, for whom treatment with capecitabine was considered medically acceptable. Patients had measurable or evaluable locally advanced or metastatic disease (locally advanced disease could not be amenable to resection with curative intent) and had failed taxane and an anthracycline-containing chemotherapy regimen, or had received an alternative therapy when anthracycline therapy was not indicated. Patients had received no more than one prior chemotherapy for locally advanced or metastatic breast cancer, and were required to have discontinued chemotherapy at least 3 weeks prior to randomization.

9.3.1 Inclusion criteria

1. Histologically or cytologically confirmed adenocarcinoma of the breast.
2. Measurable or evaluable locally advanced or metastatic disease. (Locally advanced disease must not be amenable to resection with curative intent.) All scans used to

document measurable or evaluable disease must have been done within 4 weeks prior to randomization.

3. Age ≥18 years.
4. Patients who had failed taxane* and an anthracycline-containing chemotherapy regimen or for whom anthracycline therapy was not indicated.

   *Patients who had failed taxane and an anthracycline-containing chemotherapy regimen, OR had received an alternative therapy when anthracycline therapy was not indicated. A memo was provided to the sites in December 2007 (at the time point when 10 patients had been enrolled in the study) with the intent of clarifying this Inclusion Criterion (#4); all patients met the Inclusion Criterion.

5. No more than one prior chemotherapy for locally advanced or metastatic breast cancer.
6. Patients must have discontinued previous chemotherapy at least 3 weeks prior to randomization.
7. Prior hormonal therapy for locally advanced or metastatic disease was allowed.
8. Prior radiation therapy was allowed but must have been completed at least 3 weeks prior to randomization. Previously radiated area(s) must not have been the only site of disease.
9. ECOG-PS of 0 or 1.
10. Adequate bone marrow, liver, and renal function as assessed by the following:
    - Hemoglobin (HGB) ≥9.0 g/dl
    - Absolute neutrophil count (ANC) ≥1,500/mm^3
    - Platelet count ≥100,000/mm^3
    - Total bilirubin ≤2.0 times the upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST ≤ 2.5 x ULN; ≤ 5 x ULN for patients with liver involvement)
    - International Normalized Ratio for Prothrombin Time (PT-INR) ≤1.5 and activated partial thromboplastin time (aPTT) within normal limits
    - Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin may be allowed to participate. For patients on warfarin, the International Normalized Ratio (INR) was to be measured prior to initiation of sorafenib/placebo and monitored at least weekly, or as defined by the local standard of care, until INR was stable.
    - Creatinine ≤ 2.0 times the ULN
11. Women of childbearing potential must have had a negative serum pregnancy test performed within 7 days prior to randomization and must have agreed to use adequate contraception prior to randomization and for the duration of study participation.
12. Patients must have been able and willing to sign a written informed consent. A signed informed consent must have been appropriately obtained prior to any study specific procedures.

13. Patients must have been able to swallow and retain oral medication.
14. Patients must have been willing and able to fill out patient-reported outcome questionnaires. In the event that the patient was unable to hold a pen or pencil, an accompanying family member/friend or a nurse coordinator may have filled in the questionnaire with the answers that the patient provided to him or her.

Table 4: Changes to Inclusion Criteria by Protocol Amendment

	Original Protocol[a, b] 14 February 2007	Amendment 1 20 July 2007	Amendment 2[c] 18 April 2008
1	Histologically or cytologically confirmed adenocarcinoma of the breast.	No change	No change
2	Measurable or evaluable locally advanced or metastatic disease. (Locally advanced disease must not be amenable to resection with curative intent.) All scans used to document measurable or evaluable disease must be done within 4 weeks prior to randomization.	No change	No change
3	Age ≥18 years.	No change	No change
4	Failed taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.	No change	No change
5	No more than one prior chemotherapy for locally advanced or metastatic breast cancer.	No change	No change
6	Patients must have discontinued chemotherapy at least 3 weeks prior to randomization.	No change	No change
7	Prior hormonal therapy for locally advanced or metastatic disease is allowed but must be discontinued at least 3 weeks prior to randomization.	No change	Prior hormonal therapy for locally advanced or metastatic disease is allowed.
8	Prior radiation therapy is allowed but must be completed at least 3 weeks prior to randomization. Previously radiated area(s) must not be the only site of disease.	No change	No change
9	ECOG Performance Status of 0 or 1 (See Protocol Appendix A).	No change	No Change
10	Adequate bone marrow, liver, and renal function as assessed by the following: • Hemoglobin ≥9.0 g/dl • Absolute neutrophil count (ANC) ≥1,500/mm^3 • Platelet count ≥100,000/mm3 • Total bilirubin ≤1.5 x the upper limit of normal (ULN) • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN (≤5 x ULN for patients with liver involvement) • International Normalized Ratio for Prothrombin Time (PT-INR) ≤1.5 and activated partial thromboplastin time (aPTT) within normal limits. • Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin may be allowed to participate. For patients on warfarin, the INR should be measured prior to initiation of sorafenib/placebo and monitored at least weekly, or as defined by the local standard of care, until INR is stable. • Creatinine ≤1.5 x ULN.	No change	Changes as follows: Total bilirubin **≤2.0** times the upper limit of normal (ULN) Creatinine **≤2.0** times the ULN

	Original Protocol[a, b] 14 February 2007	Amendment 1 20 July 2007	Amendment 2[c] 18 April 2008
11	Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to randomization, and must agree to use adequate contraception (barrier method of birth control) prior to randomization and for the duration of study participation.	No Change	No change
12	Patients must be able and willing to sign a written informed consent. A signed informed consent must be appropriately obtained prior to any study specific procedures.	No Change	No change
13	Patients must be able to swallow and retain oral medication.	No Change	No change
14		New criterion: Patients must be willing and able to fill out patient-reported outcome questionnaires. In the event that the patient is unable to hold a pen or pencil, an accompanying family member/friend or a nurse coordinator may fill in the questionnaire with the answers that the patient provides to him or her.	No change

a. Item numbers do not correlate with the item numbers listed in each protocol.

b. A summary of the major changes in each protocol amendment and the rationale for the changes is presented in Section 9.8.1.

c. Amendment 3 is not included, because no changes were made to inclusion criteria in Amendment 3.

9.3.2 Exclusion criteria

1. Patients with breast cancer over-expressing human epidermal growth factor receptor 2 (HER-2) (gene amplification by fluorescence *in situ* hybridization (FISH) or 3+ over-expression by immunohistochemistry). Patients with unknown HER-2 status are not eligible.
2. Patients with active brain metastases. Patients with neurological symptoms must undergo a contrast CT scan or MRI of the brain to exclude active brain metastasis. Patients with treated brain metastases are eligible provided they have no evidence of brain disease and are off definitive therapy (including steroids) at least 3 months prior to randomization.
3. Patients who received prior capecitabine therapy.
4. Major surgery, open biopsy, or significant traumatic injury within 4 weeks of randomization.
5. Evidence or history of bleeding diathesis or coagulopathy.
6. Serious, non-healing wound, ulcer, or bone fracture.
7. Substance abuse, or medical, psychological, or social condition that may interfere with the patient's participation in the study or evaluation of the study results.
8. Use of cytochrome P450 enzyme-inducing anti-epileptic drugs (such as phenytoin, carbamazepine, or phenobarbital) is not allowed.

9. Cardiac disease:
    - Congestive heart failure > class II New York Health Association (NYHA), or
    - Unstable angina (anginal symptoms at rest), or new-onset angina (begun within the last 3 months), or myocardial infarction within the 6 months prior to randomization, or
    - Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.
10. Uncontrolled hypertension (systolic blood pressure >150 mm Hg or diastolic pressure >90 mm Hg) despite optimal medical management.
11. Thrombolic, embolic, venous, or arterial events, such as a cerebrovascular accident including transient ischemic attacks, within the past 6 months.
12. Pulmonary hemorrhage/bleeding event > Grade 2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) within 4 weeks of randomization.
13. Any other hemorrhage/bleeding event ≥ Grade 3 NCI-CTCAE within 4 weeks of randomization.
14. Active clinically serious infection > Grade 2 NCI-CTCAE.
15. Known human immunodeficiency virus (HIV) infection or chronic hepatitis B or C.
16. Previous or concurrent cancer that is distinct in primary site or histology from breast cancer within 5 years prior to randomization EXCEPT cervical cancer in situ, treated basal cell carcinoma, superficial bladder tumors [Ta and Tis].
17. Known or suspected allergy to sorafenib, or hypersensitivity to capecitabine or to any of the excipients or fluorouracil.
18. History of severe and unexpected reactions to fluoropyrimidine therapy or patients with known dihydropyrimidine dehydrogenase deficiency.
19. Prior or concurrent treatment with sorivudine or its chemically related analogues, such as brivudine.
20. Concurrent or use of St. John's Wort or rifampin (rifampicin) within 1 week of randomization.
21. Prior treatment with bevacizumab or any other drugs (licensed or investigational) that target VEGF or VEGF receptors (VEGFR).
22. Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than capecitabine and sorafenib/placebo. This includes agents such as Dasatinib, Sunitinib, pazopanib, motesanib, SU-14813, AZD2171, Zactima (DZ6474), ABT-869, and XL647.
23. Women who are pregnant or breast feeding.
24. Use of any investigational drug within 30 days or 5 half-lives, whichever is longer, preceding randomization.

Table 2: Changes to the Exclusion Criteria by Protocol Amendment

	Original Protocol[a, b, c] 14 February 2007	Amendment 1 20 July 2007	Amendment 2 [c] 18 April 2008
1	Patients with breast cancer over-expressing human epidermal growth factor receptor 2 (HER-2) (gene amplification by fluorescence *in situ* hybridization (FISH) or 3+ over-expression by immunohistochemistry). Patients with unknown HER-2 status are not eligible.	No change	No change
2	Patients with active brain metastases. Patients with neurological symptoms must undergo a contrast computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to exclude active brain metastasis. Patients with treated brain metastases are eligible provided they have no evidence of brain disease and are off definitive therapy (including steroids) within 3 months prior to randomization.	No change	No change
		New exclusion: Patients who received prior capecitabine therapy.	No change
3	Major surgery, open biopsy, or significant traumatic injury within 4 weeks of randomization.	No Change	No change
4	Evidence or history of bleeding diathesis or coagulopathy.	No Change	No change
5	Serious, non-healing wound, ulcer, or bone fracture.	No change	No change
6	Substance abuse, or medical, psychological, or social condition that may interfere with the patient's participation in the study or evaluation of the study results.	No change	No change
7	Use of cytochrome P450 enzyme-inducing anti-epileptic drugs (such as phenytoin, carbamazepine, or phenobarbital) is not allowed.	No change	No change
8	Cardiac disease: • Congestive heart failure >class II New York Health Association (NYHA) (see Appendix D), or • Unstable angina (anginal symptoms at rest), or new-onset angina (began within the last 3 months), or myocardial infarction within the 6 months prior to randomization, or • Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.	No change	No change
9	Uncontrolled hypertension (systolic blood pressure >150 mm Hg or diastolic pressure >90 mm Hg) despite optimal medical management.	No change	No change
10	Thrombolic, embolic, venous, or arterial events, such as a cerebrovascular accident including transient ischemic attacks, within the past 6 months.	No change	No change

	Original Protocol[a, b, c] 14 February 2007	Amendment 1 20 July 2007	Amendment 2 [c] 18 April 2008
11	Pulmonary hemorrhage/bleeding event >National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 within 4 weeks of randomization.	Pulmonary hemorrhage/bleeding event > **Grade 2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)** within 4 weeks of randomization.	No change
12	Any other hemorrhage/bleeding event ≥ NCI-CTCAE Grade 3 within 4 weeks of randomization.	Any other hemorrhage/bleeding event ≥ **Grade 3 NCI-CTCAE** within 4 weeks of randomization.	No change
13	Active clinically serious infection >NCI-CTCAE Grade 2.	Active clinically serious infection > **Grade 2 NCI-CTCAE**.	No change
14	Known human immunodeficiency virus (HIV) infection or chronic hepatitis B or C.	No change	No change
15	Previous or concurrent cancer that is distinct in primary site or histology from breast cancer EXCEPT cervical cancer in-situ, treated basal cell carcinoma, superficial bladder tumors [Ta and Tis], or any cancer curatively treated >5 years prior to randomization.	No change	Previous or concurrent cancer that is distinct in primary site or histology from breast cancer **within 5 years prior to randomization** EXCEPT cervical cancer in situ, treated basal cell carcinoma, superficial bladder tumors [Ta and Tis]
16	Known or suspected allergy to sorafenib, or hypersensitivity to capecitabine or to any of the excipients or fluorouracil.	No change	No change
17	History of severe and unexpected reactions to fluoropyrimidine therapy or patients with known dihydropyrimidine dehydrogenase deficiency.	No change	No change
18	Prior or concurrent treatment with sorivudine or its chemically related analogues, such as brivudine.	No change	No change
19	Concurrent or use of St. John's Wort or rifampin (rifampicin) within 3 weeks of randomization.	No change	Concurrent or use of St. John's Wort or rifampin (rifampicin) within **1** week of randomization.
20	Prior treatment with bevacizumab or any other drugs (licensed or investigational) that target vascular endothelial growth factor (VEGF) or VEGF receptors (VEGFR).	No change	No change
21	Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than capecitabine and sorafenib/placebo.	No change	Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than capecitabine and

	Original Protocol[a, b, c] 14 February 2007	Amendment 1 20 July 2007	Amendment 2 [c] 18 April 2008
			sorafenib/placebo. **This includes agents such as Dasatinib, Sunitinib, pazopanib, motesanib, SU-14813, AZD2171, Zactima (DZ6474), ABT-869, and XL647.**
22	Women who are pregnant or breast feeding.	No change	No change
23	Use of any investigational drug within 30 days or 5 half-lives, whichever is longer, preceding randomization.	No change	No change

a. Item numbers do not correlate with the item numbers listed in each protocol.

b. A summary of the major changes in each protocol amendment and the rationale for the changes is presented in Section 9.8.1.

c. Amendment 3 is not included, because no changes were made to exclusion criteria in Amendment 3.

9.3.3 Removal of patients from therapy or assessment

Patients were to receive study treatment (capecitabine + sorafenib or placebo) unless the following occurred:

- Documented disease progression
- Extraordinary medical circumstances: If at any time the constraints of the protocol were detrimental to the patient's health, study treatment was to be discontinued.
- Intolerable toxicities
- Voluntary withdrawal of study treatment

Patients were to enter the follow-up period upon documentation of disease progression, extraordinary medical circumstances, intolerable toxicities, or voluntary withdrawal of study treatment. Every reasonable effort was taken to encourage patients to continue to be followed for evidence of disease progression even after study treatment discontinuation for reasons other than progressive disease (PD). All patients were followed for survival until the planned number of events for survival (120) was reached; with the exception of patients who withdrew consent to participate in the study. Assessment of survival was performed approximately every 4 months (+/- 2 weeks) .

Patients were to be discontinued from the treatment-continuation period of the study at the time of disease progression or at patient or physician request. The investigators were responsible for performing final assessments, as they deemed appropriate, per standard practice. Onyx Drug Safety was to be notified of the discontinuation of each study patient, using the forms provided to each site.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time were classified as having symptomatic deterioration and were categorized as PD.

For capecitabine, non-hematologic Grade 3 and 4 AEs other than hand-foot skin reaction, diarrhea and fatigue: capecitabine therapy was to be held until ≤ Grade 1. At the start of the next cycle, the dose of capecitabine was to be reduced one dose level for all subsequent cycles. If Grade 3 or 4 toxicity persisted for > 3 weeks, the patient was to discontinue capecitabine treatment, but could continue sorafenib/placebo alone.

For sorafenib/placebo, non-hematologic Grade 3 and 4 AEs other than dermatologic events, gastrointestinal events and fatigue: sorafenib/placebo therapy was to be held until ≤ Grade 2, with no change in dose. If Grade 3 or 4 toxicity persisted for > 3 weeks, the patient was to discontinue sorafenib/placebo treatment, but could continue capecitabine alone.

Study therapy could be discontinued due to patient incidence of treatment-emergent AEs, SAEs, treatment-related AEs, and AEs.

9.4 Treatments

9.4.1 Treatments administered

The treatments for the initial cycle were as follows, either:

Group A, Capecitabine/Sorafenib:

- Capecitabine: 1000 mg/m^2 orally, BID within 30 minutes after a meal for 14 days, followed by a 7-day rest period (without capecitabine)
- Sorafenib: 400 mg (2 tablets) administered orally BID (approximately every 12 hours) 1 hour before a meal, or 2 hours after a meal, continuous administration

Group B, Capecitabine/placebo:

- Capecitabine: 1000 mg/m^2 orally, BID within 30 minutes after a meal for 14 days, followed by a 7-day rest period (without capecitabine)
- Placebo: (2 x 200 mg tablets that match sorafenib) administered orally BID (approximately every 12 hours) 1 hour before a meal, or 2 hours after a meal, continuous administration

If < Grade 2 AEs were experienced, the capecitabine dose could be escalated by 25% in the subsequent cycle to 1,250 mg/m^2 BID (2,500 mg/m^2 daily). If ≥ Grade 2 AEs (NCI-CTC AE version 3) were experienced, the dose could be reduced as per Section 9.4.5.1. These dose reductions were consistent with the labeling for capecitabine.

Capecitabine dose modifications or delays did not impact sorafenib/placebo therapy. Patients who required a delay or dose modification of their capecitabine therapy were to continue to receive continuous sorafenib/placebo as scheduled.

If a dose reduction of sorafenib/placebo was required, but the toxicity resolved and no additional toxicities were seen after 2 cycles of treatment at the reduced sorafenib/placebo dose, sorafenib/placebo could be increased to the dose prior to the reduction, not to exceed the original dose of 400 mg BID or two tablets twice daily. Dose reductions for sorafenib/placebo are outlined in Section 9.4.5.2.

Cycles were repeated every 21 days.

Treatment cycles continued until disease progression was documented, intolerable toxicities, or voluntary withdrawal of study treatment.

Amendment 3 modified the protocol to allow patients who were receiving treatment with sorafenib and/or capecitabine at the time that the OS results were unblinded, and the sites and the patients were unblinded, to continue to receive the study treatment to which they were originally randomized, until disease progression occurred or the patients discontinued from the study for any reason. This period of the study was referred to as the "treatment-continuation" phase. During the treatment-continuation phase of the study, patients received study treatment until the time of disease progression or at patient or physician request to stop taking medication.

9.4.2 Identity of investigational product(s)

Detailed patient information for multiple batches is identified in Appendix 16.1.6.

The following investigational products were used in the study:

- Sorafenib 200 mg tablets
- Matching placebo tablets

Sorafenib tablets were manufactured by Bayer HealthCare AG. Sorafenib 200 mg tablets were packed in bottles for sites in Spain and France. Sorafenib 200 mg tablets were packed in Alu/Alu blister packs for sites in Brazil and were provided in cartons (each carton of blisters contained 200 tablets: 20 blisters containing 10 tablets). Bottles and blister packs were labeled according to local law and legislation. Placebo tablets were identical in appearance, and were packaged identically to the active study drug. Both sorafenib tablets and matching placebo tablets were supplied by Bayer Pharmaceuticals Corporation.

The 200 mg tablet formulation consists of sorafenib tosylate and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, magnesium stearate. The tablets have a film coating consisting of hypromellose, polyethylene glycol, titanium dioxide and red ferric oxide that has no effect on the release rate of the active sorafenib. The tablets have a red color in appearance, weigh approximately 350 mg each, and are 10 mm round in shape. The active compound of sorafenib tosylate is 4-(4-{3-[4-Chloro-3-(trifluoromethyl) phenyl] ureido}phenoxy)-N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate, and its molecular weight is 637 g/mole.

The placebo tablet matrix contained inert tableting excipients that included microcrystalline cellulose, lactose, magnesium stearate, and the coating consisting of hypromellose, polyethylene glycol, titanium dioxide, and red ferric oxide. Placebo tablets had the same storage/handling guidelines as the active tablet.

The tablets did not need protection from light. They were sufficiently stable towards light, oxidation, thermal stress, and hydrolytic degradation. The formulation is presented as an immediate-release dosage form, i.e., the active ingredient is allowed to completely dissolve under in vitro test conditions within a short period of time with no intention of delaying or prolonging dissolution.

The batch numbers used for sorafenib in this study were as follows:

BAY 43-9006 200 mg tablets: BX028RK, BX02E8D, BX02E8C, BX02SET, AM119, and AM095.

The batch numbers used for placebo in this study were as follows:

BAY 43-9006 Placebo 200 mg tablets: BX02DCG, BX028Vw, BX02DCH, BX02PXW, and BX02V9A.

Patient data on kit assignment is included in Appendix 16.1.6.

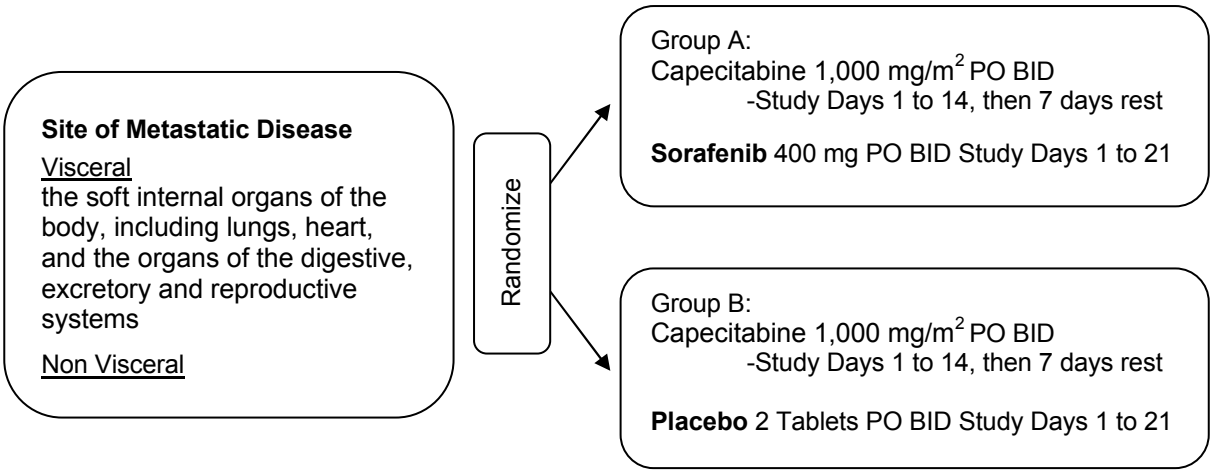
Commercially available capecitabine tablets were provided to all sites in 2 dosage strengths: 150 mg (60 tablets per carton) and 500 mg (120 tablets per carton). The dose administered was recorded in the source documentation and in the electronic case report form (eCRF).

9.4.3 Method of assigning patients to treatment groups

Patients were randomized in a double-blind fashion in a 1:1 ratio to sorafenib or placebo in combination with capecitabine (see Figure 1). During the randomization process, patients were stratified by site of metastatic disease: visceral disease versus nonvisceral (osseous or soft tissue) disease.

Randomization was performed via a web-based randomization and product inventory control system (RPIC) provided by a third-party vendor.

Figure 1: Randomization Stratification for Protocol 0701



Abbreviations: BID = *bis in die* (BID); and PO = *per os* (orally).

9.4.4 Selection of doses in the study

The safety and efficacy of the combination of sorafenib with capecitabine have been tested in a single Phase 1 dose escalation trial of 35 patients with unresectable and/or metastatic solid

tumors [Awada 2006]. Four cohorts were tested: sorafenib 200 mg BID with capecitabine 2,100 mg/m^2; sorafenib 400 mg BID with capecitabine 2,100 mg/m^2; sorafenib 200 mg BID for the first 2 cycles, then 400 mg BID thereafter with capecitabine 2,100 mg/m^2; and sorafenib 400 mg BID with capecitabine 1,700 mg/m^2. In this trial, the median duration on sorafenib was 147 days (range 2-925) and 131 days (range 9-903) for capecitabine. The most frequently reported drug-related toxicities (all grades) over all cycles were hand-foot skin reactions (HFSR, 89%), diarrhea (71%), and fatigue (69%). The maximum-tolerated dose was not reached in any of the cohorts; and therefore, a Phase 2 dose recommendation could not be made from this study. Dose limiting toxicities were recorded in each of the 4 cohorts. In Cohort 1, two of the 13 patients treated experienced Grade 3 HFSR. In Cohort 2, one of the 4 patients treated had HFSR. In Cohort 3, one case of Grade 3 HFSR was recorded out of the 6 patients treated. In Cohort 4, two DLTs were recorded in the 12 patients treated, both were due to HFSR. In the study, drug-drug interactions were minimal. The PK of sorafenib (200 and 400 mg BID) was not affected to a clinically relevant degree by capecitabine, and sorafenib caused only a moderate increase (30-40%) in capecitabine exposure. One heavily pretreated patient with breast cancer and skin lymphangitis (Cohort 1) and 2 patients in Cohort 4 (RCC, n=1; urothelial cancer, n=1) had tumor shrinkage.

Based on these findings, the regimen selected for the experimental arm of this Phase 2b trial was sorafenib 400 mg oral (PO) BID with capecitabine 2,000 mg/m^2 PO daily in two divided doses (1,000 mg/m^2 BID); this dose accounted for the increase in capecitabine exposure seen in the Phase 1 trial described above by reducing the dose of capecitabine by 25% from the labeled dose. The schedule also fell within the range of doses found to be tolerable in the same trial [Awada 2006] and is consistent with doses commonly delivered in other trials of capecitabine [Ershler 2006] and in clinical practice. In order to account for the possibility that higher doses of capecitabine may have been tolerable in this combination and to insure that patients received the maximum tolerated dose of capecitabine, dose escalation was allowed for patients who experienced less than Grade 2 AEs in Cycle 1. Additionally, an interim analysis for safety was performed after the 20th patient finished his/her second cycle of therapy. In addition, PK sampling was performed in this Phase 2b study.

9.4.5 Selection and timing of dose for each patient

Sufficient study treatment for two cycles of sorafenib or placebo (400 mg or placebo orally BID) and 1 cycle for capecitabine was provided to patients on Day 1 to enable them to dose at home. Dose calculations for capecitabine were made according to body surface area (BSA) on Day 1. Table 5 displays the dose calculation for capecitabine 1,000 mg/m^2 BID and Table 6 displays the dose calculation for capecitabine 1,250 mg/m^2 BID.

A cycle was defined as 21 days (i.e., 21 days of sorafenib or placebo and 14 days of capecitabine with a 7-day rest). Sorafenib or placebo was re-supplied to patients on an every-other-cycle basis, and doses were not modified unless there was toxicity. Capecitabine was re-supplied to patients on a per-cycle basis, and doses were not modified unless there was a change of 20% of body weight or toxicity.

Patients initially received capecitabine 2,000 mg/m^2 daily (1,000 mg/m^2 BID). If < Grade 2 AEs occurred, the capecitabine dose could be escalated by 25% in the subsequent cycle to 2,500 mg/m^2 daily (1,250 mg/m^2 BID). If ≥ Grade 2 AEs (NCI-CTC AE version 3) occurred,

the dose could be maintained or reduced as per Table 7. These dose reductions were consistent with the labeling for capecitabine.

Sorafenib/placebo therapy was not impacted by capecitabine dose modifications or delays. Patients who required a delay or dose modification of their capecitabine therapy were to continue to receive continuous sorafenib/placebo as scheduled.

Table 5: Dose Calculation for Capecitabine (1,000 mg/m^2 BID)

Dose level 1,000 mg/m^2 (BID)		**Number of tablets administered in the morning**		**Number of tablets administered in the evening**	
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.26	1,150	1	2	1	2
1.27 - 1.38	1,300	2	2	2	2
1.39 - 1.52	1,450	3	2	3	2
1.53 - 1.66	1,500	-	3	-	3
1.67 - 1.78	1,650	1	3	1	3
1.79 - 1.92	1,800	2	3	2	3
1.93 - 2.06	1,950	3	3	3	3
2.07 - 2.18	2,000	-	4	-	4
≥2.19	2,150	1	4	1	4

Table 6: Dose Calculation for Capecitabine (1,250 mg/m^2 BID)

Dose level 1,250 mg/m^2 (BID)		**Number of tablets administered in the morning**		**Number of tablets administered in the evening**	
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.26	1,500	-	3	-	3
1.27 - 1.38	1,650	1	3	1	3
1.39 - 1.52	1,800	2	3	2	3
1.53 - 1.66	2,000	-	4	-	4
1.67 - 1.78	2,150	1	4	1	4
1.79 - 1.92	2,300	2	4	2	4
1.93 - 2.06	2,500	-	5	-	5
2.07 - 2.18	2,650	1	5	1	5
≥2.19	2,800	2	5	2	5

9.4.5.1 Capecitabine dose modifications

Toxicities due to capecitabine administration were managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose was reduced, it was not to be increased at a later time with the exception of those instances described in Figure 2, below. Patients taking capecitabine were informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs. Doses of capecitabine omitted for toxicity were not replaced or restored; instead the patient resumed the planned treatment cycle. In those cases where capecitabine treatment was delayed more than 1 week, the patient started a new capecitabine cycle, i.e. 14 days of treatment followed by 7 days of rest period. Patients who required a delay or dose modification of their sorafenib/placebo therapy were to continue to receive capecitabine as scheduled. Dose reductions for capecitabine are outlined in Table 7.

Table 7: Capecitabine Dose Reductions

Dose Level	+1	Baseline	-1	-2
Capecitabine	1,250 mg/m^2 BID (Table 6)	1,000 mg/m^2 BID (Table 5)	750 mg/m^2 BID (Table 8)	500 mg/m^2 BID (Table 9)

Table 8: Calculated Capecitabine Dose, Reduced to 750 mg/m^2 BID

Dose level 750 mg/m^2 (BID)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	1000	-	2	-	2
1.39 - 1.52	1150	1	2	1	2
1.53 - 1.66	1150	1	2	1	2
1.67 - 1.78	1300	2	2	2	2
1.79 - 1.92	1450	3	2	3	2
1.93 - 2.06	1500	-	3	-	3
2.07 - 2.18	1650	1	3	1	3
≥2.19	1650	1	3	1	3

Table 9: Calculated Capecitabine Dose, Reduced to 500 mg/m^2 BID

Dose level 500 mg/m^2 (BID)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.30	650	1	1	1	1
1.31 – 1.44	650	1	1	1	1
1.45 – 1.60	800	2	1	2	1
1.61 -11.90	950	3	1	3	1
1.91 – 2.00	1000	-	2	-	2
2.01 – 2.30	1150	1	2	1	2
≥2.31	1150	1	2	1	2

9.4.5.2 Sorafenib/Placebo dose modifications

If a dose reduction of sorafenib/placebo was required, but the toxicity resolved and no additional toxicities were seen after 2 cycles of treatment at the reduced sorafenib/placebo dose, sorafenib/placebo could be increased to the dose prior to the reduction, but was not to exceed the original dose of 400 mg BID or two tablets BID. Dose reductions for sorafenib/placebo are outlined in Table 10.

Table 10: Sorafenib/placebo Dose Reductions

Dose Level	0	-1	-2
Sorafenib	400 mg BID (2 tablets twice a day)	400 mg QD (2 tablets once a day **in the morning**)	400 mg QOD (2 tablets every other day **in the morning**)
Placebo	2 tablets BID (2 tablets twice a day)	2 tablets QD (2 tablets once a day **in the morning**)	2 tablets QOD (2 tablets every other day **in the morning**)

9.4.5.3 Dose modifications for toxicities common to both agents

All toxicities were graded according to the NCI-CTCAE, Version 3.0.

Dermatologic toxicity (hand-foot skin reaction, rash), gastrointestinal toxicity (diarrhea), and fatigue are common toxicities to both agents. As it was difficult to determine which of these agents was causative, a pragmatic approach to dose adjustments was made in the event of their occurrence. Since the incidence of these toxicities was greater with capecitabine than

sorafenib, dose reductions with capecitabine were instituted first. If the toxicity did not resolve with capecitabine dose reduction, sorafenib/placebo was reduced. The following paragraphs and algorithm outline the details of this dose modification procedure; this dose modification algorithm also addressed the rules governing dose re-escalation:

Any appearance of Grade 1
If any of these toxicities occurred at Grade 1, doses of capecitabine and sorafenib/placebo were maintained. No dose interruption or reduction was required. The investigator was encouraged to utilize symptomatic treatment to alleviate toxicity.

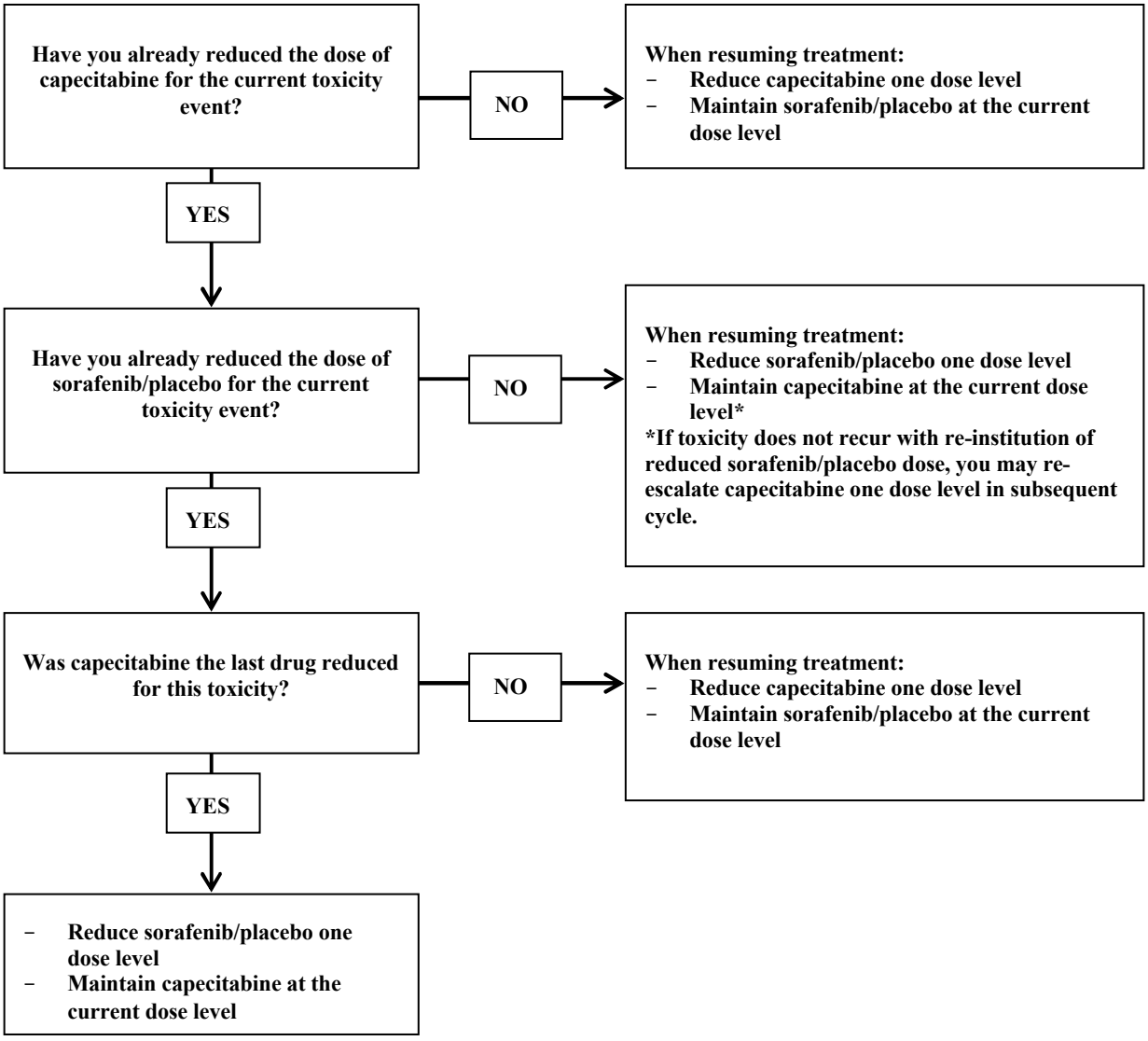
First appearance of Grade 2
If any of these toxicities occurred at Grade 2 at their first appearance, both agents were interrupted until the toxicity was resolved to ≤ Grade 1. Both agents could be re-started at the same dose level. No dose modification was required. The investigator was encouraged to utilize symptomatic treatment to alleviate toxicity.

Subsequent appearance of similar toxicity of Grade 2 or any appearance of ≥ Grade 3

If the same Grade 2 toxicity reappeared or if any of these toxicities occurred at Grade 3 or higher (any occurrence), both agents were interrupted until the toxicity resolved to ≤ Grade 1. When re-starting study treatment, the algorithm in Figure 2 was followed for dose modifications. The algorithm was re-used for each recurrence to determine which drug (capecitabine or sorafenib/placebo) was to be reduced. Patients who continued to have the toxicity and required a dose reduction to the lowest dose level of capecitabine (500 mg/m^2 BID) or sorafenib (400 mg every other day [QOD]) or placebo (2 tablets QOD) were discontinued from treatment with that agent.

The goal of the protocol was to maximize the dose intensity of capecitabine and sorafenib/placebo. If toxicity did not reappear with reduced dose of capecitabine and sorafenib/placebo, the dose of capecitabine could be re-escalated one dose level, but was not to exceed 1,250 mg/m^2 twice-daily dose in the subsequent cycle. If a dose reduction of sorafenib/placebo was required, but the toxicity resolved and no additional toxicities were seen after 2 cycles of treatment at the reduced sorafenib/placebo dose, sorafenib/placebo could be increased to the dose prior to the reduction, not to exceed the original dose of 400 mg BID or two tablets BID.

Figure 2: Recommended Dose Modifications used for Toxicities Common to Both Agents



9.4.6 Blinding

Patients were randomized to receive sorafenib or matching placebo in a double-blind fashion (i.e., the Investigator, Sponsor, and the patient were blinded to which combination was being administered). The randomization number was assigned based on information obtained from a web-based RPIC.

Sorafenib and placebo were identical in appearance in order to preserve blinding and patients were instructed to take two tablets orally both in the morning and in the evening (12 hours apart). In order to maintain the blind, sorafenib or matching placebo were labeled with a

unique number preprinted on each bottle or blister carton, which was assigned to a patient through the RPIC.

Unblinding was allowed if a severe adverse reaction necessitated identification of the medication for the welfare of the patient. The Sponsor was to be contacted prior to the unblinding to ensure reasons for the unblinding were valid. Patients could be unblinded to treatment assignment at time of progression upon request from the Principal Investigator if knowledge of treatment assignment would impact future treatments. All efforts were made to keep patients blinded to treatment assignment at the time of progression and thereafter.

9.4.7 Prior and concomitant therapy

All supportive measures consistent with optimal patient care were to be given throughout the study. Nausea and vomiting were to be controlled with standard anti-emetics. Growth factors could be used at the investigator's discretion and per American Society of Clinical Oncology (ASCO) guidelines. Patients could receive bisphosphonates. Vitamins/minerals were acceptable.

The following concomitant therapies were not allowed during the course of the study:

- Palliative radiation for painful bony lesions
- Treatment with sorivudine or its chemically related analogues, such as brivudine.
- The use of St. John's Wort or rifampin (rifampicin)
- Bevacizumab or any other drugs (licensed or investigational) that target VEGF or VEGFR
- Concurrent anti-cancer therapy (chemotherapy, hormonal therapy, radiation therapy, surgery, immunotherapy, biological therapy, or tumor embolization)
- Non-conventional therapies (e.g., herbs)

All concomitant medications and therapies administered (including start/stop dates and indication) were recorded in the patient's source documentation as well as in the appropriate pages of the CRF.

9.4.8 Treatment compliance

The dose and schedule of sorafenib/placebo plus capecitabine administered to each patient were recorded in the eCRF. Reasons for dose delay, reduction, or omission were also recorded in the eCRF. That information, plus tablet accountability, was used to assess compliance with the treatment.

Patient compliance with the treatment and protocol included willingness to comply with all aspects of the protocol, including having blood and urine collected for all safety evaluations. Patients could be discontinued from the trial for noncompliance with follow-up visits or study drug, or at the discretion of the Principal Investigator or Sponsor.

9.4.8.1 Measurements of treatment compliance

To ensure that there was appropriate management of use of capecitabine each cycle, each patient received a 14-day supply of capecitabine and unused tablets of capecitabine were be re-dispensed for subsequent cycles. Patients also received a 42-day supply of sorafenib (if assigned to the sorafenib or placebo) with instructions for taking the medication. The patient was instructed to return all unused medication at each clinic visit. The same dispensing method was continued through the treatment-continuation phase of the study.

Delays, reductions, escalations, re-escalations, and interruptions in capecitabine or sorafenib/placebo were recorded on the study drug administration eCRFs. At each visit at which study drug was dispensed, the number of tablets returned and the number dispensed were recorded to assess patient compliance with the treatment. Due to the inherent difficulty in assessing compliance for self-administered oral medications in the presence of dose reductions, delays, and interruptions, overall compliance for sorafenib/placebo was limited to a calculation of the percentage of cycles with > 90% compliance reported by the site.

9.5 Efficacy and safety variables

9.5.1 Efficacy and safety measurements assessed and study flowchart

Data for the analysis of efficacy and safety results were collected throughout the study according to the schedule presented in Table 11 in Section 9.5.1.1.

Screening period

Study entry was defined as the study treatment start date (Cycle 1, Study Day 1) which was allowed to be within 3 days of randomization.

Procedures conducted during the screening period included the following:

> Within 4 weeks (28 days) of randomization, radiological assessments (contrast CT or MRI of chest, abdomen, and pelvis) and bone scan were conducted, if clinically indicated. Clinical measurements and photographs of cutaneous lesions were taken within 7 days of randomization. Patients with bone lesions identified at baseline were further evaluated by the investigator's radiographic method of choice (i.e. CT, MRI, x-ray) provided this same method of assessment could be repeated at all subsequent tumor assessment time points to assess bone lesions. Bone lesions were evaluated as non-target lesions; therefore specific measurements were not required. Consistent follow-up was required to confirm presence, absence or unequivocal progression of existing nontarget lesions. Patients with neurological symptoms and known brain metastases treated with definitive therapy underwent contrast CT or MRI of the brain to exclude active brain metastases.

Double-blind treatment period

The treatment period began with the first dose of study treatment, and continued until the patient withdrew from treatment.

Procedures conducted during the double-blind treatment period included the following:

> Patient visits for safety evaluation were conducted on Cycle Day 1 of each 21 day cycle. Results of physical examinations, vital signs assessments (including heart rate, blood

pressure, respiration rate and temperature), electrocardiogram (ECG) data, weight, AEs, and laboratory values were recorded. Also, reasons for dose delays, modifications or omissions were provided.

The HF-QoL was administered to patients every 3 weeks for the first 24 weeks, and every 9 weeks thereafter provided this occurred prior to disease progression and the patient remained active in the trial, and at the end-of-study or withdrawal.

Disease assessments, including tumor measurements and the FACT-B health questionnaire, were conducted every 6 weeks (+/- 7 days) for the first 24 weeks and every 9 weeks (+/- 7 days) thereafter.

If the patient discontinued treatment for any reason (except death or lost to follow-up), an End-of-Treatment assessment was performed within 7 days of study withdrawal.

Follow-up period (post-progression)

During the follow-up period, periodic assessments (approximately every 4 months +/-2 week) for survival were performed until the planned number of OS events was reached. Contacts were made in person or by phone and recorded in the source documents. Patients were permitted to receive other therapy following study discontinuation. All post-study therapies for breast cancer received by the patient were to be collected and recorded on the appropriate CRF until the planned number of survival events had been reached.

Treatment-continuation period

Patients who were receiving treatment with sorafenib and/or capecitabine at the time that the OS results were unblinded, and the sites and the patients were unblinded, could continue to receive the study treatment to which they were originally randomized, in the "treatment-continuation" period until disease progression occurred or at patient or physician request. Only SAE safety data was collected during this period, and no prespecified analyses were performed.

The investigators were responsible for performing final assessments as they deemed appropriate, per standard practice. Onyx Drug Safety was to be notified of the discontinuation of each study patient, using the forms provided to each site.

Upon discontinuation of the treatment-continuation period, patients did NOT enter a follow-up period and study medication was no longer provided.

9.5.1.1 Schedule of study assessments

Table 11 displays the study evaluation flowchart and Table 12 displays the assessments conducted after unblinding.

Table 11: Study Evaluation Flowchart

Task	Prior to Randomization	Treatment Period				Follow-Up	
		Weekly for First 6 Weeks	Prior to Each 21 Day Cycle	Every 3 Weeks for First 24 Weeks; every 9 Weeks thereafter	Every 6 Weeks for First 24 Weeks; every 9 Weeks thereafter	End of Study Treat-ment	Approx. every 4 Months
Informed Consent	X						
Demographics, medical history, height, weight, ECOG PS, Physical Exam [1]	X						
Weight, ECOG-PS, brief physical exam			X (within 48 hours)				
Vital Signs (Temperature and Heart Rate)[2]	X		X			X	
Blood Pressure [2]	X		X			X	
CBC with differential, platelet count, HGB [3]	X		X (within 48 hours)				
PT-INR, aPTT,[4]	X						
Total bilirubin, AST, ALT, serum phosphate, Creatinine, BUN, amylase or lipase	X		X				
HCG[5]	X						
Study Treatment Dispensing and Assessment of Study Treatment Compliance			X			X	
FACT-B QOL	X				X	X	
HF-QoL[10]	X			X		X	
Tumor assessments by PE and CT/MRI Scan [6, 7]	X				X		
Blood draws for PK analysis[8]		Day 14 of Cycle 1					
Toxicity/Safety		X	X			X	
Investigator Survey						X	
Survival [9]							X
Study Treatment Dispensing and Assessment of Study Treatment Compliance [11]			X			X	

1. Within 1 week of randomization.
2. Blood pressure was monitored weekly during the first 6 weeks of study treatment (capecitabine + sorafenib or placebo). After the first 6 weeks, blood pressure was monitored and treated, if required, in accordance with standard medical practice.
3. CBC (with differential), platelet count, and HGB was done <48 hours prior to each cycle.
4. Patients taking concomitant warfarin were monitored regularly for changes in prothrombin time (PR), INR, or clinical bleeding, at least weekly or as defined as standard of care.
5. Required in patients of child-bearing potential only; was to be completed within 7 days prior to randomization.
6. All radiographic exams were to be done within 4 weeks of study start (contrast CT or MRI of chest, abdomen, and pelvis) and repeated every 6 weeks for the first 24 weeks and every 9 weeks thereafter. Patients with bone lesions identified at baseline were further evaluated by the investigator's radiologic method of choice (i.e. CT, MRI, x-ray,) provided the same method of assessment could be repeated at all subsequent tumor assessment time points to assess bone lesions. All other nonmeasurable lesions (including small lesions, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions, leptomengial disease and abdominal masses) were followed by the same method of assessment (clinical examination, CT, MRI or chest X-ray) and the same technique used to characterize each lesion at baseline and during follow-up. A contrast CT or MRI of the brain was performed at baseline, if neurologic symptoms were present and if known brain metastases, patients were treated with definitive therapy prior to randomization. Patients with known treated brain metastases at baseline had repeated scans performed every 6 weeks for the first 24 weeks and every 9 weeks thereafter. Tumor measurements based on Modified RECIST criteria.
7. Patients who had CR, PR, or SD at the time of discontinuing study treatment were encouraged to continue with disease assessments (including scans) every 6 weeks for the first 24 weeks and every 9 weeks thereafter until disease progression was first documented.
8. Three samples were collected per patient to measure plasma capecitabine (and 5-FU) level on Day 14 of Cycle 1 in patients willing to participate. The first draw was taken 1 hour post-capecitabine dose. The second draw was taken 4 hours post capecitabine dose and the last draw was taken 8 hours post-capecitabine dose.
9. Periodic assessments of survival were performed every 4 months (+/- 2 weeks) until the planned number of survival events had been reached. Contacts were made in person or by phone; the patient's primary care physician was the contact if the patient be unavailable. All patient contact was documented in source documents.
10. HF-QoL was administered within 2 weeks of randomization. Every 3 weeks for the first 24 weeks and every 9 weeks thereafter provided the patient had no disease progression and remained active in the trial, and again at the end-of study or withdrawal. The patient completed the HF-QoL in the waiting room prior to any procedure or clinic visit. The investigator completed the investigator's rating questions of the HF-QoL after the clinic visit.
11. Study Treatment Dispensing and Assessment of Study Treatment Compliance. Sorafenib or placebo was dispensed every 42 days (every 2 cycles). Cartons of capecitabine were dispensed to patients at the beginning of each 21 day cycle. The appropriate number of cartons of each dosage strength were dispensed to the patient to ensure that sufficient quantity was available to last for 1 cycle. Unused tablets were re-dispensed to the patients (if applicable) for subsequent cycles along with any additional cartons needed to ensure that the patient had sufficient supply of each dosage strength for that cycle.

Table 12: Summary of Study Assessments after Unblinding

	Treatment-Continuation Period				Follow-Up
	After Un-blinding	Prior to each 21 Day Cycle	According to Standard of Care	Recommended at End of Study Treatment	Approx. every 4 months
Continuation Protocol Informed Consent	x				
Weight, ECOG PS, brief physical exam			X		
Vital Signs (Temperature and Heart Rate)			X	X	
Blood Pressure			X	X	
CBC with differential, platelet count, HGB			X		
PT-INR, aPTT,[1]			X		
Total bilirubin, AST, ALT, serum phosphate, Creatinine, BUN, amylase or lipase			X		
Study Treatment Dispensing and Assessment of Study Treatment Compliance[6]		X		X	
Tumor assessments by PE and CT/MRI Scan [2]			X		
Toxicity/Safety		X		X	
Investigator Survey					
Survival[3]					
HF-QOL[4]					
FACT-B QOL[5]					

1 Patients taking concomitant warfarin were monitored regularly for changes in prothrombin time (PR), INR, or clinical bleeding, at least weekly or as defined as standard of care.

2 All radiographic exams were performed according to the hospital's standard of care.

3 Periodic assessments of survival were NOT performed after the OS analysis.

4 HF-QoL was not administered after the OS analysis.

5 FACT-B -QoL was not administered after the OS analysis.

9.5.1.2 Study Treatment Dispensing and Assessment of Study Treatment Compliance.

Sorafenib was dispensed every 42 days (every 2 cycles) to patients assigned to that treatment arm. Cartons of capecitabine were dispensed to patients at the beginning of each 21-day cycle. The appropriate numbers of cartons of each dosage strength were dispensed to the patient to ensure that sufficient quantity was available to last for 1 cycle. Unused tablets were re-dispensed to the patients (if applicable) for subsequent cycles along with any additional cartons needed to ensure that the patient would have sufficient supply of each dosage strength for that cycle.

9.5.1.3 Efficacy variables

The primary efficacy variable was PFS, as measured from the date of randomization to the date of first documented disease progression or the date of death due to any cause, if the death is before PD and within 28 weeks (three 9 week's tumor assessment schedule + 1 week) after last adequate tumor assessment. The final analysis for PFS in the study was performed when approximately 120 progression events were observed. Patients alive without documented tumor progression at the time of data cutoff were censored at their last tumor assessment before initiation of any non-protocol specified cancer therapy.

Secondary efficacy variables included:

- Overall Survival
- Time to progression
- Objective response rate
- Duration of overall response

Time to progression was calculated as the time (days) from date of randomization to date of first documented disease progression. The actual dates of tumor assessments were used for this calculation. Time to progression for patients without disease progression at the time of data cutoff or death were censored at the last date of tumor evaluation. Survival was measured from the date of randomization to death due to any cause. Duration of overall response was measured from the first documentation of complete or partial response (whichever status was recorded first) until the first date that progressive disease or death was objectively documented.

An exploratory efficacy variable was to compare change from baseline in FACT-B score, Version 4. An additional exploratory efficacy variable was to validate the HF-QoL, and if validated, to compare the effect of sorafenib and capecitabine versus placebo and capecitabine using HF-QoL.

All radiographic exams were done within 4 weeks of study start (contrast CT or MRI of chest, abdomen, and pelvis) and were repeated every 6 weeks (+/- 7 days) for the first 24 weeks and every 9 weeks (+/- 7 days) thereafter. Patients with bone lesions identified at baseline were further evaluated by the investigator's radiographic method of choice (i.e. CT, MRI, x-ray) provided the same method of assessment could be repeated at all subsequent tumor assessment time points to assess bone lesions. All other nonmeasurable lesions (including small lesions, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions, leptomengial disease and abdominal masses) were followed by the same method of assessment (clinical examination, CT, MRI, or chest X-ray) and the same technique used to characterize each lesion at baseline and during follow-up. A contrast CT or MRI of the brain was performed at baseline, if neurologic symptoms were present and if known brain metastases, patients were treated with definitive therapy prior to randomization. Patients with known treated brain metastases at baseline had repeated scans performed every 6 weeks (+/- 7 days) for the first 24 weeks and every 9 weeks (+/- 7 days) thereafter. Tumor measurements were based on Modified RECIST criteria.

If a patient discontinued treatment for any reason, efficacy assessments were conducted as part of the End-of-Treatment visit within 7 days of the discontinuation.

Patients who had complete response (CR), partial response (PR), or stable disease (SD) at the time of discontinuing study treatment were required to continue with disease assessments (including scans) under the same schedule as in the treatment period until disease progression was documented.

All patients who had PD were contacted (either in person or by telephone) to collect data on OS. The contacts were made every 4 months (+/- 2 weeks) until death was recorded.

The Investigator assessed the tumor response and disease progression based on a blinded review of diagnostic methods, including CTs, MRIs, investigator assessment of cutaneous lesions, and additional clinical information provided. Tumor response and disease progression were evaluated based on modified RECIST.

The criteria for the definitions of response were the modified RECIST Criteria, as described in Section 9.5.1.3.

9.5.1.4 Solid tumor response criteria (Modified RECIST)

To assess objective response, it was necessary to estimate the overall tumor burden at baseline to which subsequent measurements would be compared. Measurable disease was defined by the presence of at least one measurable lesion. All measurements were recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique was used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations were performed as closely as possible to the beginning of treatment and never more than 4 weeks before randomization.

At baseline, tumor lesions were characterized as either measurable or non-measurable.

9.5.1.4.1 Malignant disease evaluation: Measurable

Lesions that could be accurately measured in at least one dimension [longest diameter (LD) to be recorded] as ≥20 mm (2.0 cm) with conventional techniques with contiguous cuts of 10 mm or less in slice thickness or as ≥10 mm (1.0 cm) with spiral CT scan, provided the images are reconstructed contiguously at 5 mm intervals.

9.5.1.4.2 Malignant disease evaluation: Non-Measurable

All other lesions, including small lesions (longest diameter <20 mm (2.0 cm) with conventional techniques or <10 mm (1.0 cm) with spiral CT scan were non-measurable lesions.

Lesions considered to be non-measurable included the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions. All malignant effusions were confirmed by cytology.

Tumor lesions that were situated in a previously irradiated area were not considered measurable.

9.5.1.5 Safety variables

Safety variables included treatment-emergent AEs, laboratory parameters (chemistry, hematology, and coagulation), and vital signs. All reported AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) by preferred term and system organ class.

AEs were defined as follows:

Treatment-emergent AE: any AE that started after the first dose of study treatment or that was seen prior to the start of study treatment, but increased in severity during the treatment period.

Baseline AE: any AE collected after the patient had signed the informed consent form and before the study treatment administration.

For the drug relationship, AEs were classified as related or not related to each agent (capecitabine and/or sorafenib/placebo) separately. The toxicity grade of AEs and selected laboratory parameters were determined using NCI CTCAE, version 3.0.

At the Screening visit within 1 week (7 days) before study entry, baseline safety variables were measured, including demographic data, medical history, height, body weight, ECOG Performance Status, vital signs (pulse, body temperature, and blood pressure), clinical safety labs (complete blood count [CBC] with differential, platelets, HGB, PT-INR, aPTT, total bilirubin, ALT, AST, serum phosphate, amylase or lipase, BUN, and creatinine), clinical disease assessment (for palpable or visual lesions), and a physical exam was completed. The physical exam was to focus on a review of the inclusion/exclusion criteria. Any changes in the patient's mental or physical condition from screening to randomization that would make him/her ineligible for the study were considered. Within 1 week of randomization, a serum HCG test was obtained for all women of child-bearing potential.

On Study Day 1 (within 48 hours) of the start of each cycle, a predose blood sample was taken for hematology analysis, in addition to a blood sample for biochemistry analysis. Brief physical examinations, including ECOG-PS, weight, and a brief review of body systems were conducted. For Cycle 1, screening assessments could be used if performed within 7 days. Also within 7 days prior to randomization, a serum pregnancy test was performed for women of childbearing potential. Vital signs (heart rate, blood pressure, respiration rate and temperature), new and existing AEs/SAEs/toxicities, and any changes to concomitant medications were assessed and documented.

Weekly, for the first 6 weeks, blood pressure and new and existing AEs/SAEs/toxicities were monitored to ensure timely recognition and management of toxicities, and any changes to concomitant medications were assessed and documented.

On day 14 of Cycle 1, three additional blood samples were collected from patients willing to participate in a pharmacokinetic analysis to measure plasma capecitabine and 5-FU levels.

If the patient discontinued treatment (capecitabine and sorafenib or placebo) for any reason, vital sign assessments (blood pressure, pulse, body temperature), and final assessments of compliance, safety, and tolerability (i.e., routine collection of AEs) were performed.

At the end of the treatment period (at discontinuation of study treatment), the investigator was asked as to whether he could "guess" the patient's treatment assignment. The results of this survey was to be used to guide the blinding and endpoint review plan for any potential Phase 3 study in the future.

An interim safety analysis was conducted by the DMC (see Section 11.3.8.3) after the 20th patient completed Cycle 2 of study treatment.

9.5.1.5.1 Adverse events/serious adverse events

Patients were carefully monitored for AEs. This monitoring included clinical laboratory tests. AEs were assessed in terms of their seriousness, severity via common terminology criteria for adverse events (CTCAE) grading, and relationship to study drug. AEs were recorded and graded according to the NCI-CTCAE version 3.0.

The overall incidence of treatment-emergent AEs is presented by MedDRA system organ class and preferred term. Patients were counted at most once for each MedDRA term. The overall incidence of treatment-emergent AEs is presented separately by severity and by drug relationship. For these presentations, patients were counted at most once for each MedDRA term under the highest severity or the strongest relationship to study treatment.

Summaries of the number (%) of patients in each treatment group with at least 1 AE, classified according to MedDRA term, are provided for study treatment-related (capecitabine, and/or sorafenib/placebo) AEs.

The incidence of new onset of treatment emergent AEs by cycles for each treatment group are provided for specific hematologic events (neutropenia, leukopenia, thrombocytopenia, and anemia) and nonhematologic events (nausea, vomiting, diarrhea, fatigue, peripheral neuropathy, rash and hand-foot skin reaction).

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered with a pharmaceutical product. An AE did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

All SAEs were reported following consent to 30 days post discontinuation of study drug. All study drug-related SAEs occurring more than 30 days after study drug discontinuation were also reported.

Adverse events

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An AE occurring in the course of the use of a drug product in professional practice
- An AE occurring from an overdose whether accidental or intentional
- An AE occurring from drug abuse
- An AE occurring from drug withdrawal

- An AE where there is a reasonable possibility that the event occurred purely as a result of the patient's participation in the study (e.g., AE or SAE due to discontinuation of antihypertensive drugs during washout phase) must also be reported as an AE even if it is not related to the investigational product

The clinical manifestation of any failure of expected pharmacological action was not recorded as an AE if it was already reflected as a data point captured in the CRF. If, however, the event fulfilled any of the criteria for a "serious" adverse event, it was recorded and reported as such. Also, progression of underlying disease was NOT considered an AE. Signs and symptoms related to disease progression were graded and received a study-drug attribution determined by the investigator. Objective documentation of progression was always sought.

Serious adverse events

The incidence of on-study deaths and treatment-emergent SAEs has been summarized. The summary of treatment-emergent SAEs is presented by MedDRA system organ class and preferred term. A summary of study treatment-related (capecitabine, and/or sorafenib/placebo) SAEs is provided. Listings and narratives for all on study deaths and SAEs are provided. A death was considered as occurring on study if it occurred on or after the start of study treatment and no more than 30 days after the last dose of study treatment. Only on-study deaths were summarized at the time of the final analysis of PFS. All death data was summarized at the time of the final OS analysis.

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

Life-threatening*:* The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at immediate risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization*:* Any AE leading to hospitalization or prolongation of hospitalization was considered as serious, UNLESS at least one of the following exceptions was met:

- The admission was pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), OR
- The admission was not associated with an AE (e.g., social hospitalization for purposes of respite care)

However, invasive treatment during any hospitalization could fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical

judgment. In addition, where local regulatory authorities specifically required a more stringent definition, the local regulation took precedent.

Disability: A substantial disruption of a person's ability to conduct normal life's functions.

Important medical event*:* An AE which may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse events

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator Brochure (IB) (or Package Insert for marketed products). Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected." Specific examples would be; (a) acute renal failure as a labeled AE with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

"Unexpected" as used in this definition, refers to an AE that has not been previously observed (e.g., included in the IB) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Relationship of adverse events

The assessment of the relationship of an AE to the administration of study drug was a clinical decision based on all available information at the time of the completion of the Clinical Study Report (CSR).

An assessment of 'No' included:

- The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical site; or
- Non-Plausibility e.g., the patient is struck by an automobile when there was no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable possibility that the AE is associated with the use of study drug.

Factors considered in assessing the relationship of the AE to study drug included:

- *The temporal sequence from drug administration*: The event occurred after the drug was given. The length of time from drug exposure to event was evaluated in the clinical context of the event

- *Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge*): Patient's response after drug discontinuation (de-challenge) or patients response after drug re-introduction (re-challenge) was considered in the view of the usual clinical course of the event in question
- *Underlying, concomitant, intercurrent diseases*: Each report was evaluated in the context of the natural history and course of the disease being treated and any other disease the patient had
- *Concomitant medication or treatment*: The other drugs the patient was taking or the treatment the patient received were examined to determine whether any of them was suspected to cause the event in question
- *Known response pattern for this class of drug*: clinical/preclinical.
- *The pharmacology and pharmacokinetics of the test drug*: The PK properties (absorption, distribution, metabolism, and excretion) of the test drug(s), coupled with the individual patient's pharmacodynamics were considered.

The investigator answered the question regarding the causal relationship for both 'Sorafenib or Placebo' and 'Capecitabine' (i.e., separate causality assessments to each anti-cancer drug received by the patient for a given AE).

9.5.1.5.2 Clinical laboratory tests

Blood samples were taken for hematology analysis, coagulation analysis, and biochemistry analyses. The listed tests were conducted at local laboratories:

Hematology

- Hemoglobin (HGB)
- Hematocrit
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, and basophils)

Coagulation

- Prothrombin time (PT) or the international normalized ratio of PT (PT-INR)
- Activated partial thromboplastin time (aPTT)

Biochemistry

- Bilirubin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Serum phosphate

- Creatinine
- Blood urea nitrogen (BUN)
- Amylase or lipase

Criteria for grading toxicity evident in the laboratory data based on the NCI CTCAE version 3.0 were available for all tests except hematocrit, PT, and BUN.

The incidence of worst CTCAE toxicity grade any time after the start of study treatment (including unscheduled visits, the follow-up visits, and any data recorded after the last dose of study medication) and the change from baseline (shift table) CTCAE toxicity grade have been summarized.

A listing of all patients with laboratory values that showed grade 3 or higher CTCAE toxicity is provided (see Section 12.4.2).

9.5.2 Appropriateness of measurements

This report presents the analysis of PFS, an established surrogate endpoint for clinical activity in patients with serious or life-threatening diseases. Delay of progression may also represent a direct benefit in metastatic breast cancer because progression usually results in subsequent morbidity and death. In addition, PFS is an appropriate endpoint for evaluating putative cytostatic agents, where there may not be a significant component of tumor shrinkage.

Tumor responses were evaluated using modified RECIST, derived from one-dimensional measurements of tumor lesions. Measurements were based on standard imaging techniques. This is a standard, widely accepted approach to evaluation of tumor lesions in clinical trials.

9.5.3 Drug concentration measurements

Three additional blood samples were collected from patients who were willing to participate in a PK analysis. The objective of the PK analysis was to determine the PK parameters of capecitabine (and 5-FU) when it is administered in combination with sorafenib/placebo to breast cancer patients.

9.5.3.1 Pharmacokinetic sampling

Three samples were collected at 1, 4, and 8 hours post-capecitabine-dose on Day 14 of Cycle 1 in each participating patient to measure plasma capecitabine and 5-FU levels. Blood samples were collected from a subset of enrolled patients in the study: patients who were willing to participate in PK data collection. Approximately one-third of enrolled patients participated in PK assessment.

An outside bioanalytical laboratory provided PK sample collection, processing, storage and shipping instructions. The analytical assay used was a validated method. The documentation of the analytical methods used and their validation are presented in Appendix 16.1.11.

9.6 Data quality assurance

All clinical work conducted under this protocol was subject to the respective health authority regulations for good clinical practice (GCP) and Investigator Responsibilities. Each clinical

investigator agreed to the inspection of study-related records at any time by government regulatory agencies, SOLTI and Onyx.

Before enrolling patients into this study, investigators' meetings were held on 15th June 2007 in Barcelona, Spain and 31st August 2007 in Sao Paulo, Brazil, to review the protocol, the investigator's brochure (IB), the electronic CRF, as well as procedures for obtaining informed consent and for reporting AEs. Generally, meetings were attended by the principal investigator or sub-investigator and the study coordinator assigned to the study, as well as by SOLTI (Sponsor and CRO for Spain), representatives of Onyx / Bayer and representatives of the CROs in France (Nuvisan-Oncology formerly AAI Pharma) and in Brazil (Oncopartners).

Staff from SOLTI or their selected regional CROs monitored the study sites at regular intervals to ensure compliance with the protocol, to review source documents, and to assess drug accountability. At a minimum, data that must have been evident in the patient's medical record consisted of the following items: progress notes that indicated the primary diagnosis (including signs and symptoms at entry), laboratory and x-ray reports, telephone contacts, demographics (date of birth, sex, height, weight, race, and general status of health), and administration of informed consent. All AEs (start and stop dates, outcome, course of action), reasons for noncompliance with study drug administration, or deviations from the protocol were also to be noted in the patients' medical record.

A bulk study drug inventory was maintained by the study site staff who recorded the patient number, initials, date drug was dispensed, number of containers dispensed, and the date study drug was returned.

The patients' medical records were maintained and made available for data verification, in their entirety, during monitoring visits and/or audits by Bayer-Onyx and SOLTI or their designees, or local regulatory authorities.

Plasma samples were analyzed at North East Bioanalytical (see Section 12.7).

The Bayer Regulatory Affairs Department audited 5 sites to assess compliance with respect to Food and Drug Administration (FDA), European Medicines Agency (EMEA), and Bayer-Onyx and SOLTI regulations. Audit certificates are presented in Appendix 16.1.8 of this report.

Onyx supplied the study sites with access to an electronic data capture (EDC) computer system provided by a vendor, MedNet Solutions. The system was secured and could not be modified by investigative sites. Edit checks and data logic checks were at the point of entry and validated by Onyx Data Management personnel. All data entered into the system was transferred to a secure database maintained at Onyx.

Access to the EDC system at the site and at Onyx was password protected. Study access was granted to site personnel only after they have been trained in the use of the EDC System by MedNet personnel or their designees, either at the study site, at the investigators' meeting, or via webcast teleconference. All EDC system training history was documented and maintained by the respective CROs and at Onyx, as applicable.

The EDC System contained a system-generated audit trail that captured any changes made to a data field, including who made the change, and the date and time it was made.
This information was available both at the investigator's site and at Onyx.

Data entries made in the EDC screens were supported by source documents maintained for all patients enrolled in this study.

9.7 Statistical methods described in the protocol and determination of sample size

9.7.1 Statistical and analytical plans

For further details, please refer to the Statistical Analysis Plan (SAP) in Appendix 16.1.9.1.

Analysis populations

All primary and secondary analyses of the efficacy data were conducted using the intent-to-treat (ITT) population, defined as all patients who were randomized to treatment. For the ITT population, patients were analyzed in the treatment group assigned at randomization, regardless of the treatment received.

The primary analysis for PFS and OS endpoints were also conducted using the per-protocol population. The per-protocol population for the PFS endpoint was defined as the patients in the ITT population who did not have any major protocol deviations. The per-protocol population for OS endpoint was defined as the patients in the safety population who did not have any major protocol deviations. Major protocol deviations that occurred in this study are outlined in Section 10.3.

All summaries and analyses of the safety data were conducted using the valid-for-safety population, defined as all patients who were randomized and received any study treatment. For this population, patients were analyzed in the treatment group for which they received therapy. If a patient received the wrong treatment for an entire study treatment period, the patient was analyzed in the treatment group for which they received therapy. If a patient received the wrong treatment only for part of a study treatment period, the patient was analyzed in the randomized treatment group.

When approximately 120 PFS events were observed, a cutoff date of the database was determined. All clinical data collected before the cutoff date was included in the final analysis. Survival status and disease status of patients who were alive after the database cutoff were followed until 120 survival events were reached.

Descriptive statistics, including 95% confidence intervals, were used to summarize study endpoints. P-values were calculated for descriptive purpose only.

Disposition of patients, baseline demographics, and disease characteristics

The following data related to patient disposition were summarized by treatment group:

- number of patients who were eligible for the study (i.e., who met all inclusion/exclusion criteria)
- number of patients randomized
- number (%) of patients in each analysis population (ITT and valid-for-safety)
- number (%) of patients in each randomization stratum

- number (%) of patients who discontinued study treatment and reason for discontinuation
- number (%) of patients who discontinued the study and reason for discontinuation
- number (%) of patients whose treatments were unblinded before the PFS event
- number of screen failures
- number of patients lost to follow-up
- number of patients with consent withdrawn

Patient status at the time of the analysis for PFS was summarized as alive progression-free, alive post-progression, dead, or lost to follow-up. Lost to follow-up for the PFS data set included patients with no adequate post- baseline tumor assessment and/or survival status unknown.

Patient status at the time of OS analysis was summarized as alive, dead or lost to follow-up. 'Lost to follow-up' for the OS data set included patients with treatment or follow-up that was discontinued due to consent being withdrawn or due to the patient being lost to follow-up.

The percentages in these summary tables are based on the number of randomized patients (i.e., the ITT population).

Patients with major protocol deviations

Protocol deviations that could affect the interpretation of the analyses of the study variables were considered as major. Major protocol deviations are listed as below:

- Major inclusion exclusion criteria violations. Any major inclusion exclusion criteria violation is major protocol deviation regardless of a waiver for the violation being granted or not.
- Receipt of protocol-prohibited therapy during the study treatment period. Protocol-prohibited therapy included
    - Palliative radiation for bony lesions
    - Use of St. John’s Wort or rifampin
    - Bevacizumab or any other drugs that target VEGF or VEGF receptors
    - Concurrent anti-cancer therapy (chemotherapy, hormonal therapy, surgery , immunotherapy, biological therapy, or tumor embolization)
- Skipped scheduled tumor assessment during treatment period: A scheduled tumor assessment was considered skipped if there was no assessment within +/- 21 days of the scheduled date.
- Receipt of wrong study treatment (e.g., sorafenib instead of placebo);
- Un-blinding a patient prior to PFS event.

A list of major protocol violations was generated and the number of patients with major protocol deviations was summarized for each treatment group by the categories of deviation

described above. The patients with major protocol deviations were excluded from the per-protocol analysis. The third and fifth criteria for major protocol deviations listed above (i.e.. tumor assessment skipped during the treatment phase and unblinding prior to PFS event) were applied only up to the data cut-off time for the primary PFS analysis.

Prior and concomitant medications

Prior medications were defined as any medication taken by a patient within 30 days prior to the study drug start date. Concomitant medications were defined as any medication taken on or after Study Day 1. All medications were coded using the World Health Organization Drug Dictionary (WHO-DD). The number and percentage of patients who were administered concomitant medications classified according to the WHO-DD were summarized based on the ITT population.

Concomitant and post-treatment anti-cancer medications

Concomitant anti-cancer medication/therapy was defined as any anti-cancer medication/therapy taken on or after treatment start date. All medications were coded using the WHO-DD. Listings of concomitant and post-treatment anti-cancer medications, classified according to the anatomical-therapeutic-chemical (ATC) classification, are provided.

9.7.1.1 Efficacy analyses: Primary

All primary statistical summaries of the baseline data and primary analyses of the efficacy data were conducted using the ITT population, defined as all patients who were randomized to treatment. For the ITT population, patients were analyzed in the treatment group assigned at randomization, regardless of the treatment received.

The primary analysis for PFS endpoint was also conducted using the per-protocol population, defined as the patients in the ITT population who did not have any major protocol deviations. Major protocol deviations are defined in Section 10.3. The per-protocol population for OS endpoint was defined as the patients in the safety population who did not have any major protocol deviations.

The primary analysis for PFS was a stratified Cox regression with treatment group as a single covariate and the randomization stratification factor (visceral versus non-visceral) as strata using the ITT population. The relative risk (sorafenib to placebo) was estimated by the hazard ratio (HR) from the stratified Cox regression with a 2-sided 95% confidence interval based on normal approximation. 1-sided p-value from stratified log-rank test was presented. If a patient was stratified using incorrect values for the stratification factors, the correct values for the stratification factors for the patient based on data was used in the analyses. Kaplan-Meier estimates for quartiles of PFS and Kaplan-Meier curve were also presented for each treatment group. PFS rate at several time points were estimated for each treatment group using the Kaplan-Meier method. The difference of PFS rate between two arms was calculated with 2-sided 95% confidence interval based on normal approximation. 1-sided p-value for the difference was calculated based on normal approximation.

Survival was measured from the date of randomization to death due to any cause. Duration of overall response was measured from the first documentation of complete or partial response

(whichever status was recorded first) until the first date that progressive disease or death was objectively documented.

9.7.1.1.1 Primary efficacy variable: Progression free survival (PFS)

The primary efficacy variable was PFS, as measured from the date of randomization to the date of first documented disease progression, or the date of death due to any cause, if the death was before PD and within 28 weeks (three 9 week's tumor assessment schedule + 1 week) after last adequate tumor assessment. The final analysis for PFS was performed when approximately 120 progression events were observed.

Uncensored PFS was calculated as: PFS = date of first documented PD or death (if before PD) – randomization date.

The RECIST criteria were used to assess tumor response and progression. In this study, symptomatic deterioration was considered as disease progression.

Censoring rules in primary analysis of PFS:

- For patients who did not have any adequate post-baseline tumor assessment and there was no death within 28 weeks after randomization, PFS was assigned one day and censored in the analysis.
- If a new anti-cancer treatment or surgery was not used before the data cutoff and there was no documentation of PD or death by the time of data cutoff, then PFS was censored at the last adequate tumor assessment before the data cutoff.
- If a new anti-cancer treatment or surgery was not used before the data cutoff and the patient died without PD before the data cutoff, but more than 28 weeks after the last adequate tumor assessment, then PFS was censored at the last adequate tumor assessment.
- If a new anti-cancer treatment or surgery was used before the data cutoff and there was no documentation of PD or death before the start of the new anti-cancer treatment, then PFS was censored at the last adequate tumor assessment before the new anti-cancer treatment started, regardless whether there was a PD or death after the start of the new anti-cancer treatment.

9.7.1.1.1.1 Per protocol analysis

The primary analysis described in Section 9.7.1.1.1 (except for the analysis population) was performed using the per-protocol population. The per protocol population was defined as the patients in the ITT population that did not have any major protocol deviations.

9.7.1.2 Efficacy analyses: Secondary

Analyses of all secondary efficacy variables were based on the ITT population.
The secondary efficacy variables were:

- Overall Survival
- Time to progression
- Overall response rate
- Duration of overall response

For time-to-event variables (TTP, OS, and DOR), the relative risk (sorafenib to placebo) was estimated by the HR from the stratified Cox regression with the randomization stratification factor (visceral vs. non-visceral) as stratum. 1-sided p-value from stratified log-rank test was presented.

Kaplan-Meier estimates for the quartiles and Kaplan-Meier curve were prepared for each treatment group. The quartiles of DOR were estimated from responders only.

The best overall response was summarized for each treatment group. The overall response rate, defined as the proportion of patients achieving overall response (CR or PR) when confirmation of response was not required was estimated with a 2-sided 95% exact binomial confidence interval for each treatment group. The treatment groups were compared with respect to overall response rate using the Cochran-Mantel-Haenszel test, adjusting for the stratification factor. The same analysis was performed for objective response rate, defined as the proportion of patients achieving overall response (CR or PR) when confirmation of response was required.

While not indicated as a secondary efficacy variable, change in ECOG performance status from baseline to the visit at which the best overall response was first documented, and to the end of treatment, was summarized for each treatment group. The possible categories of change from baseline were -1 to 4.

9.7.1.2.1 Secondary efficacy variable: Time to progression (TTP)

TTP was calculated as the time (days) from date of randomization to date of first documented PD. The same censoring rules, except for death, as in primary analysis of PFS were applied in calculation of TTP.

Uncensored TTP was calculated as: TTP = date of first documented PD – randomization date.

The RECIST criteria were used to assess tumor response and progression. In this study, symptomatic deterioration was considered as disease progression.

Table 13 summarizes evaluation of overall response by modified RECIST.

Table 13: Modified RECIST Evaluation of Overall Response

Target Lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
CR or PR or SD	UNK	No	UNK
UNK	CR or SD or UNK	No	UNK
SD	CR or SD	No	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD

Abbreviations: CR: Complete response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; UNK: unknown.

9.7.1.2.2 Secondary efficacy variable: Overall survival

Overall survival was calculated as the time (days) from the date of randomization to death due to any cause:

OS = date of death – randomization date.

Survival for patients who were alive or lost to follow-up were censored at the date of the last contact alive. If there was no other contact or follow-up date except for randomization date proving a patient was alive on that day, OS was assigned one day and censored in the analysis. Patients who died, but the date of death being missing/unknown, were censored at the date of the last contact alive.

The tumor assessment data captured after the data cutoff time for the PFS analysis was not included in the OS analysis. No other efficacy endpoints (PFS, TTP, DOR, and ORR) were re-analyzed at the time of OS analysis. However, all other data including safety and study drug administration were re-analyzed at the time of OS analysis.

9.7.1.2.3 Secondary efficacy variable: Best overall response

Best overall response was the best response measured by RECIST from randomization to PD. If a patient received a new anti-cancer therapy or surgery, the overall responses from tumor assessments after the receipt of the new anti-cancer therapy or surgery was not used in deriving best overall response. The response categories used were complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). To be assigned a status of confirmed CR or PR, changes in tumor measurements had to be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met.

The primary analysis of best overall response did not require confirmation for responses and the possible values for the primary analysis of best overall response were CR, PR, SD, PD, and NE (not assessable).

The secondary analysis of best overall response required confirmation for responses. The possible values for the secondary analysis of best overall response were CR and PR. Confirmed CR or PR were called objective response. Only the patients with objective response were included as responders in the secondary analysis of best overall response.

9.7.1.2.4 Secondary efficacy variable: Overall response rate (ORR)

ORR was the proportion of patients with the best overall response of CR or PR. The ORR was calculated using 2 different definitions: 1) both confirmed and unconfirmed responses as responses, and 2) confirmed responses only (objective response). To be assigned a status of confirmed CR or PR, changes in tumor measurements had to be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met.

9.7.1.2.5 Secondary efficacy variable: Duration of overall response (DOR)

DOR was calculated as the time (days) from the first documentation of CR or PR (whichever status was recorded first) until the first documented PD or death (if before progression).

DOR = date of first PD or death (if before progression)–date of first documented CR or PR.

The patients with no documented CR or PR, DOR were assigned uncensored day of 0 and included in the analysis of DOR. The same censoring rules as in primary analysis of PFS were applied in calculation of duration of overall response. Two different definitions of responses were used in duration of OR: 1) both confirmed and unconfirmed responses, and 2) confirmed responses only. Under both definitions, DOR for the patients with no documented CR or PR was assigned uncensored day of 0. When only confirmed responses were used as responses, the date of first documented CR or PR was used in the calculation of DOR. DOR was also estimated in a subset of patients with measurable disease at baseline.

9.7.1.3 Subgroup analyses

9.7.1.3.1 Subgroup analysis: Subgroup analysis for PFS

PFS analysis was performed in the subgroups defined by following baseline covariates. Within each category of subgroups, the HR of PFS was estimated by un-stratified Cox regression and the median PFS was estimated by the Kaplan-Meier method. The primary calculation of PFS was used in this analysis.

- Prior chemotherapy for metastatic disease (yes or no)
- Hormone receptor status (ER positive or progesterone receptor (PgR) positive, ER negative and PgR negative)
- Visceral disease (yes or no)

Other subgroup analyses for PFS were performed as exploratory purpose and described in the Section below.

9.7.1.3.2 Subgroup analysis: Subgroup analysis for OS

OS analysis was performed in the subgroups defined by following baseline covariates. Within each category of subgroups, OS between the two treatment groups was compared by the HR estimated by un-stratified Cox regression and the 1-sided p-value from un-stratified log-rank test. The median OS was estimated by the Kaplan-Meier method.

- Prior chemotherapy for metastatic disease (yes or no)
- Hormone receptor status (ER positive or PgR positive or ER negative and PgR negative)
- Visceral disease (yes or no)
- Region (Brazil or France/Spain)
- Prior anthracycline and taxane received in either for non-metastatic or metastatic disease (yes or no)

9.7.1.4 Exploratory analyses

This section outlines additional analyses of PFS that were conducted for exploratory purposes.

9.7.1.4.1 Exploratory analysis: Exploratory subgroup analysis for PFS

In addition to the subgroup analysis described above in Section 9.7.1.3, PFS analysis were performed in the subgroups defined by following baseline covariates also for exploratory purpose. Within each category of subgroups, the HR of PFS was estimated by un-stratified Cox regression and the median PFS was estimated by the Kaplan-Meier method. The primary calculation of PFS was used in this analysis.

Age at enrollment (< 40, ≥ 40 and < 65, ≥ 65 years)

- Prior use of anthracycline (yes or no)
- Prior use of taxane (yes or no)

9.7.1.4.2 Exploratory analysis: Exploratory subgroup analysis for OS

- Age at enrollment (< 40, ≥ 40 and < 65, ≥ 65 years)
- ER Status (Positive or negative)
- PR status (Positive or negative)
- Measurable disease at baseline (yes or no)
- Country (Brazil, Spain or France)
- Prior use of anthracycline (yes or no)
- Prior use of taxane (yes or no)
- Number of metastatic sites (<3 or 3+)

- Months since adjuvant treatment to metastatic diagnosis (<12 or 12+)

9.7.1.5 Sensitivity analyses

The following sensitivity analyses of PFS were performed using the ITT population:

- Un-stratified Cox regression with treatment as single covariate.
- Receipt of a new anticancer therapy or surgery prior to the first documented PD was considered as PFS event. The primary analysis was performed using this alternative calculation of PFS.
- Receipt of a new anticancer treatment or surgery was neither used to censor PFS or was counted as PFS event. The primary analysis was performed using this alternative calculation of PFS.

9.7.1.6 Quality of life analyses

9.7.1.6.1 Quality of life variable: Functional assessment of cancer therapy - Breast (FACT-B) Instrument

The outcome for this variable is described in a separate report (see Section 14.5).

The FACT-B instrument was administered to measure the quality of life (QoL) of patients during study. The FACT-B consists of 5 subscales: physical well-being, social/family well-being, emotional well-being, functional well-being, and a breast cancer subscale. The total FACT-B score is the sum of all its subscales. Higher scores on the FACT-B scales indicate a higher QoL.

The FACT-B endpoints are:

- Change from baseline in total FACT-B score and all subscales to each scheduled visit
- Patient health status at each post-baseline scheduled visit: classified by the estimated minimally important differences (Eton 2004) as below:
    - Health status based on total FACT-B score:
        - Improved if the change from baseline score is ≥ +8,
        - Same if the change from baseline score is between > -8 and < +8,
        - Worsened if the change from baseline score is ≤ -8
    - Health status based on breast cancer subscale score:
        - Improved if the change from baseline score is ≥ +3,
        - Same if the change from baseline score is between > -3 and < +3,
        - Worsened if the change from baseline score is ≤ -3
- Time to health status deterioration in total FACT-B score: This was defined as the number of days from randomization to a decrease in total FACT-B score from baseline by at least 8 points or death whichever occurs first.

- Time to health status deterioration in FACT-B breast cancer subscale score: This was defined as the number of days from randomization to a decrease in FACT-B breast cancer subscale score from baseline by at least 3 points or death whichever occurs first.

9.7.1.6.2 Quality of life variable: Hand-foot reaction and quality of life (HF-QoL) Instrument

The outcome for this variable is described in a separate report (see Section 16.1.12).

The HF-QoL instrument is a new patient-reported outcome (PRO) measure designed to characterize the symptoms of hand-foot reaction and the impact (if any) of these symptoms on the patient's ability to sleep, daily activities, social life, and feelings (mood). The HF-QoL scale includes 48 items covering symptoms of hand-foot skin reaction experienced on the feet, hands or other body areas, and the impact of this skin reaction on the patient's ability to sleep, on the patient's ability to perform daily activities, on social likes and dislikes, and on the patient's feelings. The HF-QoL also includes a feeling thermometer, a question on overall rating of the severity of the skin reaction, and a question on how the severity of the skin reaction has changed since the patient last completed the questionnaire (a global rating of change question).

Subscale scores were to be derived if HF-QoL passed validation, and was then used to compare treatment groups.

9.7.1.7 Safety analyses

The summaries of the safety data were completed for the Valid-for-Safety population.

In addition to summaries of AEs classified according to MedDRA preferred term and system organ class, safety analyses included evaluation of clinically significant laboratory test results and vital signs. The toxicity grade of selected laboratory values was determined using the NCI-CTCAE, Version 3.0.

All summaries and analyses of the safety data were conducted using the Valid-for-Safety population, defined as all patients who were randomized and received any study treatment. For this population, patients were analyzed in the treatment group for which they received therapy. If a patient received the wrong treatment for entire study treatment period, the patient was analyzed in the treatment group for which they received therapy. If a patient received the wrong treatment only for part of study treatment period, the patient was analyzed in the randomized treatment group.

9.7.1.7.1 Adverse events

A treatment-emergent AE was defined as an AE that started after the first dose of study drug or that was seen prior to the start of medication but increased in severity during treatment. A baseline AE was defined as any AE collected after signing informed consent form and before the study drug administration. AEs were coded to system organ class and preferred term using MedDRA. The intensity of AEs was graded using the CTCAE, Version 3.0. For drug relationship, AEs were classified as related or not related to study drug.

The overall incidence of treatment-emergent AEs was presented by MedDRA system organ class and preferred term . Patients were counted at most once for each MedDRA term.
The overall incidence of treatment-emergent AEs was presented separately by severity and by drug relationship. For these presentations, patients were counted at most once for each MedDRA term under the highest severity or the strongest relationship to study drug.

Summaries of the number (%) of patients in each treatment group with at least 1 AE, classified according to MedDRA term, were provided for study treatment-related (capecitabine, and/or sorafenib/placebo) AEs.

The incidence of new onset of treatment emergent AEs by cycles for each treatment group were provided for specific hematologic events (neutropenia, leukopenia, thrombocytopenia, and anemia) and nonhematologic events (nausea, vomiting, diarrhea, fatigue, peripheral neuropathy, rash, and hand-foot skin reaction).

9.7.1.7.2 Deaths and serious adverse events

The incidence of on-study deaths and treatment-emergent SAEs were summarized.
The summary of treatment-emergent SAEs was presented by MedDRA system organ class and preferred term. A summary of study treatment-related (capecitabine, and/or sorafenib/placebo) SAEs were provided. Listings and narratives for all on study deaths and SAEs were provided. A death was considered as occurring on study if it occurred on or after the start of study treatment and no more than 30 days after the last dose of study treatment. Only on-study deaths were summarized at the time of the final analysis of PFS. All death data were summarized at the time of the final OS analysis.

9.7.1.7.3 Adverse events leading to discontinuation of investigational product and/or withdrawal from the study and other significant adverse events

The incidence of AEs leading to discontinuation of 1 or more study drugs were summarized and listed.

9.7.1.7.4 Clinical laboratory evaluations

The laboratory tests collected in this study were HGB, hematocrit, white blood cell count (WBC), neutrophils, lymphocytes, platelets, PT, partial thromboplastin time (PTT), INR, total bilirubin, SGOT (AST), SGPT (ALT), creatinine, BUN, amylase, and lipase. Criteria for grading toxicity evident in the laboratory data based on the NCI CTCAE version 3.0 were available for all tests except hematocrit, PT, and BUN.

The incidence of worst CTCAE toxicity grade any time after the start of study treatment (including unscheduled visits, the follow-up visits, and any data recorded after the last dose of study medication) and the change from baseline (shift table) CTCAE toxicity grade were summarized.

A listing of all patients with laboratory values that show grade 3 or higher CTCAE toxicity was prepared.

9.7.1.7.5 Other safety measures

Results of physical examinations, vital signs data (including heart rate, blood pressure, respiration rate and temperature), and weight was reviewed to identify abnormalities of clinical concern.

For each treatment cycle, vital signs were tabulated and summarized by visit. Both the observed values and changes from baseline were summarized.

9.7.1.8 Other safety analyses: Extent of exposure

Descriptive statistics were calculated for:

- total number of weeks of sorafenib/placebo received
- number of cycles with > 90% of compliance rate with sorafenib/placebo dosing
- average daily dose of sorafenib/placebo, overall and by cycle
- total number of cycles of capecitabine
- average daily dose of capecitabine, overall and by cycle
- number of cycles with > 90% of compliance rate with capecitabine dosing

The number and percentage of patients with modifications (including dose reductions, dose interruption, and dose re-escalations) from the prescribed dosing of each of the study medications (capecitabine, sorafenib/placebo) were summarized by type of dose modification and reason for the dose modification.

9.7.1.9 Pharmacokinetic analyses

Capecitabine and 5-FU plasma concentrations were measured by Northeast Bioanalytical Laboratories, Hamden, CT, using a validated LC/MS/MS assay [NEBA MET064].

Concentrations at 1, 4, and 8 hours Day 14 of Cycle 1 were evaluated. Since the study design permitted only point estimates at these selected time points, PK parameters such as exposure (area under the curve [AUC]), maximum concentration (C_{max}), and T_{max} were not computed. The context for the point estimates in this study was provided by comparison with results obtained from previous studies with comprehensive PK evaluation (REFMAL-122, Bayer Study 10955).

Descriptive statistics: Geometric mean and geometric coefficient of variation (%) for concentrations at 1 and 4 hours post capecitabine dose administration were used for the PK comparisons. Geometric mean was calculated as the n-th root of the product of n numbers: values below the limit of quantitation were denoted with letters and were excluded from the mean. At least 2/3rds of the values had to be numerical for this calculation.

9.7.2 Determination of sample size

The sample size was determined based upon 2 considerations: the requirement for PFS events and the planned accrual rate. The number of PFS events (120) for this study was approximately 25% of that expected for a Phase 3 study. Assuming an exponential

distribution for PFS, a median PFS of 6 months in the placebo group, and 9.2 months in the sorafenib group, and an escalating accrual rate in the first 3 months of the trial to 20 patients per month in subsequent months, a total enrollment of 220 patients was to result in completion of enrollment in approximately 13 months and attainment of the targeted 120 PFS events approximately 17 months after initiation of enrollment (i.e., 4 months after completion of enrollment). The study was not unblinded and the clinical database was not locked before the end of the enrollment.

In this trial, based on 120 PFS events, an observed HR $\leq$ 0.82 would provide evidence that study treatment is effective. The false positive error rate (1-sided p-value) associated with an observed HR of 0.82 is approximately 0.14. Under the alternative hypothesis that the true HR is 0.65, an observed HR of 0.82 has a false negative error rate of approximately 0.10. The false positive error rate (1-sided p-value) associated with an observed HR of 0.70 is approximately 0.025. Furthermore, under the alternative hypothesis that the HR is 0.65, this trial has power of 66% to achieve a 1-sided p-value < 0.025 (corresponding to having an observed HR of 0.70).

Patients were followed until disease progression and for survival until 120 deaths occurred. Treatment assignment for patients remained blinded until the OS analysis.

9.8 Changes in the conduct of the study or planned analysis

There were three amendments to the protocol. The original protocol, Version 1.0, dated 14 Feb 2007, was implemented at 23 sites. Amendment 1 (Version 2.0, dated 20 Jul 2007) and Amendment 2 (Version 3.0, dated 18 Apr 2008) were also implemented at all 23 sites. Amendment 3 (Version 4.0, 15 Jul 2010), which encompassed the treatment-continuation period, was implemented at the 5 sites in Brazil with 7 active patients at the time of the Amendment.

The revisions / clarifications contained in each of the three protocol amendments are outlined in Sections 9.8.1, 9.8.2, and 9.8.3.

The SAP (Version 2.0, dated 13 May 2009, provided in Section 16.1) that was completed prior to unblinding of the study treatment groups for the primary PFS analysis, provided more information and greater detail regarding the planned statistical analyses than was provided in the protocol.

The SAP clarified definitions of derived efficacy variables as well as the sensitivity analyses and subgroup analyses for the efficacy variables that were not described in the protocol.

Modifications to the planned statistical analyses were minimized. This clinical study report provides a detailed explanation for deviations from the planned analyses.

9.8.1 Protocol Amendment 1 (Version 2.0, 20 Jul 2007)

Protocol amendment 1 included the following clarifications and revisions:

AEs and SAEs:
The amendment clarified that the assessment of relationship was to be performed separately for ‘Sorafenib or Placebo’ and ‘Capecitabine’. The SAE reporting period was clarified for

patients who signed the informed consent, but discontinued from the study prior to receiving study treatment.

Dose escalation and dose reductions:
It was clarified that dose escalation in subsequent cycles was not mandatory, but optional. Clarity was provided on when dose reductions were to occur.

Drug dispensing:
Clarity was provided on how drug was to be dispensed to patients, and how blisters of sorafenib/placebo would be presented.

FACT -B:
The timing for patients to complete the FACT-B assessment was clarified.

HFQoL:
A new Section was added to introduce the health related quality of life HF-QoL which was used to compare the effect of sorafenib and capecitabine versus placebo and capecitabine on hand-foot skin reaction symptoms. A new exploratory objective was included to validate the HF-QoL. A new Inclusion Criterion was included to provide clarity regarding requirements for completion of the health related quality of life (HR-QoL) and HF-QoL questionnaires. The procedure for administering the HF-QoL questionnaire to patients was included. Details on the analysis of data from the HF-QoL assessment were included.

Inclusion and exclusion criteria:
Some inclusion and exclusion criteria were revised to provide clarity on the criteria that defined patients who were eligible versus not eligible for study entry.

Sample size:
An increase in the patient sample size from 180 patients to 220 was implemented in order to achieve 120 PFS events in a shorter overall time frame.

Serum phosphate:
Serum Phosphate was included as a safety check, and the time points for assessment were noted.

Monitoring of toxicities:
The amendment clarified that toxicities would be monitored once a week for the first 6 weeks via a call to the patient or a clinic visit as deemed appropriate by the site.

9.8.2 Protocol Amendment 2 (Version 3.0, 18 Apr 2008)

Protocol amendment 2 included the following clarifications and revisions:

AEs and SAEs:
The amendment clarified that all data, including relationship, was captured on the AE case report form page, and that in the electronic data capture system, the SAE form was a subset of the AE case report form. Inconsistencies in reporting requirements for AEs were corrected. It was noted that the IB would be updated in accordance with Bayer/Onyx SOPs.

Concomitant medication:
It was noted that any kind of growth factors could be used during the study.

Data monitoring committee:
The role and responsibilities of DMC were modified.

Dosing
The capecitabine dosing schedule was clarified in the event of a dose delay due to toxicity. It was also clarified that, although capecitabine was to be discontinued due to toxicity, sorafenib/placebo treatment could be continued AND that although sorafenib/placebo was to be discontinued due to toxicity, capecitabine treatment could be continued.

Duration of stable disease:
Duration was clarified as a period of time.

Follow-up:
The protocol was amended to allow a two-week window for the assessments that were required during the Follow-up period (Post-Progression Period).

Inclusion and exclusion criteria:
Some inclusion and exclusion criteria were revised to provide clarity on the criteria (and in some cases, provided new criteria) that defined patients who were eligible versus not eligible for study entry. Specifically, clarifications/revisions were made to Inclusion Criteria 7, 10, and 11, and to Exclusion Criteria 9, 16, 20, and 21.

Laboratory tests:
Clarity was provided on when coagulation laboratory tests were to occur.

Monitoring toxicities:
The amendment specified a requirement for patients to have blood pressure monitoring at a weekly clinic visit (rather than at home) during the first 6 weeks.

RECIST criteria:
The amendment specified radiologic follow-up requirements for patients with bone disease to fulfill requirements for full evaluation of tumor response per modified RECIST criteria. Information was also included regarding the use of a consistent method of assessment for following non-measurable disease.

Statistical methods:
Adjustment for the stratification factors in the analysis were included to reduce the risk of confounding, increase precision of the statistical tests, and account for structure imposed by stratification at randomization.

Storage of study medication:
Additional detail was included regarding storage of sorafenib and matching placebo.

9.8.3 Protocol Amendment 3 (Version 4.0, 18 Apr 2008)

Protocol amendment 3 included the following clarifications and revisions:

Treatment continuation period:

Amendment 3 modified the protocol to allow patients who were receiving treatment with sorafenib and/or capecitabine at the time that the OS results were unblinded, and the sites and the patients were unblinded, to continue to receive the study treatment to which they were

originally assigned at randomization until disease progression occurred or the patients discontinued from the study for any reason. This period of the study was referred to as the "treatment-continuation" phase. An updated informed consent form was to be signed by each patient who was eligible and elected to continue on study during the treatment-continuation period. Assessments of survival were not performed during the treatment-continuation period, safety assessments were conducted per the treating physician's standard practice. Only SAE safety data was collected during this phase, and no prespecified analyses were performed. SAEs were reported to Onyx Drug Safety using paper forms. At the time of discontinuation of the treatment-continuation period, patients did NOT enter a follow-up period, and study medication was no longer provided.

10. Patient groups

This report includes statistical analysis based on data obtained up to and including 27 March 2009, the date at which at least 120 PFS events (disease progression or death, if death occurred before progression) were confirmed to have occurred. The main efficacy focus of this report is the planned final analysis of PFS.

All patients who were randomized to one of the treatment groups form the ITT population that was analyzed for this report. For the analysis of safety, data for all patients who had taken at least 1 dose of study drug were included.

All summary tables are provided in Section 14 of this report. Data listings by center are provided in Appendix 16.2.

10.1.1 Patient enrollment by country and study center

Patient enrollment, by country and by study center, is summarized below in Table 14.

This multinational study was conducted at 24 centers. Twenty-three (23) centers screened patients, and enrolled and randomized at least 1 patient. From a total of 273 patients who were screened, 229 patients were randomized in 3 countries. Among the 229 randomized patients, 112 (49%) were randomized in Brazil, 80 (35%) in Spain, and 37 (16%) in France.

No single center randomized more than 27 (12%) patients in the study. The top 3 enrolling centers were Centro de Pesquisa em Hematologia e Oncologia da Faculdade de Medicina do ABC - CEPHO (Brazil) where 27 (12%) patients were randomized, Institut Claudius Regaud (France) where 25 (11%) patients were randomized, and Hospital Universitario 12 De Octubre (Spain) where 21 (9%) patients were randomized.

Study center was not a stratification factor for randomization, so imbalance between the treatment groups could occur at individual centers, particularly those enrolling small numbers of patients. Due to the large number of study centers and the relatively small number of patients enrolled at most centers, no investigation of potential treatment-by-center interactions was performed, and except for enrollment and disposition data, no summaries of the data by center were provided.

Table 14: Patient Enrollment by Country and Site – ITT Population

Country	Site	Treatment Group	Number of Patients		
			Enrolled	Randomized	Treated
Overall	Overall	Placebo	114	114	112
		Sorafenib	115	115	112
		Not Randomized	44	0	0
Brazil	All centers	Placebo	53	53	51
		Sorafenib	59	59	59
		Not Randomized	42	0	0
France	All centers	Placebo	18	18	18
		Sorafenib	19	19	18
		Not Randomized	0	0	0
Spain	All centers	Placebo	43	43	43
		Sorafenib	37	37	35
		Not Randomized	2	0	0
Brazil	Centro de Pesquisa em Hematologia e Oncologia da Faculdade de Medicina do ABC - CEPHO	Placebo	14	14	14
		Sorafenib	13	13	13
		Not Randomized	15	0	0
France	Institut Claudius Regaud	Placebo	15	15	15
		Sorafenib	10	10	10
		Not Randomized	0	0	0
Spain	Hospital Universitario 12 De Octubre	Placebo	14	14	14
		Sorafenib	7	7	6
		Not Randomized	2	0	0
Brazil	Santa Casa de Misericórdia de Belo Horizonte	Placebo	4	4	4
		Sorafenib	12	12	12
		Not Randomized	8	0	0
Brazil	Fundação Dr. Amaral Carvalho	Placebo	5	5	5
		Sorafenib	10	10	10
		Not Randomized	3	0	0
Brazil	Instituto do Cancer Arnaldo Vieira de Carvalho	Placebo	7	7	7
		Sorafenib	8	8	8
		Not Randomized	5	0	0
Spain	Hospital Universitario Vall D'Hebron	Placebo	7	7	7
		Sorafenib	8	8	8
		Not Randomized	0	0	0

Country	Site	Treatment Group	Number of Patients		
			Enrolled	Randomized	Treated
Spain	Hospital Clinico Universitario De Valencia	Placebo	6	6	6
		Sorafenib	8	8	8
		Not Randomized	0	0	0
Brazil	Hospital São Lucas PUCRS	Placebo	6	6	6
		Sorafenib	6	6	6
		Not Randomized	4	0	0
Spain	Hospital Universitario Arnau De Vilanova	Placebo	5	5	5
		Sorafenib	5	5	5
		Not Randomized	0	0	0
Brazil	Hospital das Clínicas - HCFMUSP	Placebo	5	5	4
		Sorafenib	4	4	4
		Not Randomized	5	0	0
Spain	Instituto Valenciano De Oncologia	Placebo	5	5	5
		Sorafenib	4	4	3
		Not Randomized	0	0	0
Brazil	Instituto de Oncologia Clínica de Piracicaba S/S Ltda	Placebo	5	5	5
		Sorafenib	2	2	2
		Not Randomized	1	0	0
France	Hôpital Saint Louis	Placebo	2	2	2
		Sorafenib	5	5	4
		Not Randomized	0	0	0
Brazil	Instituto do Câncer do Ceará - ICC	Placebo	2	2	2
		Sorafenib	3	3	3
		Not Randomized	0	0	0
Brazil	Hospital Português da Bahia	Placebo	5	5	4
		Sorafenib	1	1	1
		Not Randomized	1	0	0
Spain	Instituto Catalan De Oncologia	Placebo	1	1	1
		Sorafenib	3	3	3
		Not Randomized	0	0	0
France	Institut Jean Godinot	Placebo	0	0	0
		Sorafenib	3	3	3
		Not Randomized	0	0	0

Country	Site	Treatment Group	Number of Patients		
			Enrolled	Randomized	Treated
Spain	Hospital Clinico Univ. De Santiago De Compostela	Placebo	2	2	2
		Sorafenib	1	1	1
		Not Randomized	0	0	0
France	Hôpital Jean Minjoz	Placebo	1	1	1
		Sorafenib	1	1	1
		Not Randomized	0	0	0
Spain	Hospital De La Santa Creu I Sant Pau	Placebo	2	2	2
		Sorafenib	0	0	0
		Not Randomized	0	0	0
Spain	Hospital Mutua De Terrassa	Placebo	0	0	0
		Sorafenib	1	1	1
		Not Randomized	0	0	0
Spain	ICO Hospital Dr. Josep Trueta	Placebo	1	1	1
		Sorafenib	0	0	0
		Not Randomized	0	0	0

Source: Post-text Table 14.1.1 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

10.2 Disposition of patients

Patient disposition, including reasons for discontinuation, is summarized below in Table 15 and Figure 3. Complete tabulated enrollment and disposition data are presented in Section 14 and listings are presented in Appendix 16.2. Listings of individual patient study completion/termination data are presented in Appendix 16.4.

A total of 273 patients were screened for this study. Forty four (16.1%) patients failed screening. Most screen failures (35 patients; 79.5% of screen failures) were due to violation of one or more entry criteria, and 9 patients (20.5% of screen failures) failed screening due to reasons unknown. Patients were evenly divided between the treatment groups: A total of 229 patients were enrolled and randomized to placebo (114 patients) or to sorafenib (115 patients). Of the 229 patients that were randomized, five patients did not receive study treatment. Of the 5 patients that were not treated, 3 patients were randomized to sorafenib (2 patients withdrew consent, and 1 patient died), and 2 patients were randomized to placebo, (1 patient did not receive treatment due to "Investigator decision", and 1 patient not receive treatment for the reason "other"). Thus, 224 patients began double-blind treatment (112 in each treatment group).

The population valid for ITT analyses included the 229 randomized patients (114 in the placebo group and 115 in the sorafenib group). The population valid for the safety analyses included the 224 treated patients (112 patients in each of the groups, placebo and sorafenib). The population valid for per protocol analyses included the patients in the ITT population that

did not have major protocol deviations; thus there were 99 patients in the placebo group and 100 in the sorafenib group (see Figure 3). For the OS analyses, the per protocol analysis included patients in the safety population that did not have major protocol deviations; thus, there were 97 patients in each of the treatment groups (see Figure 3).

Of the 224 patients who did receive study treatment, 165 (72.1%) had discontinued active study treatment at the PFS data cutoff date of 27 March 2009 (90 patients [78.9%] in the placebo + capecitabine group and 75 patients [65.2%] in the sorafenib + capecitabine group). The most common reason for discontinuing active double-blind treatment was PD, recurrent or relapse, which occurred in a higher percentage of patients who discontinued placebo + capecitabine (75 [65.8%]) versus sorafenib + capecitabine (52 [45.2%]). The second most common reason for discontinuing active double-blind treatment was adverse event, which occurred in a slightly lower percentage of patients in the placebo + capecitabine group (8 [7.0%]) versus the sorafenib + capecitabine group (17 [14.8%]). At the time of PFS data cutoff, 27 March 2009, 59 patients (25.8%) were ongoing in the study and receiving active treatment, with a slightly lower percentage of these patients in the placebo + capecitabine group (22 [19.3%]) versus the sorafenib + capecitabine group (37 [32.2%]); the patients receiving active treatment continued to do so after the PFS data cut-off date

Of the 224 patients who did receive study treatment, 216 (94.3%) had discontinued active study treatment as of the OS data cutoff date of 30 June 2010 (112 patients [98.2%] in the placebo + capecitabine group and 104 patients [90.4%] in the sorafenib + capecitabine group). The most common reason for discontinuing active double-blind treatment was PD, which occurred in a higher percentage of patients who discontinued placebo + capecitabine (81.6%) versus sorafenib + capecitabine (63.5%). The second most common reason for discontinuing active double-blind treatment was adverse event, which occurred in a slightly lower percentage of patients in the placebo + capecitabine group (8.8%) versus the sorafenib + capecitabine group (20.0%). At the time of OS data cutoff, 30 June 2010, 8 patients (3.5%) were ongoing in the study and receiving active treatment. None of the active patients were in the placebo + capecitabine group (0%), and 8 (7.0%) of the active patients were in the sorafenib + capecitabine group; the patients receiving active treatment continued to do so after the OS data cut-off date.

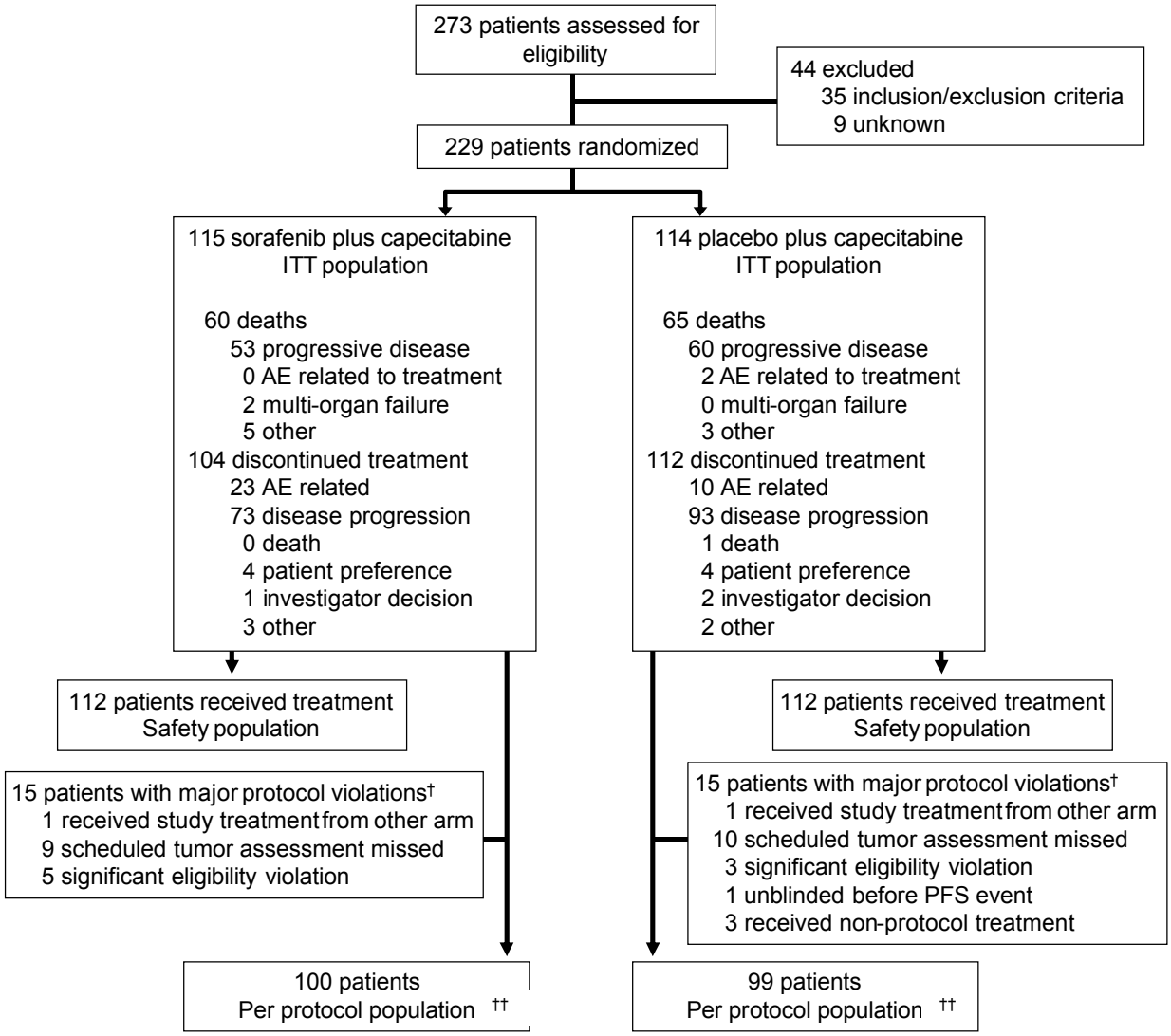
Table 15: Patient Disposition – All Patients

Status	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Screened	---	---	273
Screen failures	---	---	44 (16.1%)
Reason for patient screened but not randomized[1]			
Inclusion/exclusion criteria violation	---	---	35 (12.8%)
Unknown	---	---	9 (3.3%)
Randomized (ITT population)	114	115	229 (83.9%)
Randomized but did not receive treatment[2], n (%)	2 (1.8%)	3 (2.6%)	5 (2.2%)
Reason for patient randomized but not treated			
Consent withdrawn	0 (0%)	2 (1.7%)	2 (0.9%)
Death	0 (0%)	1 (0.9%)	1 (0.4%)
Investigator decision	1 (0.9%)	0 (0%)	1 (0.4%)
Other	1 (0.9%)	0 (0%)	1 (0.4%)
Received treatment[2], n (%)	112 (98.2%)	112 (97.4%)	224 (97.8%)
Discontinuation data from PFS data set:			
Discontinued active treatment[2], n (%)	90 (78.9%)	75 (65.2%)	165 (72.1%)
Reason for discontinuation of active treatment[2], n (%)			
Adverse event	8 (7.0%)	17 (14.8%)	25 (10.9%)
Consent withdrawn	1 (0.9%)	1 (0.9%)	2 (0.9%)
Death	1 (0.9%)	0 (0%)	1 (0.4%)
Disease progression, recurrent or relapse	75 (65.8%)	52 (45.2%)	127 (55.5%)
Investigator decision	1 (0.9%)	1 (0.9%)	2 (0.9%)
Patient requested to stop study drug administration	2 (1.8%)	2 (1.7%)	4 (1.7%)
Other	2 (1.8%)	2 (1.7%)	4 (1.7%)
Discontinued follow-up[2], n (%)	25 (21.9%)	22 (19.1%)	47 (20.5%)
Reason for discontinuation of follow-up[2], n (%)			
Deceased during or within 30 days post-treatment	5 (4.4%)	5 (4.3%)	10 (4.4%)
Deceased beyond 30 days post-treatment	19 (16.7%)	15 (13.0%)	34 (14.8%)
Lost to follow-up	1 (0.9%)	2 (1.7%)	3 (1.3%)
Patients ongoing in study[2], n (%)	87 (76.3%)	90 (78.3%)	177 (77.3%)
Active treatment	22 (19.3%)	37 (32.2%)	59 (25.8%)
Follow-up	65 (57.0%)	53 (46.1%)	118 (51.5%)

Status	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Discontinuation data from OS data set:			
Discontinued active treatment[2], n (%)	112 (98.2%)	104 (90.4%)	216 (94.3%)
Reason for discontinuation of active treatment[2], n (%)			
Adverse event	10 (8.8%)	23 (20.0%)	33 (14.4%)
Consent withdrawn	1 (0.9%)	1 (0.9%)	2 (0.9%)
Death	1 (0.9%)	0 (0%)	1 (0.4%)
Disease progression, recurrent or relapse	93 (81.6%)	73 (63.5%)	166 (72.5%)
Investigator decision	2 (1.8%)	1 (0.9%)	3 (1.3%)
Patient requested to stop study drug administration	3 (2.6%)	3 (2.6%)	6 (2.6%)
Other	2 (1.8%)	3 (2.6%)	5 (2.2%)
Discontinued follow-up[2], n (%)	68 (59.6%)	65 (56.5%)	133 (58.1%)
Reason for discontinuation of follow-up[2], n (%)			
Deceased during or within 30 days post-treatment	5 (4.4%)	7 (6.1%)	12 (5.2%)
Deceased beyond 30 days post-treatment	60 (52.6%)	53 (46.1%)	113 (49.3%)
Consent withdrawn	1 (0.9%)	1 (0.9%)	2 (0.9%)
Lost to follow-up	2 (1.8%)	4 (3.5%)	6 (2.6%)
Patients ongoing in study[2], n (%)	44 (38.6%)	47 (40.9%)	91 (39.7%)
Active treatment	0 (0%)	8 (7.0%)	8 (3.5%)
Follow-up	44 (38.6%)	39 (33.9%)	83 (36.2%)

1 Denominator is the number of patients screened and informed consent signed.
2 Denominator is the number of randomized patients (ITT population).
Abbreviations: n: number; N: number of patients.
Source: Post-text Table 14.1.2 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

Figure 3: Patient Disposition



AE, adverse event; ITT, intent-to-treat; PFS, progression-free survival
*Death occurring during study treatment period or within 30 days post-study treatment
†Defined *a prior*

†† There were 100 and 99 patients in the per protocol population at the time of the PFS analysis data cutoff (27 March 2009).

At the time of the OS analysis data cutoff (30 June 2010), there were 194 patients in the per protocol population (99 patients in the placebo + capecitabine group and 95 patients in the sorafenib + capecitabine group). The 99 patients in the in the placebo + capecitabine group of the OS population per protocol population included the 114 patients that were randomized to that group, minus the 15 patients with major protocol violations. The 95 patients in the in the sorafenib + capecitabine group of the OS population per protocol population included the 115 patients that were randomized to that group, minus the 15 patients with major protocol violations, and minus the 5 patients with significant eligibility violations.

Source: Table 14.1.2 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

10.2.1 Patient disposition by cycle

Table 16 displays the patient disposition by cycle for the PFS data set. Table 17 displays the patient disposition by cycle for the OS data set.

In the PFS data set, a total of 134 patients (61 [53.5%] placebo + capecitabine and 73 [63.5%] sorafenib + capecitabine) received at least 6 cycles of study treatment. Mean duration of treatment was slightly shorter for the placebo + capecitabine group (19.8 weeks) versus the sorafenib sorafenib + capecitabine group (23.3 weeks).

In the OS data set, a total of 139 patients (61 [53.5%] placebo + capecitabine and 73 [63.5%] sorafenib + capecitabine) received at least 6 cycles of study treatment. Mean duration of treatment was shorter for the placebo + capecitabine group (22.7 weeks) versus the sorafenib sorafenib + capecitabine group (33.9 weeks).

Table 16: Patient Disposition by Cycle – ITT Population

Duration of treatment (cycles)	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Not treated	2 (1.8%)	3 (2.6%)	5 (2.2%)
Received 1 cycle	4 (3.5%)	9 (7.8%)	13 (5.7%)
Received 2 cycles	15 (13.2%)	9 (7.8%)	24 (10.5%)
Received 3 cycles	15 (13.2%)	7 (6.1%)	22 (9.6%)
Received 4 cycles	11 (9.6%)	9 (7.8%)	20 (8.7%)
Received 5 cycles	6 (5.3%)	5 (4.3%)	11 (4.8%)
Received ≥6 cycles	61 (53.5%)	73 (63.5%)	134 (58.5%)
Duration of treatment (weeks)[1]			
N	112	112	224
Mean	19.8	23.3	21.5
SD	13.0	14.1	13.6
Median	18	22	19
Min	1	1	1
Max	59	60	60

[1] Stop date of sorafenib/placebo or capecitabine (whichever is later) - start date of sorafenib/placebo or capecitabine (whichever is earlier) + 1; for patients in treatment period, the data cutoff was used as the stop date.

Abbreviations: ITT: intent-to-treat; Max: maximum; Min: minimum; N: number of patients; SD: standard deviation.

Source: Post-text Table 14.1.5 - PFS Data Set: 27 March 2009.

Table 17: Patient Disposition by Cycle – ITT Population

Duration of treatment (cycles)	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Not treated	2 (1.8%)	3 (2.6%)	5 (2.2%)
Received 1 cycle	4 (3.5%)	9 (7.8%)	13 (5.7%)
Received 2 cycles	15 (13.2%)	9 (7.8%)	24 (10.5%)
Received 3 cycles	15 (13.2%)	7 (6.1%)	22 (9.6%)
Received 4 cycles	10 (8.8%)	9 (7.8%)	19 (8.3%)
Received 5 cycles	5 (4.4%)	2 (1.7%)	7 (3.1%)
Received ≥6 cycles	63 (55.3%)	76 (66.1%)	139 (60.7%)
Duration of treatment (weeks)[1]			
N	112	112	224
Mean	22.7	33.9	28.3
SD	16.7	28.5	23.9
Min/Max	1 / 78	1 / 126	1 / 126

[1] Stop date of sorafenib/placebo or capecitabine (whichever is later) - start date of sorafenib/placebo or capecitabine (whichever is earlier) + 1; for patients in treatment period, the data cutoff was used as the stop date.

Abbreviations: ITT: intent-to-treat; Max: maximum; Min: minimum; N: number of patients; SD: standard deviation.

Source: Post-text Table 14.1.5 - OS Data Set: 30 June 2010.

10.2.2 Patient status at analysis

Patient status at analysis is summarized below in Table 18 for the PFS data set and in Table 19 for the OS data set.

For the PFS data set, a total of 69 (30.1%) patients were alive and progression free at the analysis time point; fewer patients were alive and progression free in the placebo + capecitabine group (25 [21.9%]) versus the sorafenib + capecitabine group (44 [38.3%]). A total of 105 (45.9%) patients were alive, but had progressive disease (alive post progression); more patients were alive post progression in the placebo + capecitabine group (61 [53.5 %]) versus the sorafenib + capecitabine group (44 [38.3%]). There were 36 (15.7%) deaths post progression with 20 (17.5%) deaths post progression in the placebo + capecitabine group versus 16 (13.9%) deaths post progression in the sorafenib + capecitabine group. One patient (0.9%) in each treatment group died without progression. Seventeen patients (7.4%) were lost to follow-up: 7 (6.1%) patients in the placebo + capecitabine group and 10 (8.7%) in the sorafenib + capecitabine group.

For the OS data set, a total of 93 (40.6%) patients were alive at the analysis time point, with similar numbers of patients alive in the placebo + capecitabine group (46 [40.4%]) versus the sorafenib + capecitabine group (47 [40.9%]). A total of 126 (55.0%) patients had died, with slightly more deaths occurring in the placebo + capecitabine group (65 [57.0%]) versus the sorafenib + capecitabine group (61 [53.0%]). Ten patients (4.4%) were lost to follow-up:

3 (2.6%) patients in the placebo + capecitabine group and 7 (6.1%) in the sorafenib + capecitabine group.

The differences in numbers of patients lost to follow-up in the PFS versus OS data sets were due to the definitions used for the specific data set. For the PFS data set, lost to follow-up included patients with no adequate post- baseline tumor assessment and/or survival status unknown. For the OS data set, lost to follow-up included patients with treatment or follow-up discontinued due to consent withdrawn or lost to follow-up.

Table 18: Patient Status at Analysis – ITT Population

Status	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Alive progression free	25 (21.9%)	44 (38.3%)	69 (30.1%)
Alive post progression	61 (53.5%)	44 (38.3%)	105 (45.9%)
Death without progression	1 (0.9%)	1 (0.9%)	2 (0.9%)
Death post progression	20 (17.5%)	16 (13.9%)	36 (15.7%)
Lost to follow-up	7 (6.1%)	10 (8.7%)	17 (7.4%)

Abbreviations: N: number of patients; ITT: intent-to-treat.
Note**: Lost to follow-up for the PFS data set** included patients with no adequate post-baseline tumor assessment and/or survival status unknown. *This is a different definition than that used for Lost to follow-up for the OS data set.*
Source: Post-text Table 14.1.3 - PFS Data Set: 27 March 2009.

Table 19: Patient Status at Analysis – ITT Population

Status	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Alive	46 (40.4%)	47 (40.9%)	93 (40.6%)
Dead	65 (57.0%)	61 (53.0%)	126 (55.0%)
Lost to follow-up	3 (2.6%)	7 (6.1%)	10 (4.4%)

Abbreviations: N: number of patients; ITT: intent-to-treat.
Note: **Lost to follow-up for the OS data set** included patients with treatment or follow-up discontinued due to consent withdrawn or lost to follow-up. *This is a different definition than that used for Lost to follow-up for the PFS data set.*
Note: Patients who were randomized but not treated due to reasons other than death, disease progression, consent withdrawn, or lost to follow-up were counted in alive.
Source: Post-text Table 14.1.3 - OS Data Set: 30 June 2010.

10.3 Protocol deviations

All major protocol deviations are listed by patient in Listing 16.1.6. A summary of major protocol deviations at the time of study entry and during study participation reported in ≥ 1% of patients in either treatment group is provided in Table 20.

The treatment groups were comparable in terms of the overall incidence of major protocol deviations and incidence according to type of deviation, with the exception of the incidence of "receipt of protocol-prohibited concomitant therapy before discontinuation of study treatment" which occurred in 3 (2.6%) patients in the placebo + capecitabine group and in 0 (0.0%) patients in the sorafenib + capecitabine group. There were 30 (13.1%) patients with major protocol deviations (15 placebo + capecitabine patients and 15 sorafenib + capecitabine).

The most common major protocol deviations were "scheduled tumor assessment skipped" (10 [8.8%] placebo + capecitabine patients and 9 [7.8%] sorafenib + capecitabine patients) and "significant inclusion/exclusion criteria violation (3 [2.6%] placebo + capecitabine patients, and 5 [4.3%] sorafenib + capecitabine patients).

No major protocol deviation occurred in more than 10% of all patients.

Table 20: Summary of Major Protocol Violations – ITT Population

Status	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Patients with any major protocol violations	15 (13.2%)	15 (13.0%)	30 (13.1%)
Classification of major protocol violations			
Receipt of protocol-prohibited concomitant therapy before discontinuation of study treatment	3 (2.6%)	0 (0.0%)	3 (1.3%)
Receipt of study treatment different from treatment randomized	1 (0.9%)	1 (0.9%)	2 (0.9%)
Scheduled tumor assessment skipped	10 (8.8%)	9 (7.8%)	19 (8.3%)
Significant inclusion/exclusion criteria violation	3 (2.6%)	5 (4.3%)	8 (3.5%)
Unblinding randomization code prior to PFS event	1 (0.9%)	0 (0.0%)	1 (0.4%)

Abbreviations: ITT: intent-to-treat; N: number of patients.
Source: Post-text Table 14.1.6 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

11. Efficacy evaluation

11.1 Data sets analyzed

Refer to Figure 3 in Section 10.2 for a display of patient disposition and numbers of patients included in each distinct analysis population.

In total, 229 patients were randomized to treatment. The analyses presented in this report reflect data accumulated as of two separate data cutoff dates, as follows: 1) the cutoff date for the formal PFS analysis (27 March 2009), and 2) the cutoff date for the formal OS analysis (30 June 2010).

The primary and secondary efficacy analyses described were based on the ITT population, consisting of all 229 randomized patients (114 patients in the placebo + capecitabine group and 115 patients in the sorafenib + capecitabine group). Patients were included in the ITT population according to the treatment group to which they were randomized. Additional efficacy analyses were conducted for the PFS and OS endpoints using the per-protocol population, which included all patients in the ITT population for the PFS analysis and the Safety population for the OS analysis that did not have major protocol violations (15 patients in each treatment group had major protocol violations). The per protocol population for the PFS analysis included 199 of the 229 patients that were randomized (99 patients in the placebo + capecitabine group and 100 patients in the sorafenib + capecitabine group).

The safety analyses described in Section 12 were based on the safety population, consisting of 224 patients (out of the total of 229 randomized patients) who were randomized and received at least 1 dose of study treatment. Five patients were randomized but never received any treatment and were not considered valid for safety analysis. Patients were included in the safety population according to the treatment they received.

11.2 Demographic and other baseline characteristics

Table 21 displays demographic characteristics by treatment group for the entire ITT population. Of the 229 patients in the ITT population, 228 patients (99.6%) were women, and 196 patients (85.6%) were Caucasian. Mean age at enrollment was 55.2 years (range 29 to 80 years). The treatment groups appeared similar with regard to the demographic characteristics.

Table 21: Demographics and Baseline Characteristics – ITT Population

Status	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Age at enrollment (yrs)			
N	114	115	229
Mean age (SD)	55.4 (11.9)	55.1 (11.3)	55.2 (11.6)
Min / Max	30 / 80	29 / 79	29 / 80
Age at enrollment category (yrs)			
N	114	115	229
<40	11 (9.6%)	7 (6.1%)	18 (7.9%)
40-64	76 (66.7%)	81 (70.4%)	157 (68.6%)
65-74	19 (16.7%)	23 (20.0%)	42 (18.3%)
≥75	8 (7.0%)	4 (3.5%)	12 (5.2%)
Gender			
N	114	115	229
Male	1 (0.9%)	0 (0.0%)	1 (0.4%)
Female	113 (99.1%)	115 (100%)	228 (99.6%)
Race			
N	114	115	229
Caucasian	98 (86.0%)	98 (85.2%)	196 (85.6%)
Black	7 (6.1%)	5 (4.3%)	12 (5.2%)
Asian	0 (0.0%)	2 (1.7%)	2 (0.9%)
American Indian or Native Alaskan	1 (0.9%)	0 (0.0%)	1 (0.4%)
Mestizo	7 (6.1%)	6 (5.2%)	13 (5.7%)
Mulatto	0 (0.0%)	4 (3.5%)	4 (1.7%)
Other	1 (0.9%)	0 (0.0%)	1 (0.4%)
Weight (kg)			
N	112	114	226
Mean (SD)	67.3 (12.6)	66.6 (13.4)	66.9 (13.0)
Min / max	37 / 116	42 / 103	37 /116
BSA (m^2)			
N	111	113	224
Mean (SD)	1.7 (0.1)	1.7 (0.2)	1.7 (0.2)
Min / max	1.2 / 2.1	1.3 / 2.2	1.2 / 2.2

Abbreviations: ITT: intent-to-treat; max: maximum; min: minimum; N: number of patients; SD: standard deviation.
Source: Post-text Tables 14.1.7 and 14.1.8 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

11.2.1 Baseline disease characteristics

All patients in this study had a diagnosis of locally advanced or metastatic breast cancer. Table 22 displays baseline disease characteristics by treatment group for the entire ITT population. The treatment groups appeared generally comparable with regard to the baseline disease characteristics.

Baseline ECOG performance status was 0 for 156 (68.1%) patients overall and 1 for 68 (29.7%) patients overall. The majority of patients (191 [83.4%]) had measureable disease at baseline.

At initial diagnosis, most of the patients had been diagnosed with Stage II disease (90, 39.3%), or with Stage III disease (96 [41.9%]). Twenty four (10.5%) patients were diagnosed with Stage IV disease, 17 (7.4%) patients were diagnosed with Stage I disease, and 2 (0.9%) patients had missing information.

At the time of enrollment, the majority of patients (208 [90.8%]) had Stage IV disease and the remaining patients (20 [8.7%]) had Stage IIIB or IIIC disease; 1 patient had missing information.

The mean time since initial diagnosis was slightly lower for the for the placebo + capecitabine group (63.9 months [range 1 to 278 months]), versus the sorafenib + capecitabine group (71.0 months [range 6 to 231 months]) for the sorafenib + capecitabine group.

Table 22: Baseline Disease Characteristics – ITT Population

	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
ECOG Performance Status			
0	77 (67.5%)	79 (68.7%)	156 (68.1%)
1	34 (29.8%)	34 (29.6%)	68 (29.7%)
≥2	1 (0.9%)	1 (0.9%)	2 (0.9%)
Missing	2 (1.8%)	1 (0.9%)	3 (1.3%)
Measurable disease			
Yes	96 (84.2%)	95 (82.6%)	191 (83.4%)
No	17 (14.9%)	20 (17.4%)	37 (16.2%)
Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Stage of disease at initial diagnosis			
Stage I	9 (7.9%)	8 (7.0%)	17 (7.4%)
Stage II	42 (36.8%)	48 (41.7%)	90 (39.3%)
Stage III	47 (41.2%)	49 (42.6%)	96 (41.9%)
Stage IV	14 (12.3%)	10 (8.7%)	24 (10.5%)
Missing	2 (1.8%)	0 (0%)	2 (0.9%)
Stage of disease at enrollment			
Stage IIIB or IIIC	9 (7.9%)	11 (9.6%)	20 (8.7%)
Stage IV	104 (91.2%)	104 (90.4%)	208 (90.8%)
Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Months since initial diagnosis			
N	113	115	228
Mean (SD)	63.9 (58.6)	71.0 (52.6)	67.5 (55.6)
Min / Max	1 / 278	6 / 231	1 / 278

Note: For vital signs and ECOG, the last measurement prior to study treatment start for patients treated and the last measurement prior to randomization date for patients untreated was used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; max: maximum; min: minimum; N: number of patients; SD: standard deviation.
Source: Post-text Table 14.1.8 - PFS Data Set: 27 March 2009.

11.2.1.1 Baseline characteristics: metastasis

Table 23 displays baseline characteristics of the patients' metastases. During the randomization process, patients were stratified by site of metastatic disease: visceral disease versus nonvisceral (osseous or soft tissue) disease. Of the 229 patients in the ITT population, 171 (74.7%) patients had visceral disease and 58 (25.3%) patients had nonvisceral disease. The 171 patients with visceral disease were stratified as 84 (73.7%) patients in the placebo + capecitabine group and 87 (75.7%) patients in the sorafenib + capecitabine group.
The 58 patients with nonvisceral disease were stratified as 30 (26.3%) patients in the placebo + capecitabine group and 28 (24.3%) patients in the sorafenib + capecitabine group. Thus, the disease status was similar between the treatment groups in this study, with similar percentages of patients with visceral and nonvisceral disease in each treatment group.

The baseline characteristics were generally similar between treatment group when comparing the number of metastatic sites, sites of metastases, and brain metastases. The mean for "months since metastatic diagnosis" was slightly higher for the placebo + capecitabine group (23.1 months) versus the sorafenib + capecitabine group (19.4 months). The percentage of patients with had ≥ 24 months from adjuvant treatment to recurrence (or metastatic diagnosis) was slightly lower for patients in the placebo + capecitabine group (45 [39.5%]) versus the sorafenib + capecitabine group (57 [49.6%]).

Table 23: Baseline Characteristics of Metastasis – ITT Population

Characteristic	Criteria	Treatment Group		
		Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Months since metastatic diagnosis	N	113	115	228
	Mean (SD)	23.1 (31.3)	19.4 (22.2)	21.3 (21.3)
	Min / Max	0 / 176	0 / 113	0 / 176
	0 - 12 Months	56 (49.1%)	61 (53.0%)	117 (51.1%)
	>12 - <24 Months	21 (18.4%)	15 (13.0%)	36 (15.7%)
	≥24 Months	36 (31.6%)	39 (33.9%)	75 (32.8%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Months from adjuvant treatment to recurrence or metastatic diagnosis	0 - 12 Months	50 (43.9%)	37 (32.2%)	87 (38.0%)
	>12 - <24 Months	15 (13.2%)	16 (13.9%)	31 (13.5%)
	≥24 Months	45 (39.5%)	57 (49.6%)	102 (44.5%)
	Missing	4 (3.5%)	5 (4.3%)	9 (3.9%)
Location of metastatic sites	Non-visceral	30 (26.3%)	28 (24.3%)	58 (25.3%)
	Visceral	84 (73.7%)	87 (75.7%)	171 (74.7%)
Number of metastatic sites	1	34 (29.8%)	31 (27.0%)	65 (28.4%)
	2	45 (39.5%)	41 (35.7%)	86 (37.6%)
	3	23 (20.2%)	36 (31.3%)	59 (25.8%)
	>3	11 (9.6%)	7 (6.1%)	18 (7.9%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Sites of metastasis	Ascites	1 (0.9%)	0 (0%)	1 (0.4%)
	Bone	67 (58.8%)	66 (57.4%)	133 (58.1%)
	Breast	10 (8.8%)	11 (9.6%)	21 (9.2%)
	CNS (brain)	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Chest wall	9 (7.9%)	7 (6.1%)	16 (7.0%)
	Liver	39 (34.2%)	41 (35.7%)	80 (34.9%)
	Lung	42 (36.8%)	53 (46.1%)	95 (41.5%)
	Lymph node	49 (43.0%)	38 (33.0%)	87 (38.0%)
	Pleural effusion	3 (2.6%)	12 (10.4%)	15 (6.6%)
	Skin	11 (9.6%)	16 (13.9%)	27 (11.8%)
	Other	5 (4.4%)	6 (5.2%)	11 (4.8%)
Brain metastasis	Yes	1 (0.9%)	1 (0.9%)	2 (0.9%)
	No	112 (98.2%)	114 (99.1%)	226 (98.7%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)

Abbreviations: ITT: intent-to-treat; max: maximum; min: minimum; N: number of patients; SD: standard deviation.
Source: Post-text Table 14.1.8 - PFS Data Set: 27 March 2009.

11.2.1.2 Baseline characteristics: receptors

Table 24 displays baseline characteristics of the patients receptors for patients in the ITT population. Patients' estrogen and progesterone receptors were evaluated as positive, negative, unknown, or missing. Patients' hormone receptor status was evaluated as 1) ER-PgR-, 2) ER+ PgR-, 3) ER- PgR+, 4) ER+ PgR+, 5) unknown, or 6) missing.

Of the 229 patients in the ITT population, 168 (73.4%) patients had positive estrogen receptors and 58 (25.3%) patients had negative estrogen receptors, 2 (0.9%) patients were evaluated as unknown and 1 patient (0.4%) was evaluated as having missing information. The percentage of patients with positive estrogen receptors was slightly lower in the placebo + capecitabine group (77 [67.5%]) versus the sorafenib + capecitabine group (91 [79.1%]).

Of the 229 patients in the ITT population, 117 (51.1%) patients had positive progesterone receptors and 103 (45.0%) patients had negative progesterone receptors, 8 (3.5%) patients were evaluated as unknown, and 1 (0.4%) patient was evaluated as having missing information. The percentage of patients with positive progesterone receptors was slightly lower in the placebo + capecitabine group (51 [44.7%]) versus the sorafenib + capecitabine group (66 [57.4%]).

A hormone receptor status of ER+ PgR+ was the most common, occurring in 112 (48.9%) of the 229 patients. Fifty three (23.1%) patients had a hormone receptor status of ER-PgR-, 50 (21.8%) patients had a hormone receptor status of ER+PgR-, 5 (2.2%) patients had a hormone receptor status of ER-PgR+, 8 (3.5%) patients were evaluated as unknown, and 1 (0.4%) patient was evaluated as having missing information.

The baseline characteristics were generally similar between treatment groups when comparing the hormone receptor status. The hormone receptor status of ER-PgR- was slightly higher for the placebo + capecitabine group (33 [28.9%]) versus the sorafenib + capecitabine group (20 [17.4%]). The hormone receptor status of ER+PgR+ was slightly lower for the placebo + capecitabine group (49 [43.0%]) versus the sorafenib + capecitabine group (63 [54.8%]).

Table 24: Baseline Receptor Characteristics – ITT Population

	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
Estrogen receptor			
Positive	77 (67.5%)	91 (79.1%)	168 (73.4%)
Negative	35 (30.7%)	23 (20.0%)	58 (25.3%)
Unknown	1 (0.9%)	1 (0.9%)	2 (0.9%)
Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Progesterone receptor			
Positive	51 (44.7%)	66 (57.4%)	117 (51.1%)
Negative	60 (52.6%)	43 (37.4%)	103 (45.0%)
Unknown	2 (1.8%)	6 (5.2%)	8 (3.5%)
Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Hormone receptor status[1]			
ER-, PgR-	33 (28.9%)	20 (17.4%)	53 (23.1%)
ER+, PgR-	27 (23.7%)	23 (20.0%)	50 (21.8%)
ER-, PgR+	2 (1.8%)	3 (2.6%)	5 (2.2%)
ER+, PgR+	49 (43.0%)	63 (54.8%)	112 (48.9%)
Unknown	2 (1.8%)	6 (5.2%)	8 (3.5%)
Missing	1 (0.9%)	0 (0%)	1 (0.4%)

Note: Unknown = Either estrogen receptor status or progesterone receptor status unknown.
Abbreviations: ER: estrogen receptor; ITT: intent-to-treat; N: number of patients; PgR: progesterone receptor.
Source: Post-text Table 14.1.8 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

11.2.1.3 Baseline characteristics: FACT-B

Table 25 displays patients' baseline characteristics for Functional assessment of cancer therapy - Breast cancer (FACT-B). The mean FACT-B total score for all 229 patients in the ITT population was 98.5, and the range was 40 to 136. The mean FACT-B breast cancer subscale score for all 229 patients was 22.9, and the range was 6 to 36.

The baseline characteristics were similar between treatment groups when comparing the FACT-B total score and the mean FACT-B breast cancer subscale score.

Table 25: Baseline FACT-B Characteristics – ITT Population

	Treatment Group		
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Total N=229
FACT-B total score			
N	108	109	217
Mean (SD)	99.9 (16.7)	97.1 (21.0)	98.5 (19.0)
Median	100	99	100
Min / Max	62 / 136	40 / 130	40 / 136
FACT-B breast cancer subscale score			
N	110	110	220
Mean (SD)	23.2 (5.2)	22.6 (6.1)	22.9 (5.7)
Median	24	23	23
Min / Max	12 / 35	6 / 36	6 / 36

Abbreviations: ITT: intent-to-treat; max: maximum; min: minimum; N: number of patients; SD: standard deviation.
Source: Post-text Table 14.1.8 - PFS Data Set: 27 March 2009.

11.2.2 Prior anticancer therapy for non-metastatic or metastatic disease

Protocol Inclusion Criterion 4 stated that patients were to have "failed taxane and an anthracycline-containing chemotherapy regimen or for whom anthracycline therapy is not indicated". This criterion was interpreted by the sites as two separate inclusion criteria, and thus, patients included in the study had failed taxane and an anthracycline-containing chemotherapy regimen, OR patients had received an alternative therapy when anthracycline therapy was not indicated. In addition, per protocol, patients were allowed to receive one prior chemotherapy for locally advanced or metastatic breast cancer, and were also allowed to receive prior hormonal therapy for locally advanced or metastatic disease and/or prior radiation therapy.

A summary of prior anticancer therapies and other cancer treatments for non-metastatic disease is provided in Table 26, and a summary of prior anticancer therapies and other cancer treatments for metastatic disease is provided in Table 27.

Prior anticancer therapy for non-metastatic disease included prior surgery undergone by 195 (85.2%) patients, prior radiotherapy received by 159 (69.4%) patients, prior endocrine therapy received by 125 (54.6%) patients, and prior chemotherapy received by 182 (79.5%) patients. These prior anticancer therapies for non-metastatic disease were received in comparable percentages in each treatment group.

The most common type of prior chemotherapy received for non-metastatic disease was prior anthracycline therapy, which was received by 160 (87.9%) of the 182 patients that received prior chemotherapy. The second most common type of prior chemotherapy received for non-metastatic disease was adjuvant chemotherapy, which was received by 143 (78.6%) of the 182 patients that received prior chemotherapy. The treatment groups appeared similar with regard to the usage of prior chemotherapy for non-metastatic disease.

Prior anticancer therapy for metastatic disease included prior surgery undergone by 38 (16.6%) patients, prior radiotherapy received by 62 (27.1%) patients, prior endocrine therapy received by 133 (58.1%) patients, and prior chemotherapy received by 116 (50.7%) patients. The prior anticancer therapies for metastatic disease of prior surgery, prior radiotherapy, and prior endocrine therapy were received in generally comparable percentages in each treatment group. The percentage of patients who received prior chemotherapy for metastatic disease was slightly lower in the placebo + capecitabine group (51 [44.7%]) versus the sorafenib + capecitabine group (65 [56.5%]).

The most common type of prior chemotherapy received for metastatic disease was prior taxane therapy, received by 68 (58.6%) of the 116 patients that received prior chemotherapy. The second most common type of prior chemotherapy received for metastatic disease was anthracycline therapy, received by 59 (50.9%) of the 116 patients that received prior chemotherapy. The treatment groups appeared similar with regard to the usage of prior anthracycline therapy. The percentage of patients who received prior taxane therapy for metastatic disease was slightly lower in the placebo + capecitabine group (28 [54.9%]) versus the sorafenib + capecitabine group (31 [47.7%]).

Table 26: Prior Therapy for Non-metastatic Disease – ITT Population

	Treatment Group		
	Placebo + Capecitabine N=114	**Sorafenib + Capecitabine N=115**	**Total N=229**
Prior surgery	**95 (83.3%)**	**100 (87.0%)**	**195 (85.2%)**
Prior radiotherapy	**76 (66.7%)**	**83 (72.2%)**	**159 (69.4%)**
Prior endocrine therapy	**58 (50.9%)**	**67 (58.3%)**	**125 (54.6%)**
Prior chemotherapy	**89 (78.1%)**	**93 (80.9%)**	**182 (79.5%)**
Type of prior chemotherapy			
N	89 (100%)	93 (100%)	182 (100%)
Adjuvant	70 (78.7%)	73 (78.5%)	143 (78.6%)
Neo-adjuvant	39 (43.8%)	44 (47.3%)	83 (45.6%)
Taxane[1]	42 (47.2%)	36 (38.7%)	78 (42.9%)
Anthracycline[1]	80 (89.9%)	80 (86.0%)	160 (87.9%)
Anthracycline dose (mg/m^2)			
N	74	80	154
Mean (SD)	330.9 (177.8)	340.3 (176.0)	335.7 (176.4)
Median	300	300	300
Min / Max	60 / 876	36 / 800	36 / 876

Abbreviations: ITT: intent-to-treat; max: maximum; mg/m^2: milligrams per meter squared; min: minimum; N: number of patients; SD: standard deviation.

Source: Post-text Table 14.1.9 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

1:. Patients included in the study had failed taxane and an anthracycline-containing chemotherapy regimen, or had received an alternative therapy when anthracycline therapy was not indicated (refer to footnote for Inclusion Criterion #4 in Section 9.3.1).

Table 27: Prior Therapy for Metastatic Disease – ITT Population

	Treatment Group		
	Placebo + Capecitabine N=114	**Sorafenib + Capecitabine N=115**	**Total N=229**
Prior surgery	**23 (20.2%)**	**15 (13.0%)**	**38 (16.6%)**
Prior radiotherapy	**31 (27.2%)**	**31 (27.0%)**	**62 (27.1%)**
Prior endocrine therapy	**66 (57.9%)**	**67 (58.3%)**	**133 (58.1%)**
Prior chemotherapy	**51 (44.7%)**	**65 (56.5%)**	**116 (50.7%)**
Number of chemotherapy regimens			
0	62 (54.4%)	50 (43.5%)	112 (48.9%)
1	51 (44.7%)	65 (56.5%)	116 (50.7%)
Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Type of prior chemotherapy			
N	51 (100%)	65 (100%)	116 (100%)
Taxane	28 (54.9%)	40 (61.5%)	68 (58.6%)
Anthracycline	28 (54.9%)	31 (47.7%)	59 (50.9%)
Anthracycline dose (mg/mg^2)			
N	28	30	58
Mean (SD)	326.8 (186.1)	311.0 (178.5)	318.6 (180.8)
Median	300	300	300
Min / Max	75 / 960	60 / 900	60 / 960

Abbreviations: ITT: intent-to-treat; max: maximum; mg/m^2: milligrams per meter squared; min: minimum; N: number of patients; SD: standard deviation.
Source: Post-text Table 14.1.10 - PFS Data Set: 27 March 2009.

11.2.3 Medical history

One or more prior medical findings were noted for all of the 229 (100.0%) patients in their history. The treatment groups appeared similar with regard to the presence of prior medical findings. Post-text Tables displaying the physical examination and medical history findings by patient are located in Appendix 16.2.

11.2.4 Concomitant medications

All concomitant medications were coded using the World Health Organization (WHO) medication dictionary. By-patient Listings of concomitant and post-treatment anti-cancer medications, classified according to the anatomical-therapeutic-chemical (ATC) classification, are provided in Appendix 16.2.

11.2.4.1 Concomitant anti-cancer medication/therapy

During the course of the study (at any time on or after the start date), patients were not allowed to receive concomitant anti-cancer therapy, including chemotherapy, hormonal therapy, radiation therapy, surgery, immunotherapy, biological therapy, or tumor

embolization. Three (2.7%) patients received concomitant anti-cancer therapy. The 3 patients were in the placebo + capecitabine treatment group and all 3 patients received radiotherapy.

Table 28: Concomitant Anti-Cancer Medication/Therapy – Safety Population

	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Radiotherapy	**3 (2.7%)**	**0 (0.0%)**
Surgery	**0 (0.0%)**	**0 (0.0%)**
Medication	**0 (0.0%)**	**0 (0.0%)**

Note: A frequency in this table represents the number of patients who took the corresponding therapy/medication anytime during the study treatment.
Source: Post-text Table 14.1.13 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010, respectively.

11.2.4.2 Post-treatment anti-cancer medication/therapy

Post-treatment anti-cancer medications and/or therapies were recorded for patients after discontinuation of the study treatment. However, for the patients who had disease progression, recording post-treatment anti-cancer medications and/or therapies was not required. A summary of post-treatment anti-cancer medications and therapies that were received by ≥2% of patients in either treatment group, for the safety population, is provided in Table 29 for the PFS data set, and in Table 30 for the OS data set.

In the PFS data set, post-treatment anti-cancer medication was received by 34 (30.4%) of the 112 patients in the placebo + capecitabine group and in 31 (27.7%) of the 112 patients in the sorafenib + capecitabine group. Post-treatment anti-cancer radiotherapy was received by 4 (3.6%) of patients in the placebo + capecitabine group and in 5 (4.5%) of patients in the sorafenib + capecitabine group. One (0.9%) patient in the sorafenib + capecitabine group underwent post-treatment anti-cancer surgery. The most common post-treatment anti-cancer medications that were received were antineoplastic and immunomodulating agents / taxanes, which were received by 18 (16.1%) patients in the placebo + capecitabine group and in 14 (12.5%) patients in the sorafenib + capecitabine group. The second most common post-treatment anti-cancer medications that were received were antineoplastic and immunomodulating agents / pyrimidine analogues, which were received by 18 (16.1%) patients in the placebo + capecitabine group and in 10 (8.9%) patients in the sorafenib + capecitabine group.

In the OS data set, post-treatment anti-cancer medication was received by 49 (43.8%) of the 112 patients in the placebo + capecitabine group and in 50 (44.6%) of the 112 patients in the sorafenib + capecitabine group. Post-treatment anti-cancer radiotherapy was received by 5 (4.5%) of patients in the placebo + capecitabine group and in 8 (7.1%) of patients in the sorafenib + capecitabine group. One (0.9%) patient in the sorafenib + capecitabine group underwent post-treatment anti-cancer surgery. The most common post-treatment anti-cancer

medications that were received were antineoplastic and immunomodulating agents / taxanes, which were received by 30 (26.8%) patients in the placebo + capecitabine group and in 24 (21.4%) patients in the sorafenib + capecitabine group. The second most common post-treatment anti-cancer medications that were received were antineoplastic and immunomodulating agents / pyrimidine analogues, which were received by 28 (25.0%) patients in the placebo + capecitabine group and in 21 (18.8%) patients in the sorafenib + capecitabine group.

Table 29: Post-Treatment Anti-Cancer Medications/Therapy Received by ≥ 2% of Either Treatment Group – Safety Population *(PFS data)*

Concomitant Therapy / Medication	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Radiotherapy (non-medication)	**4 (3.6%)**	**5 (4.5%)**
Surgery	**0 (0.0%)**	**1 (0.9%)**
Medication	**34 (30.4%)**	**31 (27.7%)**
Antineoplastic and immunomodulating agents; monoclonal antibodies	**5 (4.5%)**	**1 (0.9%)**
Avastin [bevacizumab]	3 (2.7%)	0 (0.0%)
Bevacizumab	1 (0.9%)	1 (0.9%)
Trastuzumab	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; platinum compounds	**10 (8.9%)**	**1 (0.9%)**
Carboplatin	3 (2.7%)	1 (0.9%)
Cisplatin	8 (7.1%)	0 (0.0%)
Antineoplastic and immunomodulating agents; pyrimidine analogues	**18 (16.1%)**	**10 (8.9%)**
5-fu [flurouracil]	0 (0.0%)	1 (0.9%)
Capecitabine	6 (5.4%)	7 (6.3%)
Gemcitabine	9 (8.0%)	2 (1.8%)
Gemzar [gemcitabine]	4 (3.6%)	0 (0.0%)
Antineoplastic and immunomodulating agents; taxanes	**18 (16.1%)**	**14 (12.5%)**
Docetaxel	6 (5.4%)	2 (1.8%)
Paclitaxel	7 (6.3%)	8 (7.1%)
Taxol [paclitaxel]	4 (3.6%)	5 (4.5%)
Taxotere [docetaxel]	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; vinca alkaloids and analogues	**2 (1.8%)**	**5 (4.5%)**
Navelbine [vinorelbine]	2 (1.8%)	3 (2.7%)
Vinorelbine	0 (0.0%)	2 (1.8%)

Note: A frequency in this table represents the number of patients who took the corresponding therap y/medication after discontinuation of the study treatment.
Note: Therapy with medications classified by WHO-DD are only included under "Medication Classified by WHO-DD".
Source: Post-text Table 14.1.14 - PFS Data Set : 27 March 2009.

Table 30: Post-Treatment Anti-Cancer Medications/Therapy Received by ≥ 2% of Either Treatment Group – Safety Population *(OS data)*

Concomitant Therapy / Medication	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Radiotherapy (non-medication)	**5 (4.5%)**	**8 (7.1%)**
Surgery	**0 (0.0%)**	**1 (0.9%)**
Medication	**49 (43.8%)**	**50 (44.6%)**
Antineoplastic and immunomodulating agents; anti-estrogens	**4 (3.6%)**	**5 (4.5%)**
Faslodex [fulvestrant]	3 (2.7%)	2 (1.8%)
Fulvestrant	1 (0.9%)	1 (0.9%)
Tamoxifen	0 (0.0%)	2 (1.8%)
Antineoplastic and immunomodulating agents; enzyme inhibitors	**9 (8.0%)**	**11 (9.8%)**
Anastrozole	3 (2.7%)	3 (2.7%)
Arimidex [anastrozole]	4 (3.6%)	5 (4.5%)
Aromasine (exemestane)	1 (0.9%)	0 (0.0%)
Exemestane	0 (0.0%)	2 (1.8%)
Letrozole	1 (0.9%)	1 (0.9%)
Antineoplastic and immunomodulating agents; folic acid analogues	**5 (4.5%)**	**2 (1.8%)**
Methotrexate	5 (4.5%)	2 (1.8%)
Antineoplastic and immunomodulating agents; monoclonal antibodies	**6 (5.4%)**	**2 (1.8%)**
Avastin [bevacizumab]	3 (2.7%)	0 (0.0%)
Bevacizumab	2 (1.8%)	2 (1.8%)
Trastuzumab	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; nitrogen mustard analogues	**8 (7.1%)**	**3 (2.7%)**
Cyclophosphamide	7 (6.3%)	3 (2.7%)
Genuxal (cyclophosphamide)	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; platinum compounds	**16 (14.3%)**	**5 (4.5%)**
Carboplatin	4 (3.6%)	3 (2.7%)
Cisplatin	14 (12.5%)	2 (1.8%)
Oxaliplatin	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; progestogens	**1 (0.9%)**	**3 (2.7%)**
Megestat (megestrol)	1 (0.9%)	3 (2.7%)

Concomitant Therapy / Medication	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Antineoplastic and immunomodulating agents; pyrimidine analogues	**28 (25.0%)**	**21 (18.8%)**
5-fu [flurouracil]	4 (3.6%)	3 (2.7%)
Ara-c (cytarabine)	0 (0.0%)	1 (0.9%)
Capecitabine	6 (5.4%)	7 (6.3%)
Gemcitabine	14 (12.5%)	8 (7.1%)
Gemzar [gemcitabine]	9 (8.0%)	2 (1.8%)
Antineoplastic and immunomodulating agents; taxanes	**30 (26.8%)**	**24 (21.4%)**
Docetaxel	7 (6.3%)	4 (3.6%)
Paclitaxel	11 (9.8%)	11 (9.8%)
Taxol [paclitaxel]	8 (7.1%)	7 (6.3%)
Taxotere [docetaxel]	8 (7.1%)	4 (3.6%)
Antineoplastic and immunomodulating agents; vinca alkaloids and analogues	**9 (8.0%)**	**12 (10.7%)**
Navelbine [vinorelbine]	8 (7.1%)	7 (6.3%)
Vinorelbine	1 (0.9%)	5 (4.5%)

Note: A frequency in this table represents the number of patients who took the corresponding therap y/medication after discontinuation of the study treatment.
Source: Post-text Table 14.1.14 - OS Data Set: 30 June 2010.

11.3 Efficacy analysis

The primary efficacy variable of this study was PFS based on the assessment by the investigator. PFS was measured from the date of randomization to the date of first observed disease progression (radiological or clinical, whichever was earlier) or the date of death due to any cause (if before progression). The final analysis for PFS in the study performed at the data cutoff date of 27 March 2009, when 142 progression events were observed in the ITT population. At this time, 125 progression events had occurred in the per protocol population. Patients alive without documented tumor progression at the time of data cutoff were censored at their last tumor assessment before any non-protocol anti-cancer therapies were received.

The secondary endpoints of the study were OS, TTP, ORR, and duration of overall response. Quality of life (FACT-B and HF-QoL) endpoints were also analyzed and presented in separate reports (included in 16.1.11).

Survival was measured from the date of randomization to death due to any cause. Duration of overall response was measured from the first documentation of complete or partial response (whichever status was recorded first) until the first date that progressive disease or death was objectively documented.

11.3.1 Analysis of progression-free survival: ITT population

Table 31 displays a summary of the analysis of PFS for the ITT population according to modified RECIST criteria. Figure 4 displays a Kaplan-Meier curve for PFS by treatment group.

A total of 142 patients had progressed or died as of the data cutoff date of 27 March 2009 based on the independent review. The 142 events of progression or death included 80 (70.2%) patients in the placebo + capecitabine group and 62 (53.9%) patients in the sorafenib + capecitabine group. The number of censored patients was lower in the placebo + capecitabine group (34 [29.8%]) versus the sorafenib + capecitabine group (53 [46.1%]).

The median PFS was 126 days (95% CI, 93, 168) for the placebo + capecitabine group and 194 days (95% CI, 161, 237) for the sorafenib + capecitabine group. The prespecified significance level for the analysis of PFS was 0.14, thus the observed difference between the treatment groups with 1-sided P-value of 0.0006 (from stratified log-rank test) was significant at the study significance level of 0.14.

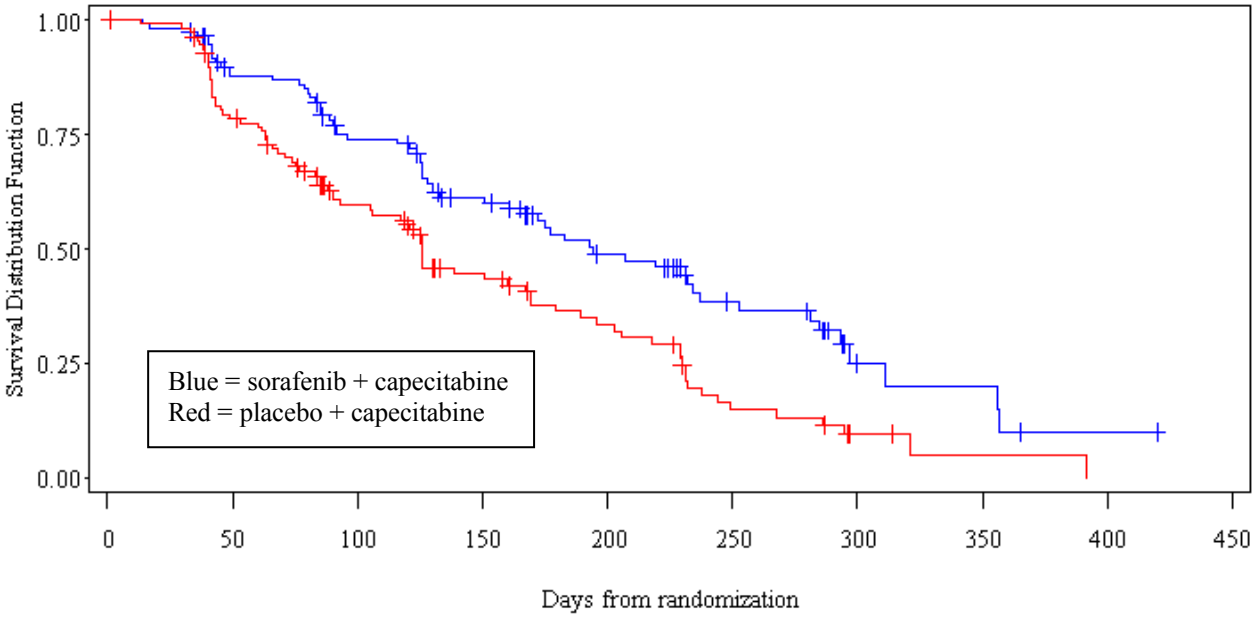
The estimated HR (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.576 (95% CI, 0.410, 0.809), representing a significant (42.4%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

Table 31: Progression-free Survival – ITT Population

Progression-Free Survival (Days)	Treatment Group	
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115
Number of events (progression/death)	80 (70.2%)	62 (53.9%)
Number of censored	34 (29.8%)	53 (46.1%)
Hazard ratio (95% CI) sorafenib/placebo	0.576 (0.410,0.809)	
1-sided p-value	0.0006	
25th percentile (95% CI)	63 (43,83)	92 (83,126)
Median (95% CI)	126 (93,169)	194 (161,237)
75th percentile (95% CI)	230 (189,244)	297 (281,357)
Progression-free survival rate at day 90 (95% CI)	0.606 (0.504,0.693)	0.770 (0.676,0.839)
Rate difference (95% CI) sorafenib-placebo		0.164 (0.039,0.288)
Progression-free survival rate at day 180 (95% CI)	0.363 (0.263,0.463)	0.531 (0.424,0.628)
Rate difference (95% CI) sorafenib-placebo		0.169 (0.024,0.313)
Progression-free survival rate at day 270 (95% CI)	0.130 (0.064,0.222)	0.363 (0.253,0.475)
Rate difference (95% CI) sorafenib-placebo		0.233 (0.095,0.371)

Abbreviations: CI: confidence interval; ITT: intent-to-treat; N: number of patients.
Note: P-value was from stratified log rank test. Hazard ratio was from stratified Cox regression. Visceral disease status is stratification factor.
Source: Post-text Table 14.2.1-1 - PFS Data Set: 27 March 2009.

Figure 4: Progression Free Survival - ITT Population



11.3.1.1 Event types of progression-free survival: ITT population

Table 32 displays a summary of the types of events that were included in the analysis of PFS for the ITT population. Most (123) of the 142 total events of progression or death were radiological progression assessed by RECIST criteria. Radiologic progression occurred in 69 (86.3%) of the 80 progression events in the placebo + capecitabine group and in 54 (87.1%) of the 62 progression events in the sorafenib + capecitabine group. Clinical progression occurred in 6 (7.5%) of the 80 progression events in the placebo + capecitabine group and in 3 (4.8%) of the 62 patients in the sorafenib + capecitabine group. Death without progression occurred in 5 (6.3%) patients in the placebo + capecitabine group and in 5 (8.1%) patients in the sorafenib + capecitabine group.

Table 32: Event Types of Progression-free Survival – ITT Population

Event Type	Treatment Group	
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115
Number of events (progression/death)	80 (70.2%)	62 (53.9%)
Radiological progression (RECIST)	69 (86.3%)	54 (87.1%)
Clinical progression	6 (7.5%)	3 (4.8%)
Death without progression	5 (6.3%)	5 (8.1%)
Number censored	34	53

Abbreviations: ITT: intent-to-treat; N: number of patients.
Note: Only uncensored progression or death (without progression) were counted as events.
Note: Denominator in percentage calculation is the number of events.
Source: Post-text Table 14.2.2 - PFS Data Set.

11.3.1.2 Analyses of progression-free survival: Per protocol population

Table 33 displays a summary of the analysis of PFS for the per protocol population according to modified RECIST criteria.

A total of 199 patients were eligible for and included in the per protocol population. Of the 199 patients in the per protocol population, a total of 125 patients had progressed or died as of the data cutoff date of 27 March 2009 based on the independent review. The 125 events of progression or death included 71 (71.7%) patients in the placebo + capecitabine group and 54 (54.0%) patients in the sorafenib + capecitabine group. The number of censored patients was lower in the placebo + capecitabine group (28 [28.3%]) versus the sorafenib + capecitabine group (46 [46.0%]).

The median PFS for the per protocol population was 121 days (95% CI, 85, 160) for the placebo + capecitabine group and 183 days (95% CI, 133, 234) for the sorafenib + capecitabine group. The 1-sided *P*-value (from stratified log-rank test) was significant at *P*=0.0005 for comparing the treatment groups based on PFS.

For the per protocol population, the estimated HR (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.541 (95% CI, 0.374, 0.784), representing a significant (45.9%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

Table 33: Progression-free Survival – Per Protocol Population

Progression-Free Survival (Days)	Treatment Group	
	Placebo + Capecitabine 99	Sorafenib + Capecitabine 100
Number of events (progression/death)	71 (71.7%)	54 (54.0%)
Number of censored	28 (28.3%)	46 (46.0%)
Hazard ratio (95% CI) sorafenib/placebo	0.541 (0.374,0.784)	
1 sided p-value	0.0005	
25th percentile (95% CI)	53 (42,75)	92 (80,126)
Median (95% CI)	121 (85,160)	183 (133,234)
75th percentile (95% CI)	230 (179,249)	311 (237,357)
Progression-free survival rate at day 90 (95% CI)	0.564 (0.456,0.659)	0.768 (0.666,0.842)
Rate difference (95% CI) sorafenib-placebo		0.204 (0.069,0.338)
Progression-free survival rate at day 180 (95% CI)	0.347 (0.243,0.453)	0.511 (0.394,0.617)
Rate difference (95% CI) sorafenib-placebo		0.164 (0.010,0.319)
Progression-free survival rate at day 270 (95% CI)	0.120 (0.052,0.220)	0.331 (0.215,0.452)
Rate difference (95% CI) sorafenib-placebo		0.211 (0.063,0.359)

Abbreviations: CI: confidence interval.
Note: P-value was from stratified log rank test. Hazard ratio was from stratified Cox regression. Visceral disease status is stratification factor.
Source: Post-text Table 14.2.1-2 - PFS Data Set.

11.3.1.3 Analysis of progression-free survival: Subgroup analyses

Table 34 displays a summary of the subgroup analyses of PFS for the ITT population according to modified RECIST criteria. Figure 5 and Figure 6 display Kaplan-Meier curves for PFS by the subgroup analysis groups of patients who had prior chemotherapy and patients who had no prior chemotherapy for metastatic breast cancer. The subgroup analyses included subgroups defined by prior chemotherapy for metastatic breast cancer (yes versus no), defined by hormone receptor status (ER+ or PgR+ versus ER- and PGR-), and defined by visceral disease (yes versus no).

A total of 116 patients with 73 PFS events had received prior chemotherapy, and a total of 112 patients with 69 PFS events received no prior chemotherapy. For the patients that had received prior chemotherapy, the HR (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.652, representing a significant (34.8%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine (*P*=0.0339). For the patients that received no prior chemotherapy, the estimated HR (sorafenib/placebo) was 0.498, representing a significant (50.2%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine, and suggesting a trend favoring the sorafenib + capecitabine group (*P*=0.0022).

A total of 173 patients with 100 PFS events had a hormone receptor status of ER+ or PgR+. A total of 53 patients with 42 PFS events had a hormone receptor status of ER- and PgR-. For the patients that had a hormone receptor status of ER+ or PgR+, the estimated HR was 0.615, representing a significant (38.5%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine, and suggesting a trend favoring the sorafenib + capecitabine group for these patients (*P*=0.0071). For the patients that had a hormone receptor status of ER- and PgR-, the estimated HR was 0.596 which represented a 40.4% reduction in hazard with sorafenib + capecitabine (*P*=0.0546).

A total of 171 patients with 102 PFS events had visceral disease. A total of 58 patients with 40 PFS events did not have visceral disease. For the patients that had visceral disease, the estimated HR (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.532, representing a significant (46.8%) reduction in hazard with sorafenib + capecitabine, and suggesting a trend favoring the sorafenib + capecitabine group (*P*=0.0008). For the patients that did not have visceral disease, the estimated HR was 0.713 (*P*=0.1492).

Table 34: Progression-free Survival Subgroup Analysis – ITT Population

Sub-group	N	# Events	P-value (1-sided)	Median Days per Group		Hazard Ratio Sorafenib/Placebo	
				Placebo + Capecitabine	Sorafenib + Capecitabine	Estimate	95% CI
Prior chemotherapy for metastatic breast cancer							
Yes	116	73	0.0339	126	175	0.652	(0.410,1.037)
No	112	69	0.0022	126	232	0.498	(0.304,0.816)
Hormone receptor status							
ER+ or PgR+	173	100	0.0071	169	232	0.615	(0.415,0.912)
ER- and PgR-	53	42	0.0546	77	130	0.596	(0.311,1.141)
Visceral disease							
Yes	171	102	0.0008	151	219	0.532	(0.357,0.792)
No	58	40	0.1492	90	130	0.713	(0.373,1.363)

Abbreviations: ER: estrogen receptor; N: number; PgR: progesterone receptor.
Note: P-value was from log rank test within each subgroup.
Note: Patients who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Source: Post-text Table 14.2.3-1 - PFS Data Set: 27 March 2009.

Figure 5: Subgroup Analysis of Progression-Free Survival: Randomized Patients Who Had Prior Chemotherapy for Metastatic Breast Cancer

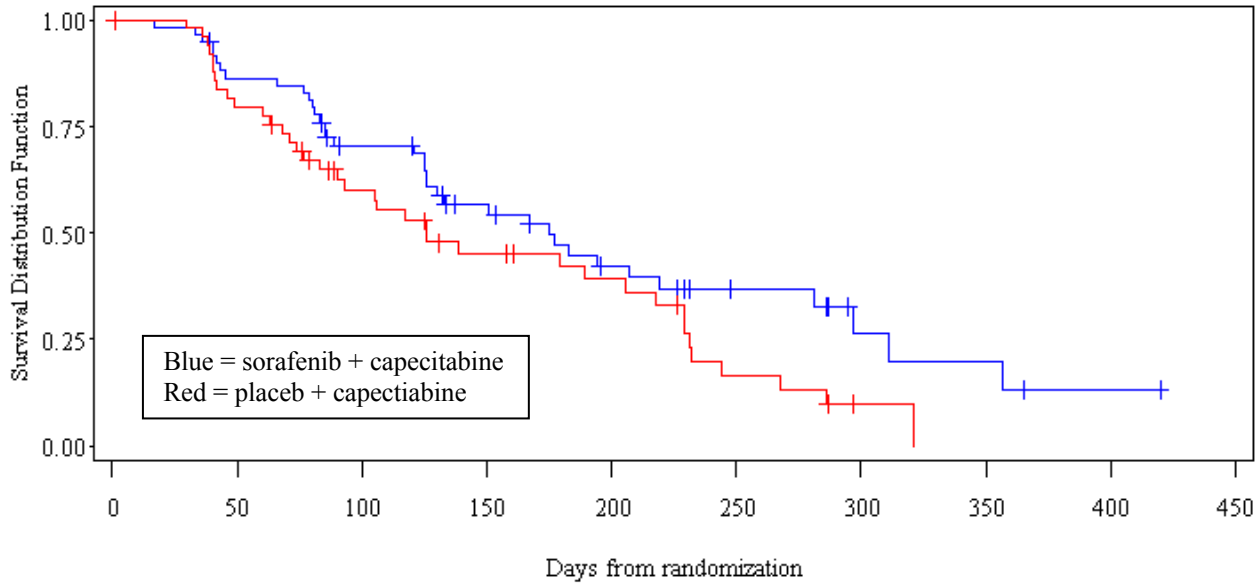
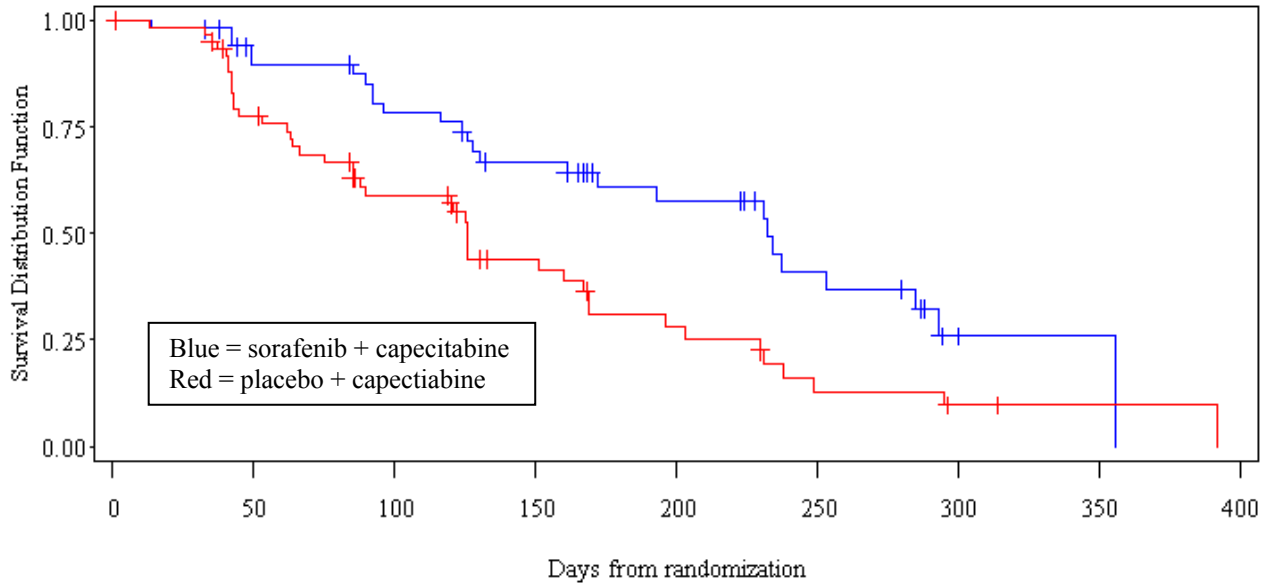


Figure 6: Subgroup Analysis of Progression-Free Survival: Randomized Patients Who Had No Prior Chemotherapy for Metastatic Breast Cancer



11.3.1.4 Analysis of progression-free survival: Exploratory analyses

Table 35 displays a summary of the exploratory analyses of PFS for the ITT population. The exploratory analyses included subgroups defined by age (< 40 years, ≥ 40 years, < 65 years, ≥ 65 years), defined by prior use of anthracycline (yes versus no), defined by prior use of taxane (yes versus no), defined by estrogen receptors (positive versus negative), defined progesterone receptors (positive versus negative), and defined by measurable disease (yes versus no).

For the exploratory analysis of PFS defined by age, the HR for the age group of ≥ 40 years was 0.569, representing a significant (43.1%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 126 days for the placebo + capecitabine group and 207 days for the sorafenib + capecitabine group (*P*=0.0007). The HRs also appeared favorable for the sorafenib + capecitabine group for the < 65 and ≥ 65 age groups with HRs of 0.606 (*P*=0.0038) and 0.503 (*P*=0.0408), respectively. The HR for the < 40 age group was 0.836 (*P*=0.3719).

For the exploratory analysis of PFS defined by prior use of anthracycline the HR for patients that had prior use of anthracycline was 0.594, representing a significant (40.6%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 126 days for the placebo + capecitabine group and 177 days for the sorafenib + capecitabine group (*P*=0.0013). For patients that had no prior use of anthracycline, the HR was 0.263, representing a significant (73.7%) reduction in hazard with sorafenib + capecitabine; median PFS was 230 days for the placebo + capecitabine group and 356 days for the sorafenib + capecitabine group (*P*=0.0403).

For the exploratory analysis of PFS defined by prior use of taxane, the HR for patients that had prior use of taxane was 0.616, representing a significant (38.4%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 106 days for the placebo + capecitabine group and 167 days for the sorafenib + capecitabine group (*P*=0.0113). For patients that had no prior use of taxane, the HR was 0.559, representing a significant (44.1%) reduction in hazard with sorafenib + capecitabine; median PFS was 167 days for the placebo + capecitabine group and 232 days for the sorafenib + capecitabine group (*P*=0.0178).

For the exploratory analysis of PFS defined by estrogen receptors, the HR for patients that had positive estrogen receptors was 0.634, representing a significant (36.6%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 169 days for the placebo + capecitabine group and 232 days for the sorafenib + capecitabine group (*P*=0.0119). For patients that had negative estrogen receptors, the HR was 0.527, representing a significant (47.3%) reduction in hazard with sorafenib + capecitabine; median PFS was 77 days for the placebo + capecitabine group and 130 days for the sorafenib + capecitabine group (*P*=0.0195).

For the exploratory analysis of PFS defined by progesterone receptors, the HR for patients that had negative progesterone receptors was 0.490, representing a significant (51.0%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 106 days for the placebo + capecitabine group and 172 days for the sorafenib + capecitabine group (*P*=0.0015). The HR for patients that had positive progesterone receptors was 0.711, representing a 28.9% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine, and median PFS was 169 days for the placebo + capecitabine group and 232 days for the sorafenib + capecitabine group (*P*=0.0854).

For the exploratory analysis of PFS by measurable disease, measurable disease was defined as having at least one target lesion at baseline. For this exploratory analysis the HR for patients that had measurable disease was 0.558, representing a significant (44.2%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 126 days for the placebo + capecitabine group and 194 days for the sorafenib + capecitabine group (*P*=0.0007). The HR for patients that did not have measurable disease was 0.678 and median PFS was 121 days for the placebo + capecitabine group and 177 days for the sorafenib + capecitabine group (*P*=0.1829).

Table 35: Progression-free Survival Exploratory Analyses – ITT Population

Sub-group	N	# Events	P-value (1-sided)	Median Days per Group		Hazard Ratio Sorafenib/Placebo	
				Placebo + Capecitabine	Sorafenib + Capecitabine	Estimate	95% CI
Age							
< 40	18	15	0.3719	105	121	0.836	(0.284,2.463)
≥ 40	211	127	0.0007	126	207	0.569	(0.400,0.809)
< 65	175	113	0.0038	126	183	0.606	(0.416,0.881)
≥ 65	54	29	0.0408	126	281	0.503	(0.227,1.112)
Prior use of anthracycline							
Yes	202	132	0.0013	126	177	0.594	(0.421,0.839)
No	25	9	0.0403	230	356	0.263	(0.052,1.321)
Prior use of taxane							
Yes	135	87	0.0113	106	175	0.616	(0.404,0.941)
No	91	54	0.0178	167	232	0.559	(0.321,0.972)
Estrogen receptor							
Positive	168	97	0.0119	169	232	0.634	(0.425,0.946)
Negative	58	45	0.0195	77	130	0.527	(0.281,0.987)
Progesterone receptor							
Positive	117	65	0.0854	169	232	0.711	(0.435,1.163)
Negative	103	74	0.0015	106	172	0.490	(0.301,0.798)
Measurable disease[1]							
Yes	191	120	0.0007	126	194	0.558	(0.388,0.803)
No	37	22	0.1829	121	177	0.678	(0.290,1.583)

Abbreviations: N: number.
1: Measurable disease defined as having at least one target lesion at baseline. Patients with no baseline tumor assessment were excluded.
Note: P-value was from log rank test within each subgroup.
Source: Post-text Table 14.2.3-2 - PFS Data Set: 27 March 2009.

11.3.1.4.1 Analysis of progression-free survival: Exploratory analyses: Patients who received taxanes and anthracycline

Table 36 displays a summary of the exploratory analyses of PFS for the subgroup defined by prior use of taxane or anthracycline.

A total of 86 PFS events occurred in the 132 patients in the ITT population who received taxane and anthracycline prior to the study; 46 events (73.0%) occurred in the placebo + capecitabine group and 40 (58.0%) events occurred in the sorafenib + capecitabine group. The number of censored patients was lower in the placebo + capecitabine group (17 [27.0%]) versus the sorafenib + capecitabine group (29 [42.0%]).

The median PFS for the per protocol population was 105 days (95% CI, 77, 126) for the placebo + capecitabine group and 175 days (95% CI, 128, 253) for the sorafenib +

capecitabine group. The 1-sided *P*-value (from stratified log-rank test) was significant at *P*=0.0075 for comparing the treatment groups based on prior taxane and anthracycline use.

For patients who received taxane and anthracycline prior to the study, the estimated HR (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.595 (95% CI, 0.388, 0.911), representing a significant (40.5%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

Table 36: Progression-free Survival in Patients who Received Taxane and Anthracycline Prior to Study – ITT Population

Progression-Free Survival (Days)	Treatment Group	
	Placebo + Capecitabine 63	Sorafenib + Capecitabine 69
Number of events (progression/death)	46 (73.0%)	40 (58.0%)
Number of censored	17 (27.0%)	29 (42.0%)
Hazard ratio (95% CI) sorafenib/placebo	0.595 (0.388,0.911)	
1 sided p-value	0.0075	
25th percentile (95% CI)	60 (42,74)	92 (80,128)
Median (95% CI)	105 (77,126)	175 (128,253)
75th percentile (95% CI)	218 (126,268)	293 (237,311)
Progression-free survival rate at day 90 (95% CI)	0.532 (0.395,0.652)	0.752 (0.622,0.843)
Rate difference (95% CI) sorafenib-placebo		0.220 (0.050,0.389)
Progression-free survival rate at day 180 (95% CI)	0.314 (0.190,0.446)	0.489 (0.350,0.613)
Rate difference (95% CI) sorafenib-placebo		0.174 (-0.012,0.361)
Progression-free survival rate at day 270 (95% CI)	0.131 (0.050,0.252)	0.330 (0.197,0.469)
Rate difference (95% CI) sorafenib-placebo		0.199 (0.025,0.373)

Abbreviations: CI: confidence interval.
Note: P-value was from stratified log rank test. Hazard ratio was from stratified Cox regression.
Source: Post-text Table 14.2.9 - PFS Data Set: 27 March 2009.

11.3.1.5 Analysis of progression-free survival: Sensitivity analysis

For all efficacy analyses, sensitivity analyses were performed based on observational data without imputation or substitution of missing values. The primary analysis used stratified Cox regression and stratified log-rank test of the PFS, calculated using primary censoring rules. Primary censoring rules of PFS included censoring PFS at the last adequate tumor assessment before receipt of a new anticancer therapy or surgery (NPT), if NPT was prior to first documented PD or death. The following sensitivity analyses of PFS were performed using the ITT population:

- Primary: The primary analysis

- Unstratified analysis: Un-stratified Cox regression with treatment as single covariate
- New anticancer therapy or surgery (NPT) considered as a PFS event: Receipt of a NPT prior to the first documented PD was considered as PFS event. The primary analysis was performed using this alternative calculation of PFS.
- New anticancer therapy or surgery (NPT) neither considered as a PFS event nor used to censor PFS: Receipt of a NPT was neither used to censor PFS or was counted as PFS event. The primary analysis was performed using this alternative calculation of PFS.

Table 37 displays a summary of the sensitivity analyses of PFS for the ITT population.

For the sensitivity analysis of PFS by primary analysis, the HR was 0.576 (95% CI, 0.410, 0.809), representing a significant (42.4%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 126 days for the placebo + capecitabine group and 194 days for the sorafenib + capecitabine group (*P*=0.0006).

For the sensitivity analysis of PFS by un-stratified analysis, the HR was 0.573 (95% CI, 0.410, 0.799), representing a significant (42.7%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 126 days for the placebo + capecitabine group and 194 days for the sorafenib + capecitabine group (*P*=0.0004).

For the sensitivity analysis of PFS with NPT considered as a PFS event, the HR was 0.599 (95% CI, 0.438, 0.819), representing a significant (40.1%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 126 days for the placebo + capecitabine group and 194 days for the sorafenib + capecitabine group (*P*=0.0005).

For the sensitivity analysis of PFS with NPT neither considered as a PFS event nor used to censor PFS, the HR was 0.614 (95% CI, 0.443, 0.851), representing a 38.6% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median PFS was 126 days for the placebo + capecitabine group and 194 days for the sorafenib + capecitabine group (*P*=0.0015).

Table 37: Progression-free Survival Sensitivity Analysis – ITT Population

Analysis	N	# Events	Median Days	P-value (1-sided)	Hazard Ratio Sorafenib / Placebo	
					Estimate	95% CI
Primary						
Placebo	114	80 (70.2%)	126	0.0006	0.576	(0.410,0.809)
Sorafenib	115	62 (53.9%)	194			
Un-stratified analysis						
Placebo	114	80 (70.2%)	126	0.0004	0.573	(0.410,0.799)
Sorafenib	115	62 (53.9%)	194			
NPT considered as PFS event						
Placebo	114	91 (79.8%)	121	0.0005	0.599	(0.438,0.819)
Sorafenib	115	73 (63.5%)	177			
NPT neither considered as PFS event nor used to censor PFS						
Placebo	114	85 (74.6%)	126	0.0015	0.614	(0.443,0.851)
Sorafenib	115	65 (56.5%)	194			

Abbreviations: ITT: intent-to-treat; CI: confidence interval. N: number; NPT: new anti-cancer treatment or therapy of curative intent; PFS: progression free survival.
Note: Primary analysis used stratified Cox regression and stratified log-rank test on the PFS, calculated using primary censoring rules. Primary censoring rules of PFS included censoring PFS at last adequate tumor assessment before NPT, if NPT was prior to first documented PD or death.
Note: P-value was from un-stratified log-rank test for "Un-stratified analysis". P-value was from stratified log-rank test for all other analyses. Visceral disease status is a stratification factor.
Source: Post-text Table 14.2.4 - PFS Data Set: 27 March 2009.

11.3.2 Analysis of overall survival: ITT population

Table 38 displays a summary of the analysis of OS for the ITT population. Figure 7 displays a Kaplan-Meier curve for OS by treatment group.

At the time of the data cutoff date of 30 June 2010, a total of 125 of 229 patients had died. The 125 events of death included 65 (57.0%) of 114 patients in the placebo + capecitabine group and 60 (52.2%) of 115 patients in the sorafenib + capecitabine group. The number of censored patients was slightly lower in the placebo + capecitabine group (49 [43.0%]) versus the sorafenib + capecitabine group (55 [47.8%]).

The median OS was 637 days (95% CI, 489, 734) for the placebo + capecitabine group and 675 days (95% CI, 550, 812) for the sorafenib + capecitabine group. The 1-sided *P*-value (from stratified log-rank test) was *P*=0.2075 for comparing the treatment groups based on OS.

The estimated HR (risk of death with sorafenib + capecitabine versus placebo + capecitabine) was 0.864 (95% CI, 0.608, 1.228), representing a 13.6% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

Table 38: Overall Survival – ITT Population

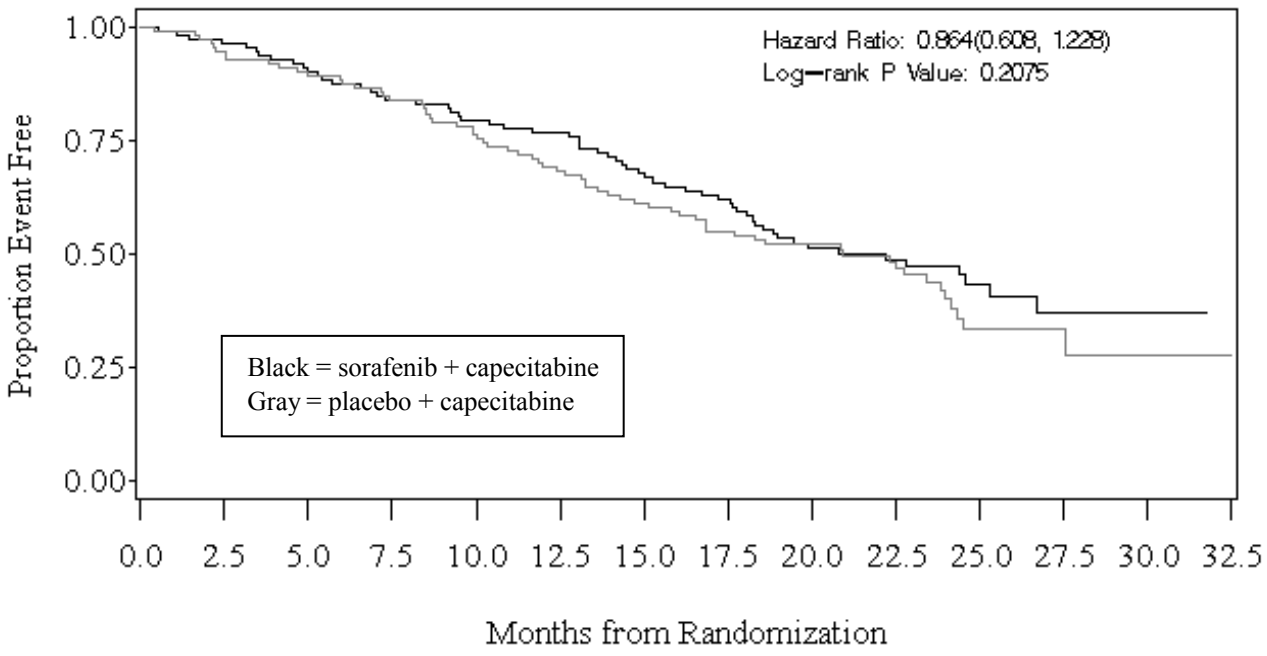
Overall Survival (Days)	Treatment Group	
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115
Number of events (death)	65 (57.0%)	60 (52.2%)
Number of censored	49 (43.0%)	55 (47.8%)
Hazard ratio (95% CI) sorafenib/placebo	0.864 (0.608,1.228)	
1-sided p-value	0.2075	
25th percentile (95% CI)	310 (258,404)	398 (281,464)
Median (95% CI)	637 (489,734)	675 (550,812)
75th percentile (95% CI)	NR (740,NE)	NR (812,NE)
Overall survival rate at day 360 (95% CI)	0.712 (0.618,0.787)	0.769 (0.680,0.837)
Rate difference (95% CI) sorafenib-placebo		0.057 (-0.058,0.172)
Overall survival rate at day 540 (95% CI)	0.541 (0.444,0.628)	0.593 (0.495,0.678)
Rate difference (95% CI) sorafenib-placebo		0.052 (-0.079,0.182)
Overall survival rate at day 720 (95% CI)	0.436 (0.335,0.534)	0.473 (0.373,0.567)
Rate difference (95% CI) sorafenib-placebo		0.037 (-0.103,0.177)

Abbreviations: CI: confidence interval; ITT: intent-to-treat; N: number of patients; NE: not estimable or not assessable.

Note: P-value was from stratified log rank test. Hazard ratio was from stratified Cox regression. Visceral disease status is a stratification factor.

Source: Post-text Table 14.2.1.1 - OS Data Set: 30 June 2010.

Figure 7: Overall Survival



11.3.2.1 Analysis of overall survival: Per protocol population

Table 39 displays a summary of the analysis of OS for the per protocol population.

A total of 194 patients were eligible for and included in the per protocol population for the OS analysis. Of the 194 patients in the per protocol population, a total of 111 patients had died as of the data cutoff date of 30 June 2010. The 111 events of death included 57 (58.8%) patients in the placebo + capecitabine group and 54 (55.7%) patients in the sorafenib + capecitabine group. The number of censored patients was similar in the placebo + capecitabine group (40 [41.2%]) versus the sorafenib + capecitabine group (43 [44.3%]).

The median OS for the per protocol population was 637 days (95% CI, 489, 734) for the placebo + capecitabine group and 605 days (95% CI, 537, 769) for the sorafenib + capecitabine group. The 1-sided *P*-value (from stratified log-rank test) was *P*=0.3029 for comparing the treatment groups based on OS.

For the per protocol population, the estimated hazard ratio (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.906 (95% CI, 0.623, 1.317), representing a 9.4% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

Table 39: Overall Survival – Per Protocol Population

Overall Survival (Days) (1-sided p-value=0.3029)	Treatment Group	
	Placebo + Capecitabine 97	Sorafenib + Capecitabine 97
Number of events (death)	57 (58.8%)	54 (55.7%)
Number of censored	40 (41.2%)	43 (44.3%)
Hazard ratio (95% CI) sorafenib/placebo	0.906 (0.623,1.317)	
1-sided p-value	0.3029	
25th percentile (95% CI)	333 (259,415)	398 (280,475)
Median (95% CI)	637 (489,734)	605 (537,769)
75th percentile (95% CI)	NR (740,NE)	NR (769,NE)
Overall survival rate at day 360 (95% CI)	0.719 (0.618,0.798)	0.770 (0.672,0.842)
Rate difference (95% CI) sorafenib-placebo		0.051 (-0.073,0.174)
Overall survival rate at day 540 (95% CI)	0.542 (0.437,0.635)	0.586 (0.479,0.678)
Rate difference (95% CI) sorafenib-placebo		0.044 (-0.098,0.185)
Overall survival rate at day 720 (95% CI)	0.418 (0.307,0.524)	0.446 (0.339,0.548)
Rate difference (95% CI) sorafenib-placebo		0.029 (-0.124,0.181)

Abbreviations: CI: confidence interval; NE: not estimable or not assessable.
Note: P-value was from stratified log rank test. Hazard ratio was from stratified Cox regression. Visceral disease status is stratification factor.
Note: Patients who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Note: Per-protocol population consists of patients in safety population without major protocol deviations.
Source: Post-text Table 14.2.1.2 - OS Data Set: 30 June 2010.

11.3.2.2 Analysis of overall survival: Subgroup analysis

Table 40 displays a summary of the subgroup analyses of OS for the ITT population. The subgroup analyses included subgroups defined by hormone receptor status (ER+ or PgR+ versus ER- and PGR-), visceral disease (yes versus no), region of enrollment (Brazil versus France or Spain), prior chemotherapy for metastatic breast cancer (yes versus no), and defined by prior anthracycline and taxane (yes versus no).

A total of 173 patients with 86 events (deaths) had a hormone receptor status of ER+ or PgR+, and a total of 53 patients with 38 events (deaths) had a hormone receptor status of ER- and PgR-. For the patients that had a hormone receptor status of ER+ or PgR+, the estimated HR (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.935, representing 6.5% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. For the patients that had a hormone receptor status of ER- and PgR-, the estimated HR was 0.977 which represented a 2.3% reduction in hazard with sorafenib + capecitabine.

A total of 171 patients with 96 events (deaths) had visceral disease, and a total of 58 patients with 29 events (deaths) did not have visceral disease. For the patients that had visceral disease, the estimated HR was 0.834, representing a 16.6% reduction in hazard with sorafenib + capecitabine. For the patients that did not have visceral disease, the estimated HR was 0.970 which represented a 3.0% reduction in hazard with sorafenib + capecitabine.

A total of 112 patients with 67 events (deaths) were located in the Region of Brazil, and a total of 117 patients with 58 events (deaths) were located in the Region of France or Spain. For the patients located in the Region of Brazil, the estimated HR was 0.953, representing a 4.7% reduction in hazard with sorafenib + capecitabine. For the patients located in the Region of France or Spain, the estimated HR was slightly lower (0.757) which represented a slightly greater reduction (24.3%) in hazard with sorafenib + capecitabine (P=0.1469).

A total of 116 patients with 62 events (deaths) had received prior chemotherapy for metastatic setting, and a total of 112 patients with 63 events (deaths) received no prior chemotherapy for metastatic setting. For the patients that received no prior chemotherapy for metastatic setting, the estimated HR (sorafenib/placebo) was 0.666, representing 33.4% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine and suggesting a trend favoring the sorafenib + capecitabine group (P=0.0567). For the patients that had received prior chemotherapy for metastatic setting, the HR was 1.076.

A total of 133 patients with 80 events (deaths) had received prior anthracycline and taxane, and a total of 93 patients with 44 events (deaths) received no prior anthracycline and taxane. For the patients that received no prior anthracycline and taxane, the estimated HR (sorafenib/placebo) was 0.877, representing 12.3% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. For the patients that had received no prior anthracycline and taxane, the HR was 0.879, representing 12.1% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

Table 40: Overall Survival Subgroup Analysis – ITT Population

Sub-group	N	# Events	P-value (1-sided)	Median Days per Group		Hazard Ratio Sorafenib/Placebo	
				Placebo + Capecitabine	Sorafenib + Capecitabine	Estimate	95% CI
Hormone receptor status							
ER+ or PgR+	173	86	0.3790	729 (567, NE)	742 (565, NE)	0.935	(0.612,1.430)
ER- and PgR-	53	38	0.4755	489 (310, 685)	534 (174, 694)	0.977	(0.504,1.894)
Visceral disease							
Yes	171	96	0.1881	557 (404, 725)	593 (494, NE)	0.834	(0.558,1.246)
No	58	29	0.4671	740 (482, NE)	694 (557, NE)	0.970	(0.468,2.011)
Region							
Brazil	112	67	0.4227	557 (482, 740)	573 (432, NE)	0.953	(0.590,1.539)
France or Spain	117	58	0.1469	692 (404, NE)	742 (565, NE)	0.757	(0.450,1.274)
Prior chemotherapy for metastatic breast cancer							
Yes	116	62	0.3868	713 (404, NE)	578 (440, NE)	1.076	(0.651,1.779)
No	112	63	0.0567	557 (448, 740)	694 (550, NE)	0.666	(0.401,1.105)
Prior anthracycline and taxane							
Yes	133	80	0.2801	526 (448, 729)	633 (494, 769)	0.877	(0.565,1.361)
No	93	44	0.3343	725 (423, NE)	NR (537, NE)	0.879	(0.486,1.589)

Abbreviations: ER: estrogen receptor; N: number; NE: not estimable or not assessable; PgR: progesterone receptor.
Note: P-value was from log rank test within each subgroup.
Note: Patients who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Source: Post-text Table 14.2.2 - OS Data Set: 30 June 2010.

11.3.2.3 Analysis of overall survival: Exploratory analysis

Table 41 displays a summary of the exploratory analyses of OS for the ITT population. The exploratory analyses included subgroups defined by age (< 40 years, ≥ 40 years, < 65 years, ≥ 65 years), defined by Country (Brazil, France, Spain), defined by prior use of anthracycline (yes versus no), defined by prior use of taxane (yes versus no), defined by estrogen receptors (positive versus negative), defined progesterone receptors (positive versus negative), defined by measurable disease (yes versus no), defined by number of metastatic sites (< 3, ≥ 3), and defined by months from adjuvant treatment to recurrence or metastatic diagnosis (≤ 12 months, > 12 months). Note that any extreme result in a small subgroup (e.g., age < 40, or prior anthracycline=no) should be interpreted with caution.

For the exploratory analysis of OS defined by age, the HR for the age group of < 40 years was 1.420, suggesting favor of the placebo + capecitabine group. The HRs for the age groups of ≥ 40 years and < 65 were similar at 0.834 and 0.818, respectively, representing 16.6% and

18.2% (respectively) reductions in hazard with sorafenib + capecitabine versus placebo + capecitabine. The HR for the ≥ 65 years group was 0.962, representing a 3.8% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

For the exploratory analysis of OS defined by country, the HR for patients in France was 0.543, representing a significant (45.7%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median OS was 363 days for the placebo + capecitabine group and 694 days for the sorafenib + capecitabine group (*P*=0.0770). The HRs for the countries of Brazil and Spain were similar at 0.953 and 0.916, respectively, representing 4.7% and 8.4% (respectively) reductions in hazard with sorafenib + capecitabine versus placebo + capecitabine.

For the exploratory analysis of OS defined by prior use of anthracycline, the HR for patients that had no prior use of anthracycline was 0.301, representing a significant (69.9%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median OS was 126 days for the placebo + capecitabine group and was NE (not estimable) for the sorafenib + capecitabine group (*P*=0.0613). For patients that had prior use of anthracycline, the HR was 0.9245, representing 7.6% reduction in hazard with sorafenib + capecitabine.

For the exploratory analysis of OS defined by prior use of taxane, the HR for patients that had prior use of taxane was 0.857, representing 14.3% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. For patients that had no prior use of taxane, the HR was 0.915, representing 8.5% reduction in hazard with sorafenib + capecitabine.

For the exploratory analysis of OS defined by estrogen receptors, the HR for patients that had positive estrogen receptors was 1.019, suggesting slight favor of the placebo + capecitabine group. For patients that had negative estrogen receptors, the HR was 0.761, representing 23.9% reduction in hazard with sorafenib + capecitabine.

Hazard ratios for the exploratory analysis of OS defined by progesterone receptors were similar to those for the analysis of OS defined by estrogen receptors. The HR for patients that had positive progesterone receptors was 1.000, suggesting favor of neither group. For patients that had negative progesterone receptors, the HR was 0.815, representing 18.5% reduction in hazard with sorafenib + capecitabine.

For the exploratory analysis of OS by measurable disease, measurable disease was defined as having at least one target lesion at baseline. For this exploratory analysis the HR for patients that had measurable disease was 0.789, representing 21.1% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median OS was 567 days for the placebo + capecitabine group and 694 days for the sorafenib + capecitabine group (*P*=0.1139). The HR for patients that did not have measurable disease was 1.319, suggesting favor of the placebo + capecitabine group.

For the exploratory analysis of OS by number of metastatic sites, the HR for patients that had ≥ 3 metastatic sites was 0.596, representing 40.4% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine; median OS was 384 days for the placebo + capecitabine group and 578 days for the sorafenib + capecitabine group (*P*=0.0381). The HR

for patients with < 3 metastatic sites was 0.966, representing 3.4% reduction in hazard with sorafenib + capecitabine.

For the exploratory analysis of OS by months from adjuvant treatment to recurrence or metastatic diagnosis, the HR for patients that had ≤ 12 months was 1.043, suggesting slight favor of the placebo + capecitabine group. The HR for patients with > 12 months from adjuvant treatment to recurrence or metastatic diagnosis was 0.871, representing 12.9% reduction in hazard with sorafenib + capecitabine.

Table 41: Overall Survival Exploratory Analysis – ITT Population

Subgroup	N	# Events	P-value (1-sided)	Median Days per Group		Hazard Ratio Sorafenib/Placebo	
				Placebo + Capecitabine	Sorafenib + Capecitabine	Estimate	95% CI
Age							
< 40	18	12	0.2745	504 (399, NE)	424 (106, NE)	1.420	(0.448,4.498)
>=40	211	113	0.1669	679 (482, 734)	694 (555, NE)	0.834	(0.576,1.206)
< 65	175	93	0.1664	635 (482, 734)	742 (540, NE)	0.818	(0.544,1.229)
>=65	54	32	0.4584	692 (404, 839)	578 (398, NE)	0.962	(0.478,1.934)
Country							
Brazil	112	67	0.4227	557 (482, 740)	573 (432, NE)	0.953	(0.590,1.539)
France	37	22	0.0770	363 (225, 734)	694 (540, NE)	0.543	(0.231,1.274)
Spain	80	36	0.3984	729 (423, NE)	742 (550, NE)	0.916	(0.474,1.772)
Prior use of anthracycline							
Yes	202	116	0.3359	637 (482, 729)	593 (524, 769)	0.924	(0.642,1.330)
No	25	8	0.0613	839 (306, 839)	NR (NE, NE)	0.301	(0.060,1.510)
Prior use of taxane							
Yes	136	80	0.2475	539 (448, 729)	675 (509, 812)	0.857	(0.552,1.331)
No	90	44	0.3843	725 (423, NE)	593 (524, NE)	0.915	(0.506,1.655)
Estrogen receptor							
Positive	168	84	0.4666	734 (635, NE)	675 (557, NE)	1.019	(0.663,1.566)
Negative	58	40	0.2084	460 (302, 539)	550 (214, 747)	0.761	(0.395,1.466)
Progesterone receptor							
Positive	117	58	0.4999	740 (482, NE)	675 (565, NE)	1.000	(0.595,1.682)
Negative	103	63	0.2165	513 (434, 713)	555 (457, NE)	0.815	(0.489,1.359)
Measurable disease[1]							
Yes	191	104	0.1139	567 (434, 734)	694 (555, NE)	0.789	(0.536,1.161)
No	37	21	0.2654	679 (504, NE)	540 (414, NE)	1.319	(0.553,3.146)
Number of metastatic sites							
< 3	150	78	0.4399	713 (539, 839)	694 (550, NE)	0.966	(0.618,1.508)
>=3	78	47	0.0381	384 (262, 567)	578 (440, NE)	0.596	(0.334,1.063)
Months from adjuvant treatment to recurrence or metastatic diagnosis							
<= 12 months	87	59	0.4366	509 (342, 679)	475 (388, 633)	1.043	(0.622,1.750)
> 12 months	133	59	0.2998	734 (635, NE)	812 (573, NE)	0.871	(0.522,1.454)

Abbreviations: ITT: intent-to-treat; N: Number; NE: not estimable or not assessable.
1: Measurable disease defined as having at least one target lesion at baseline. Patients with no baseline tumor assessment were excluded.
Note: P-value was from log rank test within each subgroup.
Note: Patients who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff - OS Data Set.
Source: Post-text Table 14.2.3 - OS Data Set: 30 June 2010.

11.3.3 Analysis of time to progression

Table 42 displays a summary of the analysis of TTP for the ITT population, conducted using the PFS data set.

At the time of the data cutoff date of 27 March 2009, the 229 patients in the ITT population had 132 progression events. The 132 progression events included 75 (65.8%) of 114 patients in the placebo + capecitabine group, and 57 (49.6%) of 115 patients in the sorafenib + capecitabine group. The number of censored patients was slightly lower in the placebo + capecitabine group (39 [34.2%]) versus the sorafenib + capecitabine group (58 [50.4%]).

The median TTP was 126 days (95% CI, 105, 179) for the placebo + capecitabine group and 207 days (95% CI, 167, 253) for the sorafenib + capecitabine group. The 1-sided *P*-value (from stratified log-rank test) was *P*=0.0005 for comparing the treatment groups based on TTP.

The estimated HR (risk of death with sorafenib + capecitabine versus placebo + capecitabine) was 0.562 (95% CI, 0.394, 0.799), representing 43.8% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

Table 42: Time to Progression – ITT Population

Time to Progression (Days) (1-sided p-value=0.0005)	Treatment Group	
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115
N	114	115
Number of events (progression)	75 (65.8%)	57 (49.6%)
Number of censored	39 (34.2%)	58 (50.4%)
Hazard ratio (95% CI) sorafenib/placebo	0.562 (0.394,0.799)	
1-sided p-value	0.0005	
25th percentile (95% CI)	63 (43,85)	121 (85,130)
Median (95% CI)	126 (105,179)	207 (167,253)
75th percentile (95% CI)	231 (196,249)	311 (285,357)
Progression-free rate at day 90 (95% CI)	0.619 (0.515,0.706)	0.790 (0.696,0.858)
Rate difference (95% CI) sorafenib-placebo	---	0.171 (0.046,0.296)
Progression-free rate at day 180 (95% CI)	0.386 (0.281,0.489)	0.551 (0.440,0.649)
Rate difference (95% CI) sorafenib-placebo	---	0.166 (0.017,0.315)
Progression-free rate at day 270 (95% CI)	0.139 (0.068,0.235)	0.371 (0.255,0.487)
Rate difference (95% CI) sorafenib-placebo	---	0.232 (0.087,0.377)

Abbreviations: CI: confidence interval; ITT: intent-to-treat; N: number of patients.
Note: P-value was from Cochran-Mantel Haenszel test for treatment group difference. Visceral disease status is stratification factor.
Source: Post-text Table 14.2.6 - PFS Data Set: 27 March 2009.

11.3.4 Analysis of overall response rate

Table 43 displays a summary of the analysis of response and response rate for the ITT population, conducted using the PFS data set.

At the time of the data cutoff date of 27 March 2009, the analysis of best response showed CR in 1 (0.9%) placebo + capecitabine patient and 2 (1.7%) sorafenib + capecitabine patients, and PR in 34 (29.8%) placebo + capecitabine patients and 42 (36.5%) sorafenib + capecitabine patients. SD was seen in 43 (37.7%) placebo + capecitabine patients and 50 (43.5%) sorafenib + capecitabine patients.

The overall response rate was 30.7% for the placebo + capecitabine group and 38.3% for the sorafenib + capecitabine group (P=0.1229).

Analysis of objective response, including only confirmed responses, showed CR in 1 (0.9%) placebo + capecitabine patient and 2 (1.7%) sorafenib + capecitabine patients, and PR in 24 (21.1%) placebo + capecitabine patients and 27 (23.5%) sorafenib + capecitabine patients.

The objective response rate was 21.9% for the placebo + capecitabine group and 25.2% for the sorafenib + capecitabine group (P=0.2914).

Table 43: Summary of Response and Response Rate – ITT Population

		Treatment Group	
		Placebo + Capecitabine N=114	**Sorafenib + Capecitabine N=115**
Best response	CR	1 (0.9%)	2 (1.7%)
	PR	34 (29.8%)	42 (36.5%)
	SD	43 (37.7%)	50 (43.5%)
	PD	27 (23.7%)	12 (10.4%)
	NE	3 (2.6%)	1 (0.9%)
Overall response rate	Estimate (95% CI[1])	30.7% (22.4%,40.0%)	38.3% (29.4%,47.8%)
1-sided p-value		0.1229	
Objective response[2]	CR	1 (0.9%)	2 (1.7%)
	PR	24 (21.1%)	27 (23.5%)
Objective response rate	Estimate (95% CI[1])	21.9% (14.7%,30.6%)	25.2% (17.6%,34.2%)
1-sided p value		0.2914	

Abbreviations: CI: confidence interval; ITT: intent-to-treat; N: number of patients; CR: Complete response; NE: not estimable or not assessable; PD: progressive disease; PR: partial response; SD: stable disease.
Note: P-value was from Cochran-Mantel Haenszel test for treatment group difference. Visceral disease status is stratification factor.
1: Exact 95% confidence interval from binomial distribution.
2: Only confirmed responses are summarized.
Source: Post-text Table 14.2.5 - PFS Data Set: 27 March 2009.

11.3.5 Analysis of duration of response rate

Table 44 displays a summary of the analysis of duration of response rate for the ITT population, conducted using the PFS data set.

Duration of response for this analysis was defined as the time from the first documented CR or PR, until the first documented PD or death. The patients without CR or PR were included as events with a DOR of 0 days. At the time of the data cutoff date of 27 March 2009, the 229 patients in the ITT population had 190 events assessed for duration of response rate. The 190 events included 100 (87.7%), including 79 non-responders, of 114 patients in the placebo + capecitabine group, and 90 (78.3%), including 71 non-responders, of 115 patients in the sorafenib + capecitabine group. The number of censored patients was slightly lower in the placebo + capecitabine group (14 [12.3%]) versus the sorafenib + capecitabine group (25 [21.7%]). The number of events from responders was similar between treatment groups with 21 (18.4%) of 114 patients in the placebo + capecitabine group, and 19 (16.5%) of 115 patients in the sorafenib + capecitabine group. The HR for duration of response was 0.846 (95% CI, 0.635, 1.127), representing a 15.4% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. The median DOR was 124 days for the placebo + capecitabine group, and 188 days for the sorafenib + capecitabine group (P=0.0477).

A total of 191 patients with measurable disease (defined as having at least one target lesion at baseline) had 152 events assessed for duration of response rate. The 152 events included 82 (85.4%), including 61 non-responders, of 96 patients in the placebo + capecitabine group, and 70 (73.7%), including 51 non-responders, of 95 patients in the sorafenib + capecitabine group. The number of censored patients was slightly lower in the placebo + capecitabine group (14 [14.6%]) versus the sorafenib + capecitabine group (25 [26.3%]). The number of events from responders was similar between treatment groups with 21 (21.9%) of 96 patients in the placebo + capecitabine group, and 19 (20.0%) of 95 patients in the sorafenib + capecitabine group. For patients with measurable disease, the HR for duration of response was 0.799 (95% CI, 0.579, 1.102), representing a 20.1% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. The median DOR was 124 days for the placebo + capecitabine group, and 188 days for the sorafenib + capecitabine group (P=0.0336).

Table 44: Duration of Response Rate – ITT Population

Duration of Response (Days)	Treatment Group		Treatment Group: Patients with Measurable Disease[1]	
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Placebo + Capecitabine N=96	Sorafenib + Capecitabine N=95
N	114	115	96	95
Number of censored	14 (12.3%)	25 (21.7%)	14 (14.6%)	25 (26.3%)
Number of events	100 (87.7%)	90 (78.3%)	82 (85.4%)	70 (73.7%)
Number of non-responders	79 (69.3%)	71 (61.7%)	61 (63.5%)	51 (53.7%)
Number of events from responders	21 (18.4%)	19 (16.5%)	21 (21.9%)	19 (20.0%)
Hazard ratio (95% CI) sorafenib/placebo	0.846 (0.635,1.127)		0.799 (0.579,1.102)	
1-sided p-value	0.0477		0.0336	
Quartiles of DOR of responders				
N	35	44	35	44
25th percentile (95% CI)	85 (81,116)	89 (49,147)	85 (81,116)	89 (49,147)
Median (95% CI)	124 (88,189)	188 (93,255)	124 (88,189)	188 (93,255)
75th percentile (95% CI)	189 (127,249)	255 (232,316)	189 (127,249)	255 (232,316)

Abbreviations: CI: confidence interval; ITT: intent-to-treat; N: number of patients.
Note: P-value was from Cochran-Mantel Haenszel test for treatment group difference. Visceral disease status is stratification factor.
Note: Duration of response is the time from the first documented CR or PR until the first documented PD or death (if before progression). For the patients with no documented CR or PR, duration of response is not censored and assigned 0 day.
1: Measurable disease defined as having at least one target lesion at baseline.
Source: Post-text Table 14.2.7-1 - PFS Data Set: 27 March 2009.

11.3.6 Analysis of duration of objective response

Table 45 displays a summary of the analysis of duration of objective response for the ITT population, conducted using the PFS data set.

Duration of objective response was defined as the time from the first documented CR or PR, for confirmed responses, until the first documented PD or death (if before progression). For patients with no documented confirmed CR or PR, duration of objective response was not censored and was assigned 0 days.

At the time of the data cutoff date of 27 March 2009, the 229 patients in the ITT population had 203 events assessed for duration of objective response. The 203 events included 105 (92.1%), including 89 non-responders, of 114 patients in the placebo + capecitabine group, and 98 (85.2%), including 86 non-responders, of 115 patients in the sorafenib + capecitabine group. The number of censored patients was slightly lower in the placebo + capecitabine group (9 [7.9%]) versus the sorafenib + capecitabine group (17 [14.8%]). The number of events from responders was similar between treatment groups with 16 (14.0%) of 114 patients in the placebo + capecitabine group, and 12 (10.4%) of 115 patients in the sorafenib + capecitabine group. The hazard ratio for duration of objective response was 0.877 (95% CI, 0.665, 1.158), representing a 12.3% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. The median duration of objective response was 127 days for the placebo + capecitabine group, and 232 days for the sorafenib + capecitabine group (P=0.0533).

A total of 191 patients with measurable disease (defined as having at least one target lesion at baseline) had 165 events assessed for duration of objective response. The 165 events included 87 (90.6%), including 71 non-responders, of 96 patients in the placebo + capecitabine group, and 78 (82.1%), including 66 non-responders, of 95 patients in the sorafenib + capecitabine group. The number of censored patients was slightly lower in the placebo + capecitabine group (9 [9.4%]) versus the sorafenib + capecitabine group (17 [17.9%]). The number of events from responders was similar between treatment groups with 16 (16.7%) of 96 patients in the placebo + capecitabine group, and 12 (12.6%) of 95 patients in the sorafenib + capecitabine group. For patients with measurable disease, the HR for duration of objective response was 0.843 (95% CI, 0.619, 1.147), representing a 15.7% reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. The median duration of objective response was 127 days for the placebo + capecitabine group, and 232 days for the sorafenib + capecitabine group (P=0.0417).

Table 45: Duration of Objective Response – ITT Population

Duration of Response (Days)	Treatment Group		Treatment Group: Patients with Measurable Disease[1]	
	Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115	Placebo + Capecitabine 96	Sorafenib + Capecitabine 95
N	114	115	96	95
Number of censored	9 (7.9%)	17 (14.8%)	9 (9.4%)	17 (17.9%)
Number of events	105 (92.1%)	98 (85.2%)	87 (90.6%)	78 (82.1%)
Number of non-responders	89 (78.1%)	86 (74.8%)	71 (74.0%)	66 (69.5%)
Number of events from responders	16 (14.0%)	12 (10.4%)	16 (16.7%)	12 (12.6%)
Hazard ratio (95% CI) sorafenib/placebo	0.877 (0.665,1.158)		0.843 (0.619,1.147)	
1-sided p-value	0.0533		0.0417	
Quartiles of DOR of responders				
N	25	29	25	29
25th percentile (95% CI)	85 (83,116)	129 (89,232)	85 (83,116)	129 (89,232)
Median (95% CI)	127 (87,189)	232 (147,255)	127 (87,189)	232 (147,255)
75th percentile (95% CI)	231 (127,260)	255 (232,316)	231 (127,260)	255 (232,316)

Abbreviations: CI: confidence interval; ITT: intent-to-treat; N: number of patients.
Note: P-value was from stratified log rank test. Hazard ratio was from stratified Cox regression. Visceral disease status is stratification factor.
Note: Duration of objective response was the time from the first documented CR or PR for confirmed responses until the first documented PD or death (if before progression). For the patients with no documented conformed CR or PR, duration of objective response was not censored and was assigned 0 days.
1: Measurable disease defined as having at least one target lesion at baseline.
Source: Post-text Table 14.2.7-2 - PFS Data Set: 27 March 2009.

11.3.7 Analysis of ECOG performance status

Table 46 displays a summary of the analysis of change in ECOG performance status for the ITT population, conducted using the PFS data set. Change in ECOG performance status was assessed from baseline to the visit at which the best response was first documented and to the end of treatment.

At the visit at which best overall response was first documented, improvement (-1 point) from baseline ECOG performance status was noted for 13 patients in the placebo + capecitabine (11.4%) versus the versus the sorafenib + capecitabine group (5 [4.3%]). Deterioration from baseline ECOG performance status by 1 point was noted for more patients in the placebo + capecitabine (16 [14.0%]) versus the sorafenib + capecitabine group (6 [5.2%]). Deterioration from baseline ECOG PS by 2 points was noted for fewer patients (1 [0.9%]) patient in the placebo + capecitabine group versus the sorafenib + capecitabine group (6 [5.2%]).

At the end of treatment, an improvement (-1 point) from baseline in ECOG performance status was noted for slightly more patients in the placebo + capecitabine group (7 [6.1%]) versus the sorafenib + capecitabine group (4 [3.5%]). A 1-point increase (deterioration) from baseline in ECOG performance status was noted for slightly more patients in the placebo + capecitabine group (26 [22.8%]) versus the sorafenib + capecitabine group (21 [18.3%]). A 2-point increase from baseline ECOG PS was noted for similar numbers of patients in the placebo + capecitabine group (4 [3.5%]) and the in the sorafenib + capecitabine group (5 [4.3%]). A 3-point increase from baseline ECOG PS was noted for fewer patients (1 [0.9%]) in the placebo + capecitabine group versus the sorafenib + capecitabine group (6 [5.3%]).

Table 46: ECOG Performance Status: Change from Baseline – ITT Population

		Treatment Group	
		Placebo + Capecitabine N=114	Sorafenib + Capecitabine N=115
Change from baseline in performance status at the visit at which the best overall response was first documented	**Missing**	26 (22.8%)	38 (33.0%)
	-1	13 (11.4%)	5 (4.3%)
	0	58 (50.9%)	65 (56.5%)
	1	16 (14.0%)	6 (5.2%)
	2	1 (0.9%)	1 (0.9%)
Change from baseline in performance status at the visit at the end of treatment	**Missing**	3 (2.6%)	4 (3.5%)
	-2	1 (0.9%)	0 (0.0)
	-1	7 (6.1%)	4 (3.5%)
	0	72 (63.2%)	75 (65.2%)
	1	26 (22.8%)	21 (18.3%)
	2	4 (3.5%)	5 (4.3%)
	3	1 (0.9%)	6 (5.2%)

Abbreviations: ITT: intent-to-treat; N: number of patients.
Note: The last performance status before end of study treatment was used if end of study treatment performance status was not available.
Source: Post-text Table 14.2.8 - PFS Data Set: 27 March 2009.

11.3.8 Statistical/ analytical issues

11.3.8.1 Adjustments for covariates

The treatment groups were compared with respect to PFS using a stratified log-rank test with visceral disease as the stratification factor. Hazard ratio was from stratified Cox regression.

Sensitivity analyses of PFS were performed using the ITT population; unstratified Cox regression was used with treatment as a single covariate for the following:

- Receipt of a new anticancer therapy or surgery prior to the first documented PD was considered as PFS event. The primary analysis was performed using this alternative calculation of PFS.
- Receipt of a new anticancer treatment or surgery was neither used to censor PFS or was counted as PFS event. The primary analysis was performed using this alternative calculation of PFS.

As specified in the SAP, subgroup and exploratory statistical analyses were performed to determine the effect of certain demographic variables and baseline disease characteristics on PFS. Within each category of subgroups, the HR of PFS was estimated by un-stratified Cox regression and the median PFS were estimated by the Kaplan-Meier method.

Subgroup analyses:

- Prior chemotherapy for metastatic disease (yes or no)

- Hormone receptor status (ER positive or PgR positive, ER negative and PgR negative)
- Visceral disease (yes or no)
- Region (Brazil or France/Spain)
- Prior chemotherapy for breast cancer (yes or no)
- Prior anthracycline and taxane (yes or no)

Exploratory analyses:

- Age at enrollment (< 40, ≥ 40 and < 65, ≥ 65 years)
- Prior use of anthracycline (yes or no)
- Prior use of taxane (yes or no)
- Estrogen receptor (positive or negative)
- Progesterone receptor (positive or negative)
- Measurable disease (yes or no)
- Number of metastatic sites (< 3 or ≥ 3)
- Months from adjuvant treatment to recurrence or metastatic diagnosis (≤ 12 or > 12)
- Country (Brazil, France, or Spain)

The effect of each variable was investigated independently using stratified Cox regression.

11.3.8.2 Handling of dropouts or missing data

Missing or unevaluable or unknown tumor assessments were not taken into account in the calculation of PFS. An "adequate" tumor assessment was defined as a tumor assessment with its overall result not being either "missing", "unevaluable" or "unknown" and with non-missing assessment date.

Survival for patients who were alive or lost to follow-up was censored at the date of the last contact alive. If there was no other contact or follow-up date except for the randomization date proving a patient was alive on that day, OS was assigned one day and censored in the analysis. Patients who died, but the date of death was missing/unknown were censored at the date of the last contact alive

In order to achieve the goal of a well conducted clinical study according to Good Clinical Practice (GCP), every effort was made to collect all data. Any missing or partial data is presented in the patient data listing, as they were recorded on the case report form (CRF).

For efficacy variables summarized at the end of the treatment period, if the data for the End of Treatment visit were missing, the last available post-randomization value was used

No imputation of missing values for the performance status data were performed except for the End of Treatment value, as described above.

Summaries of the number of patients with missing assessments of disease status at scheduled visits, assessments performed out of range, and the pattern of missing and out-of-range

assessments were examined and additional analyses (Sensitivity Analyses) were performed to determine the impact of any missing data, out-of-range assessments, and imbalance between the treatment groups on the analysis of progression-free survival. A tumor assessment with unknown/unevaluable or missing overall result was not included in the analysis of efficacy variables.

There were no apparent differences between the treatment groups with respect to numbers or reasons for missing scans, or missing data (see Table 37).

11.3.8.3 Interim analyses and data monitoring

The safety outcomes of this study were monitored by a DMC. The operation of the DMC was guided by a DMC charter. The committee included 3 members, including an independent statistician and 2 oncologists. A safety review meeting was held after the 20th patient completed Cycle 2 of study treatment (see Appendix 16.1.13). At that meeting, data were reviewed for clinically important differences between treatment groups in SAEs, toxicities, and deaths. The study was not paused for this initial safety review. In addition, the DMC met on a regular basis every 3-4 months to review the cumulative safety data from the study. The DMC operated independently of the Sponsor and participating Investigators.

11.3.8.4 Multicenter studies

A total of 229 patients were enrolled in this study at 23 centers in 3 countries (see Appendix 16.1.4 for a complete list of investigative centers). All of the 23 centers randomized at least 1 patient. No single center enrolled more than 12% of the patients who were randomized in the study. Because of the large number of study centers and the relatively small number of patients enrolled at each center, no investigation of potential treatment-by-center interactions were performed and except for enrollment and disposition data, no summaries of the data by center were provided.

11.3.8.5 Multiple comparison/ multiplicity

This is not applicable. There was a single primary efficacy endpoint, PFS, for this study and a single final analysis of this endpoint. There were only 2 treatment groups. Hence no adjustment for multiplicity or multiple comparisons was required.

11.3.9 Tabulation of individual response data

These listings are available upon request.

11.3.10 Drug dose, drug concentration, and relationships to response

This section is not applicable to this report.

11.3.11 Drug-drug and drug-disease interactions

This section is not applicable to this report.

11.3.12 By-patient displays

By patient displays are available upon request.

11.3.13 Efficacy results

The two treatment groups differed significantly in favor of sorafenib + capecitabine in terms of the primary efficacy variable of PFS based on the ITT population (*P*=0.006). The median PFS was 126 days for the placebo + capecitabine group and 194 days for the sorafenib + capecitabine group and the HR (risk of progression with sorafenib + capecitabine versus placebo + capecitabine) was 0.576 (95% CI, 0.410, 0.809), representing a significant (42.4%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine. Most (123) of the 142 total events of progression or death were of the event type "radiological progression", and this event type occurred at a similar rate (percentage) between the two treatment groups ([86.3%] events in the placebo + capecitabine group and [87.1%] in the sorafenib + capecitabine group).

The two treatment groups also differed significantly in terms of the analysis of PFS based on the per protocol population (*P*=0.005). The median PFS was 121 days for the placebo + capecitabine group and 183 days for the sorafenib + capecitabine group and the HR was 0.541, representing a significant (45.9%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

With regard to the subgroup analysis of PFS, the HRs showed a consistent trend favoring the sorafenib + capecitabine group, with the strongest trends occurring in the subgroup analyses of patients that had no prior chemotherapy for metastatic setting (*P*=0.0022; HR 0.498), patients with visceral disease (*P*=0.0008, HR 0.532), and hormone receptor status of ER+ or PgR+ (*P*=0.0071; HR 0.615).

In the exploratory subgroup analyses of PFS, the HRs showed a consistent trend favoring the sorafenib + capecitabine group, with the strongest trends occurring in the exploratory subgroups of age ≥ 40 years (*P*=0.0007; HR 0.569), patients with measurable disease (*P*=0.0007; HR 0.558), and patients with negative progesterone receptors (*P*=0.0015; HR 0.490). Prior use of anthracycline also appeared to favored the sorafenib + capecitabine group (*P*=0.0013; HR 0.594), but no prior use of anthracycline also appeared favorable (*P*=0.0403; HR 0.263).

The post-hoc exploratory analysis of PFS in patients who received taxane and anthracycline prior to the study also appeared to favor the sorafenib + capecitabine group (*P*=0.0075; HR was 0.595).

The sensitivity analyses of PFS consistently showed a trend favoring the sorafenib + capecitabine group, including the analysis of PFS by primary analysis (*P*=0.0006; HR 0.576), analysis of PFS by un-stratified analysis (*P*=0.0004; HR 0.573), analysis of PFS with NPT considered as a PFS event (*P*=0.0015; HR 0.599), and analysis of PFS with NPT neither considered as a PFS event nor used to censor PFS (*P*=0.0015; HR 0.614).

The two treatment groups differed significantly in terms of the secondary efficacy variable of time to progression based on the ITT population (*P*=0.0005). The median TTP was 126 days for the placebo + capecitabine group and 207 days for the sorafenib + capecitabine group and

the HR was 0.562, representing a significant (43.8%) reduction in hazard with sorafenib + capecitabine versus placebo + capecitabine.

The analysis of overall response rate showed a trend in favor of sorafenib + capecitabine (38.3%, *P*=0.1229), but less of a trend was seen in the analysis of objective response rate (30.7%, *P*=0.2914). The analysis of best response showed CR in 1 (0.9%) placebo + capecitabine patient and 2 (1.7%) sorafenib + capecitabine patients, and PR in 34 (29.8%) placebo + capecitabine patients and 42 (36.5%) sorafenib + capecitabine patients.

Duration of response was defined as the time from the first documented CR or PR, until the first documented PD or death. A slight trend in favor of sorafenib + capecitabine was seen in the analysis of duration of response rate with a median duration of response of 124 days for the placebo + capecitabine group, and 188 days for the sorafenib + capecitabine group (*P*=0.0477; HR 0.846). For patients with measurable disease, the median duration of response was the same: 124 days for the placebo + capecitabine group, and 188 days for the sorafenib + capecitabine group (*P*=0.0336; HR 0.799).

Duration of objective response was defined as the time from the first documented CR or PR, for confirmed responses, until the first documented PD or death (if before progression). A slight trend in favor of sorafenib + capecitabine was seen in the analysis of duration of objective response rate with a median duration of objective response of 127 days for the placebo + capecitabine group, and 232 days for the sorafenib + capecitabine group (*P*=0.0533; HR 0.877). For patients with measurable disease, the median duration of objective response was 127 days for the placebo + capecitabine group, and 232 days for the sorafenib + capecitabine group (*P*=0.0417; HR 0.843).

Analysis of ECOG performance status at the end of study treatment showed an improvement (-1 point) for slightly more patients in the placebo + capecitabine group (7 [6.1%]) versus the sorafenib + capecitabine group (4 [3.5%]). A 1-point increase (deterioration) from baseline in ECOG performance status was noted for slightly more patients in the placebo + capecitabine group (26 [22.8%]) versus the sorafenib + capecitabine group (21 [18.3%]). A 2-point increase from baseline ECOG PS was noted for similar numbers of patients in the placebo + capecitabine group (4 [3.5%]) and the in the sorafenib + capecitabine group (5 [4.3%]). A 3-point increase from baseline ECOG PS was noted for fewer patients (1 [0.9%]) in the placebo + capecitabine group versus the sorafenib + capecitabine group (6 [5.3%]).

The two treatment groups did not differ significantly in terms of OS based on the ITT population (*P*=0.2075) or based on the per protocol population (*P*=0.3029). For the ITT population, the median OS was 637 days for the placebo + capecitabine group and 675 days for the sorafenib + capecitabine group with a HR of 0.864. For the per protocol population, the median OS was 637 days for the placebo + capecitabine group and 605 days for the sorafenib + capecitabine group with a HR of 0.906.

This slight reduction in hazard for OS, with no significant difference between the treatment groups, was apparent in the OS subgroup analyses of hormone receptor status, visceral disease, region (regional location of the patient), and prior use of taxane and anthracycline. A trend in favor of sorafenib + capecitabine appears to have occurred in the subgroup analysis of patients that received no prior chemotherapy in metastatic setting (P=0.0567;

HR 0.666), versus patients that received prior chemotherapy in metastatic setting (P=0.3868; HR 1.076).

The slight reduction in hazard for OS, with no significant difference between the treatment groups, also extended into the exploratory analyses of age, prior use of taxane, estrogen receptors, progesterone receptors, and months from adjuvant treatment to recurrence or metastatic diagnosis. Conversely, a slight trend in favor of sorafenib + capecitabine appears to have occurred in the exploratory analyses of country (country location of the patient), prior use of anthracycline, measurable disease, and number of metastatic sites, as follows: A trend appears to have occurred for patients in France (*P*=0.0770; HR 0.543), versus patients in Brazil (*P*=0.4227; HR 0.543) versus patients in Spain (*P*=0.3984; HR 0.916). A trend appears to have occurred for no prior use of anthracycline (*P*=0.0613; HR 0.301) versus prior use of anthracycline (P=0.3359; HR 0.924). A slight trend appears to have occurred for patients with measurable disease (*P*=0.1139; HR 0.789) versus patients with no measurable disease (*P*=0.2654; HR 1.319). A trend appears to have occurred for number of metastatic sites ≥ 3 (*P*=0.0381; HR 0.596) versus number of metastatic sites < 3 (P=0.4399; HR 0.966).

12. Safety evaluation

Overall, 229 patients (114 in the placebo + capecitabine group and 115 in the sorafenib + capecitabine group) were randomized and received at least 1 dose of study treatment and were included in the safety analyses.

12.1 Extent of exposure

12.1.1 Exposure

12.1.1.1 Sorafenib/placebo and capecitabine exposure

Table 47 and Table 48 summarize the administration of sorafenib/placebo and capecitabine based on the 229 patients in the ITT population, for the PFS and OS data sets.

For the PFS data set (Table 47):

The mean daily dose for sorafenib/placebo was higher in the placebo + capecitabine group (mean daily dose of placebo was equivalent to 748.7 mg) versus the sorafenib + capecitabine group (602.7 mg). The mean daily dose for capecitabine was not reported.

The median duration of treatment for sorafenib/placebo was lower in the placebo + capecitabine group (median daily dose of placebo was equivalent to 18 weeks; range 1 to 59) versus the sorafenib + capecitabine group (22 weeks; range 1 to 60). The median duration of treatment for capecitabine was lower in the placebo + capecitabine group (median duration of treatment was 6 cycles; range 1 to 18) versus the sorafenib + capecitabine group (7 cycles; range 1 to 19).

For the OS data set (Table 48):

The mean daily dose for sorafenib/placebo was higher in the placebo + capecitabine group (mean daily dose of placebo was equivalent to 745.1 mg) versus the sorafenib +

capecitabine group (583.9 mg). The mean daily dose for capecitabine was higher in the placebo + capecitabine group (1839.3 mg) versus the sorafenib + capecitabine group (1460.7 mg).

The median duration of treatment for sorafenib/placebo was lower in the placebo + capecitabine group (median daily dose of placebo was equivalent to 19 weeks; range 1 to 77) versus the sorafenib + capecitabine group (26 weeks; range 1 to 126). The median duration of treatment for capecitabine was lower in the placebo + capecitabine group (median duration of treatment was 6 cycles; range 1 to 26) versus the sorafenib + capecitabine group (9 cycles; range 1 to 39).

Table 47: Sorafenib/Placebo and Capecitabine Administration – ITT Population *(PFS data)*

	Placebo N=114	Sorafenib N=115
Sorafenib / Placebo		
Planned daily dose (mg)	800 mg	800 mg
Average daily dose (mg)[a]		
Mean (SD)	748.7 (104.6)	602.7 (178.4)
Median	800	659
Min / max	213 / 800	235 / 800
Duration of treatment (weeks)[b]		
N	112	112
Mean (SD)	19.6 (12.9)	23.2 (14.1)
Median	18	22
Min / max	1 / 59	1 / 60
Duration of treatment (weeks) n (%)		
Not treated	2 (1.8%)	3 (2.6%)
<=3 weeks	4 (3.5%)	6 (5.2%)
> 3 - 6 weeks	10 (8.8%)	10 (8.7%)
> 6 - 9 weeks	18 (15.8%)	5 (4.3%)
> 9 -12 weeks	7 (6.1%)	6 (5.2%)
>12 -15 weeks	7 (6.1%)	8 (7.0%)
>15 -18 weeks	12 (10.5%)	5 (4.3%)
>18 -21 weeks	12 (10.5%)	13 (11.3%)
>21 -24 weeks	6 (5.3%)	11 (9.6%)
>24 -27 weeks	3 (2.6%)	5 (4.3%)
>27 -30 weeks	11 (9.6%)	8 (7.0%)
>30 -33 weeks	2 (1.8%)	4 (3.5%)
>33 -36 weeks	4 (3.5%)	9 (7.8%)
>36 -39 weeks	4 (3.5%)	2 (1.7%)
>39 -42 weeks	3 (2.6%)	5 (4.3%)

	Placebo N=114	Sorafenib N=115
>42 -45 weeks	4 (3.5%)	8 (7.0%)
>45 -48 weeks	4 (3.5%)	2 (1.7%)
>48 weeks	1 (0.9%)	5 (4.3%)
Capecitabine		
Planned daily dose	2000 mg/m^2 for 14 days followed by 7 day rest period	2000 mg/m^2 for 14 days followed by 7 day rest period
Duration of treatment (cycles)[b]		
N	112	112
Mean (SD)	6.6 (4.2)	7.5 (4.5)
Median	6	7
Min / max	1 / 18	1 / 19
Duration of treatment (cycles) n (%)		
Not treated	2 (1.8%)	3 (2.6%)
<=1 cycle	5 (4.4%)	9 (7.8%)
> 1 - 2 cycles	15 (13.2%)	11 (9.6%)
> 2 - 3 cycles	15 (13.2%)	6 (5.2%)
> 3 - 4 cycles	11 (9.6%)	9 (7.8%)
> 4 - 5 cycles	5 (4.4%)	5 (4.3%)
> 5 - 6 cycles	12 (10.5%)	12 (10.4%)
> 6 - 7 cycles	10 (8.8%)	9 (7.8%)
> 7 - 8 cycles	5 (4.4%)	8 (7.0%)
> 8 - 9 cycles	6 (5.3%)	9 (7.8%)
> 9 -10 cycles	5 (4.4%)	4 (3.5%)
>10 -11 cycles	6 (5.3%)	8 (7.0%)
>11 -12 cycles	3 (2.6%)	1 (0.9%)
>12 -13 cycles	5 (4.4%)	7 (6.1%)
>13 -14 cycles	3 (2.6%)	6 (5.2%)
>14 -15 cycles	4 (3.5%)	2 (1.7%)
>15 -16 cycles	1 (0.9%)	4 (3.5%)
>16 -17 cycles	0 (0.0%)	1 (0.9%)
>17 -18 cycles	1 (0.9%)	0 (0.0%)
>18 cycles	0 (0.0%)	1 (0.9%)

a Average is of intended daily dose.
b Only treated patients were included. Duration of treatment is presented in weeks for sorafenib / placebo and is presented in cycles for capecitabine.
Abbreviations: ITT: intent-to-treat; mg: milligrams; min: minimum; max: maximum; N: number of patients; and SD: standard deviation.
Source: Tables 14.1.11.1 and 14.1.12.1 - PFS Data Set: 27 March 2009.

Table 48: Sorafenib/Placebo and Capecitabine Administration – ITT Population *(OS data)*

	Placebo N=114	Sorafenib N=115
Sorafenib / Placebo		
Planned daily dose (mg)	800 mg	800 mg
Average daily dose (mg)[a]		
Mean (SD)	745.1 (108.7)	583.9 (190.2)
Median	800	611
Min / max	213 / 800	220 / 800
Duration of treatment (weeks)[b]		
N	112	112
Mean (SD)	22.5 (16.6)	33.8 (28.5)
Median	19	26
Min / max	1 / 77	1 / 126
Duration of treatment (weeks) n (%)		
Not treated	2 (1.8%)	3 (2.6%)
<=3 weeks	4 (3.5%)	6 (5.2%)
>3 - 6 weeks	10 (8.8%)	10 (8.7%)
>6 - 9 weeks	18 (15.8%)	5 (4.3%)
>9 - 12 weeks	7 (6.1%)	6 (5.2%)
>12 - 15 weeks	6 (5.3%)	8 (7.0%)
>15 - 18 weeks	8 (7.0%)	3 (2.6%)
>18 - 21 weeks	10 (8.8%)	11 (9.6%)
>21 - 24 weeks	3 (2.6%)	4 (3.5%)
>24 - 27 weeks	4 (3.5%)	4 (3.5%)
>27 - 30 weeks	11 (9.6%)	5 (4.3%)
>30 - 33 weeks	4 (3.5%)	2 (1.7%)
>33 - 36 weeks	5 (4.4%)	9 (7.8%)
>36 - 39 weeks	3 (2.6%)	1 (0.9%)
>39 - 42 weeks	2 (1.8%)	5 (4.3%)
>42 - 45 weeks	5 (4.4%)	2 (1.7%)
>45 - 48 weeks	5 (4.4%)	1 (0.9%)
>48 - 52 weeks	0 (0.0%)	5 (4.3%)
>52 - 78 weeks	7 (6.1%)	15 (13.0%)
>78 - 104 weeks	0 (0.0%)	6 (5.2%)
>104 weeks	0 (0.0%)	4 (3.5%)

	Placebo N=114	Sorafenib N=115
Capecitabine		
Planned daily dose (mg)	2000 mg/m^2 for 14 days followed by 7 day rest period	2000 mg/m^2 for 14 days followed by 7 day rest period
Average daily dose (mg)[a]	112	112
Mean (SD)	1839.3 (265.8)	1460.7 (326.9)
Median	2000	1441
Min / max	951 / 2375	683 / 2000
Duration of treatment (cycles)[b]		
N	112	112
Mean (SD)	7.4 (5.3)	10.7 (9.0)
Median	6	9
Min / max	1 / 26	1 / 39
Duration of treatment (cycles) n (%)		
Not treated	2 (1.8%)	3 (2.6%)
<=1 cycle	5 (4.4%)	9 (7.8%)
> 1 - 2 cycles	15 (13.2%)	11 (9.6%)
> 2 - 3 cycles	15 (13.2%)	6 (5.2%)
> 3 - 4 cycles	10 (8.8%)	9 (7.8%)
> 4 - 5 cycles	4 (3.5%)	3 (2.6%)
> 5 - 6 cycles	9 (7.9%)	9 (7.8%)
> 6 - 7 cycles	9 (7.9%)	4 (3.5%)
> 7 - 8 cycles	3 (2.6%)	5 (4.3%)
> 8 - 9 cycles	6 (5.3%)	6 (5.2%)
> 9 -10 cycles	6 (5.3%)	5 (4.3%)
>10 -11 cycles	7 (6.1%)	6 (5.2%)
>11 -12 cycles	3 (2.6%)	4 (3.5%)
>12 -13 cycles	3 (2.6%)	2 (1.7%)
>13 -14 cycles	5 (4.4%)	2 (1.7%)
>14 -15 cycles	5 (4.4%)	2 (1.7%)
>15 -16 cycles	0 (0.0%)	6 (5.2%)
>16 -17 cycles	1 (0.9%)	3 (2.6%)
>17 -26 cycles	6 (5.3%)	10 (8.7%)
>26 -34 cycles	0 (0.0%)	9 (7.8%)
>34 cycles	0 (0.0%)	1 (0.9%)

a The Safety Population was used for the duration of treatment calculations (only treated patients were included).
b Average is of intended daily dose.
c Only treated patients were included. Duration of treatment is presented in weeks for sorafenib / placebo and is presented in cycles for capecitabine.
Abbreviations: ITT: intent-to-treat; mg: milligrams; min: minimum; max: maximum; N: number of patients; and SD: standard deviation.
Source: Tables 14.1.11.1 and 14.1.12.1 - OS Data Set: 30 June 2010.

12.1.2 Dose modifications

A dose interruption was defined as anytime a patient did not receive study medication when the patient should have received it according to the protocol. Scheduled drug rest periods were not dose interruptions. For medications administered cyclically, an omission of a dose was an interruption.

In this study there was a 7 day rest period in the 21 day cycle for capecitabine, this was not an interruption. However, if a patient received study treatment, then had 2 days of rest from study treatment because of an AE, the dose was interrupted. If the patient was supposed to start study treatment on Day 1 of a cycle and did not start until Day 5, it was also considered a dose interruption.

12.1.2.1 Sorafenib/placebo and capecitabine dose modifications

Table 49 and Table 50 summarize the dose modifications of sorafenib/placebo and capecitabine based on the 229 patients in the ITT population, for the PFS and OS data sets.

For the PFS data set (Table 49):

The percentage of patients with dose reductions and dose interruptions was lower in the placebo + capecitabine group versus the sorafenib + capecitabine group.

One or more dose reductions of placebo were noted for 13 (11.4%) patients in the placebo + capecitabine group and of sorafenib for 55 (47.8%) patients in the sorafenib + capecitabine group. One or more of the dose reductions were due to an AE in all patients with dose reductions, (13 [11.4%] patients in the placebo + capecitabine group and 55 [47.8%] patients in the sorafenib + capecitabine group). One or more dose reductions of capecitabine were noted for 36 (31.6%) patients in the placebo + capecitabine group and for 90 (78.3%) patients in the sorafenib + capecitabine group. One or more of the dose reductions were due to an AE in 35 (30.7%) patients in the placebo + capecitabine group and in 90 (78.3%) patients in the sorafenib + capecitabine group.

One or more dose interruptions of placebo were noted for 47 (41.2%) patients in the placebo + capecitabine group and of sorafenib for 85 (73.9%) patients in the sorafenib + capecitabine group. One or more of the dose interruptions were due to an AE in 44 (38.6%) patients in the placebo + capecitabine group and in 84 (73.0%) patients in the sorafenib + capecitabine group. One or more dose interruptions of capecitabine were noted for 46 (40.4%) patients in the placebo + capecitabine group and for 87 (75.7%) patients in the sorafenib + capecitabine group. One or more of the dose interruptions were due to an AE in 42 (36.8%) patients in the placebo + capecitabine group and in 87 (75.7%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 50):

The percentage of patients with dose reductions and dose interruptions was lower in the placebo + capecitabine group versus the sorafenib + capecitabine group.

One or more dose reductions of placebo were noted for 16 (14.0%) patients in the placebo + capecitabine group and of sorafenib for 61 (53.0%) patients in the sorafenib + capecitabine group. One or more of the dose reductions were due to an AE in all patients with dose reductions, (16 [14.0%] patients in the placebo + capecitabine group and 61 [53.0%] patients in the sorafenib + capecitabine group). One or more dose reductions of capecitabine were noted for 38 (33.3%) patients in the placebo + capecitabine group and for 90 (78.3%) patients in the sorafenib + capecitabine group. One or more of the dose reductions were due to an AE in 37 (32.5%) patients in the placebo + capecitabine group and in 90 (78.3%) patients in the sorafenib + capecitabine group.

One or more dose interruptions of placebo were noted for 48 (42.1%) patients in the placebo + capecitabine group and of sorafenib for 86 (74.8%) patients in the sorafenib + capecitabine group. One or more of the dose interruptions were due to an AE in 45 (39.5%) patients in the placebo + capecitabine group and in 84 (73.0%) patients in the sorafenib + capecitabine group. One or more dose interruptions of capecitabine were noted for 47 (41.2%) patients in the placebo + capecitabine group and for 88 (76.5%) patients in the sorafenib + capecitabine group. One or more of the dose interruptions were due to an AE in 47 (41.2%) patients in the placebo + capecitabine group and in 87 (75.7%) patients in the sorafenib + capecitabine group.

Table 49: Sorafenib/Placebo and Capecitabine Dose Modifications – ITT Population *(PFS data)*

	Placebo N=114	Sorafenib N=115
Sorafenib / Placebo		
Patients with dose reduction n (%)	13 (11.4%)	55 (47.8%)
Reason for dose reduction n (%)		
Adverse event	13 (11.4%)	55 (47.8%)
Number of dose reductions per patient		
0	99 (86.8%)	57 (49.6%)
1	10 (8.8%)	38 (33.0%)
2	3 (2.6%)	17 (14.8%)
Patients with dose re-escalation n (%)	1 (0.9%)	1 (0.9%)
Patients with dose interruption n (%)	47 (41.2%)	85 (73.9%)
Reason for dose interruption n (%)		
Adverse event	44 (38.6%)	84 (73.0%)
Site error	0 (0.0%)	2 (1.7%)
Investigator or patient decision	4 (3.5%)	6 (5.2%)
Number of dose interruptions per patient		
0	65 (57.0%)	27 (23.5%)
1	31 (27.2%)	28 (24.3%)
2	9 (7.9%)	20 (17.4%)
≥ 3	7 (6.1%)	37 (32.2%)
Capecitabine		
Patients with dose reduction n (%)	36 (31.6%)	90 (78.3%)
Reason for dose reduction n (%)		
Adverse event	35 (30.7%)	90 (78.3%)
Investigator or patient decision	2 (1.8%)	1 (0.9%)
Number of dose reductions per patient		
0	76 (66.7%)	22 (19.1%)
1	27 (23.7%)	55 (47.8%)
2	9 (7.9%)	34 (29.6%)
≥ 3	0 (0.0%)	1 (0.9%)
Patients with dose re-escalation n (%)	6 (5.3%)	2 (1.7%)
Patients with dose interruption n (%)	46 (40.4%)	87 (75.7%)
Reason for dose interruption n (%)		
Adverse event	42 (36.8%)	87 (75.7%)
Patient withdrawn from the study	2 (1.8%)	0 (0.0%)
Investigator or patient decision	5 (4.4%)	4 (3.5%)

	Placebo N=114	Sorafenib N=115
Number of dose interruptions per patient		
0	66 (57.9%)	25 (21.7%)
1	27 (23.7%)	32 (27.8%)
2	14 (12.3%)	24 (20.9%)
≥ 3	5 (4.4%)	31 (27.0%)

Abbreviations: ITT: intent-to-treat; and N: number of patients.
Source: Tables 14.1.11.1 and 14.1.12.1 - PFS Data Set: 27 March 2009.

Table 50: Sorafenib/Placebo and Capecitabine Dose Modifications – ITT Population *(OS data)*

	Placebo N=114	Sorafenib N=115
Sorafenib / Placebo		
Patients with dose reduction n (%)	16 (14.0%)	61 (53.0%)
Reason for dose reduction n (%)		
Adverse event	16 (14.0%)	61 (53.0%)
Number of dose reductions per patient		
0	96 (84.2%)	51 (44.3%)
1	13 (11.4%)	38 (33.0%)
2	3 (2.6%)	22 (19.1%)
≥ 3	0 (0.0%)	1 (0.9%)
Patients with dose re-escalation n (%)	1 (0.9%)	1 (0.9%)
Patients with dose interruption n (%)	48 (42.1%)	86 (74.8%)
Reason for dose interruption n (%)		
Adverse event	45 (39.5%)	84 (73.0%)
Site error	0 (0.0%)	2 (1.7%)
Investigator or patient decision	4 (3.5%)	7 (6.1%)
Number of dose interruptions per patient		
0	64 (56.1%)	26 (22.6%)
1	31 (27.2%)	25 (21.7%)
2	9 (7.9%)	17 (14.8%)
≥ 3	8 (7.0%)	44 (38.3%)
Capecitabine		
Patients with dose reduction n (%)	38 (33.3%)	90 (78.3%)
Reason for dose reduction n (%)		
Adverse event	37 (32.5%)	90 (78.3%)
Investigator or patient decision	2 (1.8%)	2 (1.7%)
Number of dose reductions per patient		
0	74 (64.9%)	22 (19.1%)
1	28 (24.6%)	48 (41.7%)
2	10 (8.8%)	40 (34.8%)
≥ 3	0 (0.0%)	2 (1.7%)
Patients with dose re-escalation n (%)	6 (5.3%)	2 (1.7%)
Patients with dose interruption n (%)	47 (41.2%)	88 (76.5%)
Reason for dose interruption n (%)		
Adverse event	43 (37.7%)	87 (75.7%)
Patient withdrawn from the study	2 (1.8%)	0 (0.0%)
Investigator or patient decision	6 (5.3%)	7 (6.1%)

	Placebo N=114	Sorafenib N=115
Number of dose interruptions per patient		
0	65 (57.0%)	24 (20.9%)
1	26 (22.8%)	28 (24.3%)
2	15 (13.2%)	17 (14.8%)
≥ 3	6 (5.3%)	43 (37.4%)

Abbreviations: ITT: intent-to-treat; and N: number of patients.
Source: Tables 14.1.11.1 and 14.1.12.1 - OS Data Set: 30 June 2010.

12.2 Adverse events

The overall incidence of treatment-emergent AEs is presented by MedDRA (version 10.0) system organ class and preferred term. Patients were counted at most once for each MedDRA term. The overall incidence of treatment-emergent AEs is presented separately by severity and by drug relationship. For these presentations, patients were counted at most once for each MedDRA term under the highest severity or the strongest relationship to study treatment.

Summaries of the number (%) of patients in each treatment group with at least 1 AE, classified according to MedDRA term, are also provided for study treatment-related (capecitabine, and/or sorafenib/placebo) AEs.

Adverse events of special interest are neutrophils/granulocytes, leukocytes, platelets, sensory neuropathy, fatigue, hemoglobin, febrile neutropenia, diarrhea, thrombus/embolism, hypertension, mucositis, nausea, hand-foot skin reaction, rash/desquamation, dermatology-other, pruritis, and hemorrhage/bleeding, all of which may be associated with sorafenib use.

12.2.1 Brief summary of adverse events

Table 51 and Table 52 provide an overall summary of AEs based on the 224 patients in the safety population, for the PFS and OS data sets.

Drug-related AEs were those AEs related to either sorafenib/placebo or capecitabine (including those AEs related to both).

For the PFS data set (Table 51):

A total of 106 (94.6%) patients in the placebo + capecitabine group and 111 (99.1%) patients in the sorafenib + capecitabine group reported 1 or more treatment-emergent AEs. One or more drug-related AEs were reported for 97 (86.6%) patients in the placebo + capecitabine group and 108 (96.4%) patients in the sorafenib + capecitabine group. Serious adverse events were reported for 30 (26.8%) patients in the placebo + capecitabine group and 36 (32.1%) patients in the sorafenib + capecitabine group. Drug-related SAEs were reported for 11 (9.8%) patients in the placebo + capecitabine group and 20 (17.9%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 52):

A total of 109 (97.3%) patients in the placebo + capecitabine group and 112 (100%) patients in the sorafenib + capecitabine group reported 1 or more treatment-emergent AEs. One or more drug-related AEs were reported for 100 (89.3%) patients in the placebo + capecitabine group and 109 (97.3%) patients in the sorafenib + capecitabine group. Serious adverse events were reported for 31 (27.7%) patients in the placebo + capecitabine group and 40 (35.7%) patients in the sorafenib + capecitabine group. Drug-related SAEs were reported for 11 (9.8%) patients in the placebo + capecitabine group and 20 (17.9%) patients in the sorafenib + capecitabine group.

Table 51: Overview of Adverse Events - Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Any adverse event	106 (94.6%)	111 (99.1%)
Drug-related adverse events	97 (86.6%)	108 (96.4%)
Grade 3 or higher adverse events	47 (42.0%)	67 (59.8%)
Grade 3 or higher drug-related adverse events	28 (25.0%)	63 (56.3%)
Adverse events leading to discontinuation		
AEs leading to discontinuation of study treatment - overall	9 (8.0%)	15 (13.4%)
AEs leading to discontinuation of sorafenib/placebo	8 (7.1%)	14 (12.5%)
AEs leading to discontinuation of capecitabine	8 (7.1%)	14 (12.5%)
Serious adverse events	30 (26.8%)	36 (32.1%)
Drug-related serious adverse events	11 (9.8%)	20 (17.9%)

Source: Post-text Tables 14.3.1, 14.3.3, 14.3.5, 14.3.6, 14.3.7, 14.3.8, 14.3.9, 14.3.10, 14.3.11, and 14.3.12 - PFS Data Set: 27 March 2009.

Table 52: Overview of Adverse Events - Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Any adverse event	109 (97.3%)	112 (100%)
Drug-related adverse events	100 (89.3%)	109 (97.3%)
Grade 3 or higher adverse events	51 (45.5%)	70 (62.5%)
Grade 3 or higher drug-related adverse events	31 (27.7%)	64 (57.1%)
Adverse events leading to discontinuation of study treatment		
AEs leading to discontinuation of study treatment - overall	11 (9.8%)	22 (19.6%)
AEs leading to discontinuation of sorafenib/placebo	10 (8.9%)	20 (17.9%)
AEs leading to discontinuation of capecitabine	10 (8.9%)	22 (19.6%)
Serious adverse events	31 (27.7%)	40 (35.7%)
Drug-related serious adverse events	11 (9.8%)	20 (17.9%)

Source: Post-text Tables 14.3.1, 14.3.3, 14.3.5, 14.3.6, 14.3.7, 14.3.8, 14.3.9, 14.3.10, 14.3.11, and 14.3.12 - OS Data Set: 30 June 2010.

12.2.2 Display of adverse events

Table 53 and Table 54 display a summary of treatment emergent AEs occurring in ≥ 5% of either treatment group, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 53):

A total of 106 (94.6%) patients in the placebo + capecitabine group and 111 (99.1%) patients in the sorafenib + capecitabine group reported 1 or more treatment-emergent AEs. The SOC with the greatest number of AEs was "skin and subcutaneous tissue disorders" where AEs were experienced by 79 (70.5%) patients in the placebo + capecitabine group and 100 (89.3%) patients in the sorafenib + capecitabine group. The SOC with the second greatest number of AEs was "gastrointestinal disorders" where AEs were experienced by 63 (56.3%) patients in the placebo + capecitabine group and 84 (75.0%) patients in the sorafenib + capecitabine group. The SOC with the third greatest number of AEs was "general disorders and administrative site conditions" where AEs were experienced by 66 (58.9%) patients in the placebo + capecitabine group and 71 (63.4%) patients in the sorafenib + capecitabine group.

The AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 70 (62.5%) patients in the placebo + capecitabine group and 100 (89.3%) patients in the sorafenib + capecitabine group. The second most common AE was diarrhea (SOC: gastrointestinal disorders), experienced by 33 (29.5%) patients in the placebo + capecitabine group and 59 (52.7%) patients in the sorafenib + capecitabine group. The third most common AE was nausea (SOC: gastrointestinal disorders), experienced by

35 (31.3%) patients in the placebo + capecitabine group and 30 (26.8%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 54):

A total of 109 (97.3%) patients in the placebo + capecitabine group and 112 (100%) patients in the sorafenib + capecitabine group reported 1 or more treatment-emergent AEs. The SOC with the greatest number of AEs was "skin and subcutaneous tissue disorders" where these AEs were experienced by 84 (75.0%) patients in the placebo + capecitabine group and 101 (90.2%) patients in the sorafenib + capecitabine group. The SOC with the second greatest number of AEs was "gastrointestinal disorders" where these AEs were experienced by 64 (57.1%) patients in the placebo + capecitabine group and 87 (77.7%) patients in the sorafenib + capecitabine group. The SOC with the third greatest number of AEs was "general disorders and administrative site conditions" where these AEs were experienced by 69 (61.6%) patients in the placebo + capecitabine group and 73 (65.2%) patients in the sorafenib + capecitabine group.

The AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 74 (66.1%) patients in the placebo + capecitabine group and 101 (90.2%) patients in the sorafenib + capecitabine group. The second most common AE was diarrhea (SOC: gastrointestinal disorders), experienced by 34 (30.4%) patients in the placebo + capecitabine group and 65 (58.0%) patients in the sorafenib + capecitabine group. The third most common AE was nausea (SOC: gastrointestinal disorders), experienced by 36 (32.1%) patients in the placebo + capecitabine group and 32 (28.6%) patients in the sorafenib + capecitabine group.

Table 53: Treatment Emergent Adverse Events Occurring in ≥5% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems / Any Term	**106 (94.6%)**	**111 (99.1%)**
Skin and subcutaneous tissue disorders/Any Term	**79 (70.5%)**	**100 (89.3%)**
Palmar-plantar erythrodysaesthesia syndrome	70 (62.5%)	100 (89.3%)
Alopecia	5 (4.5%)	32 (28.6%)
Rash	9 (8.0%)	25 (22.3%)
Dry skin	8 (7.1%)	10 (8.9%)
Pruritus	5 (4.5%)	7 (6.3%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Gastrointestinal disorders/Any Term	**63 (56.3%)**	**84 (75.0%)**
Diarrhoea	33 (29.5%)	59 (52.7%)
Nausea	35 (31.3%)	30 (26.8%)
Vomiting	18 (16.1%)	23 (20.5%)
Constipation	11 (9.8%)	25 (22.3%)
Abdominal pain upper	12 (10.7%)	17 (15.2%)
Abdominal pain	11 (9.8%)	11 (9.8%)
Stomatitis	7 (6.3%)	7 (6.3%)
General disorders and administration site conditions/Any Term	**66 (58.9%)**	**71 (63.4%)**
Asthenia	30 (26.8%)	27 (24.1%)
Mucosal inflammation	21 (18.8%)	36 (32.1%)
Fatigue	14 (12.5%)	16 (14.3%)
Oedema peripheral	8 (7.1%)	11 (9.8%)
Pyrexia	7 (6.3%)	11 (9.8%)
Chest pain	9 (8.0%)	5 (4.5%)
Nervous system disorders/Any Term	**38 (33.9%)**	**39 (34.8%)**
Headache	17 (15.2%)	18 (16.1%)
Paraesthesia	10 (8.9%)	14 (12.5%)
Dizziness	3 (2.7%)	7 (6.3%)
Musculoskeletal and connective tissue disorders/Any Term	**35 (31.3%)**	**37 (33.0%)**
Back pain	12 (10.7%)	10 (8.9%)
Musculoskeletal pain	7 (6.3%)	13 (11.6%)
Pain in extremity	6 (5.4%)	7 (6.3%)
Arthralgia	6 (5.4%)	5 (4.5%)
Myalgia	6 (5.4%)	5 (4.5%)

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Respiratory, thoracic and mediastinal disorders/Any Term	**20 (17.9%)**	**32 (28.6%)**
Dyspnoea	13 (11.6%)	13 (11.6%)
Cough	7 (6.3%)	13 (11.6%)
Pleural effusion	2 (1.8%)	6 (5.4%)
Dysphonia	1 (0.9%)	6 (5.4%)
Vascular disorders/Any Term	**21 (18.8%)**	**28 (25.0%)**
Hypertension	13 (11.6%)	19 (17.0%)
Metabolism and nutrition disorders/Any Term	**18 (16.1%)**	**25 (22.3%)**
Anorexia	13 (11.6%)	22 (19.6%)
Blood and lymphatic system disorders/Any Term	**17 (15.2%)**	**21 (18.8%)**
Neutropenia	4 (3.6%)	12 (10.7%)
Anaemia	6 (5.4%)	9 (8.0%)
Thrombocytopenia	6 (5.4%)	2 (1.8%)
Psychiatric disorders/Any Term	**13 (11.6%)**	**15 (13.4%)**
Insomnia	6 (5.4%)	9 (8.0%)
Investigations/Any Term	**6 (5.4%)**	**21 (18.8%)**
Weight decreased	0 (0.0%)	9 (8.0%)
Eye disorders/Any Term	**19 (17.0%)**	**7 (6.3%)**
Conjunctivitis	8 (7.1%)	1 (0.9%)
Lacrimation increased	6 (5.4%)	0 (0.0%)

Source: Post-text Table 14.3.1 - PFS Data Set: 27 March 2009.

Table 54: Treatment Emergent Adverse Events Occurring in ≥5% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**109 (97.3%)**	**112 (100%)**
Skin and subcutaneous tissue disorders/Any Term	**84 (75.0%)**	**101 (90.2%)**
Palmar-plantar erythrodysaesthesia syndrome	74 (66.1%)	101 (90.2%)
Alopecia	5 (4.5%)	36 (32.1%)
Rash	9 (8.0%)	25 (22.3%)
Dry skin	8 (7.1%)	11 (9.8%)
Pruritus	6 (5.4%)	7 (6.3%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Gastrointestinal disorders/Any Term	**64 (57.1%)**	**87 (77.7%)**
Diarrhoea	34 (30.4%)	65 (58.0%)
Nausea	36 (32.1%)	32 (28.6%)
Vomiting	18 (16.1%)	28 (25.0%)
Constipation	12 (10.7%)	26 (23.2%)
Abdominal pain upper	13 (11.6%)	19 (17.0%)
Abdominal pain	12 (10.7%)	12 (10.7%)
Stomatitis	7 (6.3%)	10 (8.9%)
Dyspepsia	5 (4.5%)	6 (5.4%)
General disorders and administration site conditions/Any Term	**69 (61.6%)**	**73 (65.2%)**
Asthenia	31 (27.7%)	32 (28.6%)
Mucosal inflammation	23 (20.5%)	37 (33.0%)
Fatigue	14 (12.5%)	17 (15.2%)
Pyrexia	8 (7.1%)	14 (12.5%)
Chest pain	10 (8.9%)	10 (8.9%)
Oedema peripheral	9 (8.0%)	11 (9.8%)
Pain	6 (5.4%)	8 (7.1%)
Nervous system disorders/Any Term	**40 (35.7%)**	**43 (38.4%)**
Headache	18 (16.1%)	20 (17.9%)
Paraesthesia	10 (8.9%)	15 (13.4%)
Dizziness	4 (3.6%)	8 (7.1%)

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Musculoskeletal and connective tissue disorders/Any Term	**39 (34.8%)**	**43 (38.4%)**
Back pain	13 (11.6%)	13 (11.6%)
Pain in extremity	9 (8.0%)	12 (10.7%)
Arthralgia	7 (6.3%)	9 (8.0%)
Musculoskeletal pain	4 (3.6%)	9 (8.0%)
Myalgia	6 (5.4%)	5 (4.5%)
Bone pain	6 (5.4%)	4 (3.6%)
Musculoskeletal chest pain	6 (5.4%)	3 (2.7%)
Respiratory, thoracic and mediastinal disorders/Any Term	**24 (21.4%)**	**38 (33.9%)**
Dyspnoea	14 (12.5%)	14 (12.5%)
Cough	9 (8.0%)	16 (14.3%)
Pleural effusion	3 (2.7%)	8 (7.1%)
Dysphonia	1 (0.9%)	7 (6.3%)
Infections and infestations/Any Term	**30 (26.8%)**	**29 (25.9%)**
Influenza	6 (5.4%)	6 (5.4%)
Metabolism and nutrition disorders/Any Term	**19 (17.0%)**	**32 (28.6%)**
Anorexia	13 (11.6%)	25 (22.3%)
Vascular disorders/Any Term	**21 (18.8%)**	**29 (25.9%)**
Hypertension	13 (11.6%)	20 (17.9%)
Blood and lymphatic system disorders/Any Term	**17 (15.2%)**	**26 (23.2%)**
Anaemia	6 (5.4%)	12 (10.7%)
Neutropenia	4 (3.6%)	14 (12.5%)
Thrombocytopenia	6 (5.4%)	3 (2.7%)
Investigations/Any Term	**7 (6.3%)**	**24 (21.4%)**
Weight decreased	0 (0.0%)	11 (9.8%)
Psychiatric disorders/Any Term	**14 (12.5%)**	**16 (14.3%)**
Insomnia	6 (5.4%)	9 (8.0%)
Eye disorders/Any Term	**19 (17.0%)**	**9 (8.0%)**
Conjunctivitis	8 (7.1%)	1 (0.9%)
Lacrimation increased	7 (6.3%)	0 (0.0%)

Source: Post-text Table 14.3.1 - OS Data Set: 30 June 2010.

Summary tables for all AEs are displayed in Section 14.3.1.

12.2.3 Analysis of adverse events

12.2.3.1 Drug-related adverse events

Drug-related AEs were those AEs related to either sorafenib/placebo or capecitabine (including those AEs related to both).

Table 55 and Table 56 display a summary of drug-related treatment emergent AEs occurring in ≥ 5% of either treatment group, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 55):

A total of 97 (86.6%) patients in the placebo + capecitabine group and 108 (96.4%) patients in the sorafenib + capecitabine group reported 1 or more drug-related treatment emergent AEs. The SOC with the greatest number of drug-related AEs was "skin and subcutaneous tissue disorders" where these AEs were experienced by 77 (68.8%) patients in the placebo + capecitabine group and 100 (89.3%) patients in the sorafenib + capecitabine group. The SOC with the second greatest number of drug-related AEs was "gastrointestinal disorders" where these AEs were experienced by 58 (51.8%) patients in the placebo + capecitabine group and 75 (67.0%) patients in the sorafenib + capecitabine group. The SOC with the third greatest number of drug-related AEs was "general disorders and administrative site conditions" where these AEs were experienced by 53 (47.3%) patients in the placebo + capecitabine group and 60 (53.6%) patients in the sorafenib + capecitabine group.

The drug-related AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 170 total patients: 70 (62.5%) patients in the placebo + capecitabine group and 100 (89.3%) patients in the sorafenib + capecitabine group. The second most common drug-related AE was diarrhea (SOC: gastrointestinal disorders), experienced by 85 total patients: 28 (25.0%) patients in the placebo + capecitabine group and 57 (50.9%) patients in the sorafenib + capecitabine group. The third most common drug-related AE was nausea (SOC: gastrointestinal disorders), experienced by 56 total patients: 32 (28.6%) patients in the placebo + capecitabine group and 24 (21.4%) patients in the sorafenib + capecitabine group. The fourth most common drug-related AE was mucosal inflammation (SOC: general disorders and administrative site conditions), experienced by 55 total patients: 19 (17.0%) patients in the placebo + capecitabine group and 36 (32.1%) patients in the sorafenib + capecitabine group. The fifth most common drug-related AE was asthenia (SOC: general disorders and administrative site conditions), experienced by 51 total patients: 28 (25.0%) patients in the placebo + capecitabine group and 23 (20.5%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 56):

A total of 100 (89.3%) patients in the placebo + capecitabine group and 109 (97.3%) patients in the sorafenib + capecitabine group reported 1 or more drug-related treatment emergent AEs. The SOC with the greatest number of drug-related AEs was "skin and subcutaneous tissue disorders" where these AEs were experienced by 81 (72.3%) patients

in the placebo + capecitabine group and 101 (90.2%) patients in the sorafenib + capecitabine group. The SOC with the second greatest number of drug-related AEs was "gastrointestinal disorders" where these AEs were experienced by 59 (52.7%) patients in the placebo + capecitabine group and 81 (72.3%) patients in the sorafenib + capecitabine group. The SOC with the third greatest number of drug-related AEs was "general disorders and administrative site conditions" where these AEs were experienced by 55 (49.1%) patients in the placebo + capecitabine group and 62 (55.4%) patients in the sorafenib + capecitabine group.

The drug-related AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 175 total patients: 74 (66.1%) patients in the placebo + capecitabine group and 101 (90.2%) patients in the sorafenib + capecitabine group. The second most common drug-related AE was diarrhea (SOC: gastrointestinal disorders), experienced by 93 total patients: 29 (25.9%) patients in the placebo + capecitabine group and 64 (57.1 %) patients in the sorafenib + capecitabine group. The third most common drug-related AE was nausea (SOC: gastrointestinal disorders), experienced by 59 total patients: 33 (29.5%) patients in the placebo + capecitabine group and 26 (23.2%) patients in the sorafenib + capecitabine group. The fourth most common drug-related AE was mucosal inflammation (SOC: general disorders and administrative site conditions), experienced by 58 total patients: 21 (18.8%) patients in the placebo + capecitabine group and 37 (33.0%) patients in the sorafenib + capecitabine group. The fifth most common drug-related AE was asthenia (SOC: general disorders and administrative site conditions), experienced by 57 total patients: 29 (25.9%) patients in the placebo + capecitabine group and 28 (25.0%) patients in the sorafenib + capecitabine group.

Table 55: Drug-Related Treatment Emergent Adverse Events Occurring in ≥5% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems / Any Term	**97 (86.6%)**	**108 (96.4%)**
Skin and subcutaneous tissue disorders/Any Term	**77 (68.8%)**	**100 (89.3%)**
Palmar-plantar erythrodysaesthesia syndrome	70 (62.5%)	100 (89.3%)
Alopecia	4 (3.6%)	29 (25.9%)
Rash	9 (8.0%)	22 (19.6%)
Dry skin	7 (6.3%)	9 (8.0%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Gastrointestinal disorders/Any Term	**58 (51.8%)**	**75 (67.0%)**
Diarrhea	28 (25.0%)	57 (50.9%)
Nausea	32 (28.6%)	24 (21.4%)
Vomiting	14 (12.5%)	18 (16.1%)
Abdominal pain upper	10 (8.9%)	16 (14.3%)
Constipation	7 (6.3%)	14 (12.5%)
Abdominal pain	7 (6.3%)	8 (7.1%)
Stomatitis	7 (6.3%)	6 (5.4%)
General disorders and administration site conditions/Any Term	**53 (47.3%)**	**60 (53.6%)**
Mucosal inflammation	19 (17.0%)	36 (32.1%)
Asthenia	28 (25.0%)	23 (20.5%)
Fatigue	12 (10.7%)	16 (14.3%)
Nervous system disorders/Any Term	**26 (23.2%)**	**26 (23.2%)**
Paraesthesia	9 (8.0%)	13 (11.6%)
Headache	8 (7.1%)	9 (8.0%)
Blood and lymphatic system disorders/Any Term	**11 (9.8%)**	**19 (17.0%)**
Neutropenia	4 (3.6%)	11 (9.8%)
Anaemia	3 (2.7%)	8 (7.1%)
Vascular disorders/Any Term	**12 (10.7%)**	**17 (15.2%)**
Hypertension	10 (8.9%)	17 (15.2%)
Metabolism and nutrition disorders/Any Term	**10 (8.9%)**	**18 (16.1%)**
Anorexia	9 (8.0%)	15 (13.4%)
Eye disorders/Any Term	**14 (12.5%)**	**5 (4.5%)**
Lacrimation increased	6 (5.4%)	0 (0.0%)

Source: Post-text Table 14.3.3 - PFS Data Set: 27 March 2009.

Table 56: Drug-Related Treatment Emergent Adverse Events Occurring in ≥5% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**100 (89.3%)**	**109 (97.3%)**
Skin and subcutaneous tissue disorders/Any Term	**81 (72.3%)**	**101 (90.2%)**
Palmar-plantar erythrodysaesthesia syndrome	74 (66.1%)	101 (90.2%)
Alopecia	4 (3.6%)	33 (29.5%)
Rash	9 (8.0%)	22 (19.6%)
Dry skin	7 (6.3%)	10 (8.9%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Gastrointestinal disorders/Any Term	**59 (52.7%)**	**81 (72.3%)**
Diarrhea	29 (25.9%)	64 (57.1%)
Nausea	33 (29.5%)	26 (23.2%)
Vomiting	15 (13.4%)	21 (18.8%)
Abdominal pain upper	10 (8.9%)	16 (14.3%)
Constipation	7 (6.3%)	15 (13.4%)
Abdominal pain	8 (7.1%)	8 (7.1%)
Stomatitis	7 (6.3%)	9 (8.0%)
General disorders and administration site conditions/Any Term	**55 (49.1%)**	**62 (55.4%)**
Mucosal inflammation	21 (18.8%)	37 (33.0%)
Asthenia	29 (25.9%)	28 (25.0%)
Fatigue	12 (10.7%)	17 (15.2%)
Nervous system disorders/Any Term	**26 (23.2%)**	**26 (23.2%)**
Paraesthesia	9 (8.0%)	14 (12.5%)
Headache	8 (7.1%)	9 (8.0%)
Blood and lymphatic system disorders/Any Term	**11 (9.8%)**	**22 (19.6%)**
Neutropenia	4 (3.6%)	13 (11.6%)
Anaemia	3 (2.7%)	10 (8.9%)
Metabolism and nutrition disorders/Any Term	**10 (8.9%)**	**20 (17.9%)**
Anorexia	8 (7.1%)	17 (15.2%)
Vascular disorders/Any Term	**12 (10.7%)**	**18 (16.1%)**
Hypertension	10 (8.9%)	18 (16.1%)
Investigations/Any Term	**4 (3.6%)**	**17 (15.2%)**
Weight decreased	0 (0.0%)	6 (5.4%)
Eye disorders/Any Term	**14 (12.5%)**	**6 (5.4%)**
Lacrimation increased	6 (5.4%)	0 (0.0%)

Source: Post-text Table 14.3.3 - OS Data Set: 30 June 2010.

12.2.3.2 Grade 3 or higher adverse events

Table 57 and Table 58 display a summary of grade 3 or higher treatment emergent AEs occurring in ≥ 2% of either treatment group, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 57):

A total of 47 (42.0%) patients in the placebo + capecitabine group and 67 (59.8%) patients in the sorafenib + capecitabine group reported 1 or more grade 3 or higher treatment emergent AEs. The SOC with the greatest number of grade 3 or higher AEs was "skin and subcutaneous tissue disorders" where these AEs were experienced by 15 (13.4%) patients in the placebo + capecitabine group and 52 (46.4%) patients in the sorafenib + capecitabine group. The SOC with the second greatest number of drug-related grade 3 or higher AEs was "general disorders and administrative site conditions" where these AEs were experienced by 12 (10.7%) patients in the placebo + capecitabine group and 8 (7.1%) patients in the sorafenib + capecitabine group. The SOC with the third greatest number of grade 3 or higher AEs was "gastrointestinal disorders" where these AEs were experienced by 7 (6.3%) patients in the placebo + capecitabine group and 10 (8.9%) patients in the sorafenib + capecitabine group.

The grade 3 or higher AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 65 total patients: 15 (13.4%) patients in the placebo + capecitabine group and 50 (44.6%) patients in the sorafenib + capecitabine group.
The second most common grade 3 or higher AE was diarrhea (SOC: gastrointestinal disorders), experienced by 11 total patients: 5 (4.5%) patients in the placebo + capecitabine group and 6 (5.4%) patients in the sorafenib + capecitabine group. The third most common grade 3 or higher AE was dyspnoea (SOC: respiratory, thoracic, and mediastinal disorders), experienced by 9 total patients: 4 (3.6%) patients in the placebo + capecitabine group and 5 (4.5%) patients in the sorafenib + capecitabine group.
The fourth most common grade 3 or higher AE was neutropenia (SOC: blood and lymphatic system disorders), experienced by 8 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 5 (4.5%) patients in the sorafenib + capecitabine group.
The fifth most common grade 3 or higher AE was thrombocytopenia (SOC: blood and lymphatic system disorders), experienced by 6 total patients: 5 (4.5%) patients in the placebo + capecitabine group and 1 (0.9%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 58):

A total of 51 (45.5%) patients in the placebo + capecitabine group and 70 (62.5%) patients in the sorafenib + capecitabine group reported 1 or more grade 3 or higher treatment emergent AEs. The SOC with the greatest number of grade 3 or higher AEs was "skin and subcutaneous tissue disorders" where these AEs were experienced by 17 (15.2%) patients in the placebo + capecitabine group and 51 (45.5%) patients in the sorafenib + capecitabine group. The SOC with the second greatest number of drug-related grade 3 or higher AEs was “general disorders and administrative site conditions “where these AEs were experienced by 13 (11.6%) patients in the placebo + capecitabine group and 10 (8.9%) patients in the sorafenib + capecitabine group. There were two SOCs with

the third greatest number of grade 3 or higher AEs: "gastrointestinal disorders" and "blood and lymphatic system disorders" both had a total of 19 patients with grade 3 or higher AEs; in the SOC "gastrointestinal disorders" grade 3 or higher AEs were experienced by 7 (6.3%) patients in the placebo + capecitabine group and 12 (10.7%) patients in the sorafenib + capecitabine group; in the SOC " blood and lymphatic system disorders grade 3 or higher AEs were experienced by 8 (7.1%) patients in the placebo + capecitabine group and 11 (9.8%) patients in the sorafenib + capecitabine group.

The grade 3 or higher AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 65 total patients: 16 (14.3%) patients in the placebo + capecitabine group and 49 (43.8%) patients in the sorafenib + capecitabine group.
The second most common grade 3 or higher AE was diarrhea (SOC: gastrointestinal disorders), experienced by 12 total patients: 5 (4.5%) patients in the placebo + capecitabine group and 7 (6.3%) patients in the sorafenib + capecitabine group. The third most common grade 3 or higher AE was dyspnoea (SOC: respiratory, thoracic, and mediastinal disorders), experienced by 9 total patients: 4 (3.6%) patients in the placebo + capecitabine group and 5 (4.5%) patients in the sorafenib + capecitabine group.
The fourth most common grade 3 or higher AE was neutropenia (SOC: blood and lymphatic system disorders), experienced by 8 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 5 (4.5%) patients in the sorafenib + capecitabine group.
There were two AEs that were the fifth most common grade 3 or higher AEs: thrombocytopenia and pleural effusion were both experienced by a total of 6 patients; thrombocytopenia (SOC: blood and lymphatic system disorders) was experienced by 5 (4.5%) patients in the placebo + capecitabine group and 1 (0.9%) patients in the sorafenib + capecitabine group; pleural effusion (SOC: respiratory, thoracic, and mediastinal disorders) was experienced by 2 (1.8%) patients in the placebo + capecitabine group and 4 (3.6%) patients in the sorafenib + capecitabine group.

Table 57: Grade 3 or Higher Treatment Emergent Adverse Events, Occurring in ≥2% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**47 (42.0%)**	**67 (59.8%)**
Skin and subcutaneous tissue disorders/Any Term	**15 (13.4%)**	**52 (46.4%)**
Palmar-plantar erythrodysaesthesia syndrome	15 (13.4%)	50 (44.6%)
Rash	0 (0.0%)	3 (2.7%)
General disorders and administration site conditions/Any Term	**12 (10.7%)**	**8 (7.1%)**
Mucosal inflammation	4 (3.6%)	1 (0.9%)
Gastrointestinal disorders/Any Term	**7 (6.3%)**	**10 (8.9%)**
Diarrhea	5 (4.5%)	6 (5.4%)
Blood and lymphatic system disorders/Any Term	**8 (7.1%)**	**8 (7.1%)**
Neutropenia	3 (2.7%)	5 (4.5%)
Thrombocytopenia	5 (4.5%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	**5 (4.5%)**	**8 (7.1%)**
Dyspnoea	4 (3.6%)	5 (4.5%)
Pleural effusion	2 (1.8%)	3 (2.7%)
Respiratory failure	1 (0.9%)	3 (2.7%)
Musculoskeletal and connective tissue disorders/Any Term	**2 (1.8%)**	**5 (4.5%)**
Pain in extremity	0 (0.0%)	3 (2.7%)

Source: Post-text Table 14.3.5 - PFS Data Set: 27 March 2009.

Table 58: Grade 3 or Higher Treatment Emergent Adverse Events, Occurring in ≥2% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**51 (45.5%)**	**70 (62.5%)**
Skin and subcutaneous tissue disorders/Any Term	**17 (15.2%)**	**51 (45.5%)**
Palmar-plantar erythrodysaesthesia syndrome	16 (14.3%)	49 (43.8%)
Rash	0 (0.0%)	4 (3.6%)
General disorders and administration site conditions/Any Term	**13 (11.6%)**	**10 (8.9%)**
Mucosal inflammation	4 (3.6%)	1 (0.9%)
Asthenia	3 (2.7%)	1 (0.9%)
Fatigue	1 (0.9%)	3 (2.7%)
Blood and lymphatic system disorders/Any Term	**8 (7.1%)**	**11 (9.8%)**
Neutropenia	3 (2.7%)	5 (4.5%)
Thrombocytopenia	5 (4.5%)	1 (0.9%)
Anaemia	1 (0.9%)	4 (3.6%)
Gastrointestinal disorders/Any Term	**7 (6.3%)**	**12 (10.7%)**
Diarrhea	5 (4.5%)	7 (6.3%)
Respiratory, thoracic and mediastinal disorders/Any Term	**6 (5.4%)**	**8 (7.1%)**
Dyspnoea	4 (3.6%)	5 (4.5%)
Pleural effusion	2 (1.8%)	4 (3.6%)
Musculoskeletal and connective tissue disorders/Any Term	**2 (1.8%)**	**6 (5.4%)**
Pain in extremity	0 (0.0%)	3 (2.7%)

Source: Post-text Table 14.3.5 - OS Data Set: 30 June 2010.

12.2.3.2.1 Grade 3 or higher drug-related adverse events, by worst NCI CTC grade

Table 59 and Table 60 display all grade 3 or higher drug-related treatment emergent AEs, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 59):

A total of 28 (25.0%) patients in the placebo + capecitabine group and 63 (56.3%) patients in the sorafenib + capecitabine group reported 1 or more grade 3 or higher drug-related treatment emergent AEs. Grade 3 drug-related AEs were experienced by 25 (22.3%) patients in the placebo + capecitabine group and by 62 (55.4%) patients in the sorafenib + capecitabine group. Grade 4 drug-related AEs were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 1 (0.9%) patient in the sorafenib + capecitabine group. Grade 5 drug-related AEs were experienced by 2 (1.8%) patients in

the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 60):

A total of 31 (27.7%) patients in the placebo + capecitabine group and 64 (57.1%) patients in the sorafenib + capecitabine group reported 1 or more grade 3 or higher drug-related treatment emergent AEs. Grade 3 drug-related AEs were experienced by 28 (25.0%) patients in the placebo + capecitabine group and by 63 (56.3%) patients in the sorafenib + capecitabine group. Grade 4 drug-related AEs were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 1 (0.9%) patient in the sorafenib + capecitabine group. Grade 5 drug-related AEs were experienced by 2 (1.8%) patients in the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group.

Table 59: Grade 3 and Higher Drug-related Treatment Emergent Adverse Events – Safety Population *(PFS data)*

System Organ Class and Preferred term	Placebo + Capecitabine N=112				Sorafenib + Capecitabine N=112			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	**25 (22.3%)**	**1 (0.9%)**	**2 (1.8%)**	**28 (25.0%)**	**62 (55.4%)**	**1 (0.9%)**	**0 (0.0%)**	**63 (56.3%)**
Skin and subcutaneous tissue disorders/Any Term	**15 (13.4%)**	**0 (0.0%)**	**0 (0.0%)**	**15 (13.4%)**	**52 (46.4%)**	**0 (0.0%)**	**0 (0.0%)**	**52 (46.4%)**
Palmar-plantar erythrodysaesthesia syndrome	15 (13.4%)	0 (0.0%)	0 (0.0%)	15 (13.4%)	50 (44.6%)	0 (0.0%)	0 (0.0%)	50 (44.6%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash erythematous	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blister	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	**6 (5.4%)**	**0 (0.0%)**	**0 (0.0%)**	**6 (5.4%)**	**10 (8.9%)**	**0 (0.0%)**	**0 (0.0%)**	**10 (8.9%)**
Diarrhea	5 (4.5%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Vomiting	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Constipation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**4 (3.6%)**	**1 (0.9%)**	**0 (0.0%)**	**5 (4.5%)**	**3 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**3 (2.7%)**
Mucosal inflammation	2 (1.8%)	1 (0.9%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Fatigue	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oedema peripheral	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

System Organ Class and Preferred term	Placebo + Capecitabine N=112				Sorafenib + Capecitabine N=112			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
Nervous system disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**
Paraesthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neuropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	**5 (4.5%)**	**1 (0.9%)**	**0 (0.0%)**	**6 (5.4%)**	**5 (4.5%)**	**1 (0.9%)**	**0 (0.0%)**	**6 (5.4%)**
Neutropenia	2 (1.8%)	1 (0.9%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	5 (4.5%)
Anaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Leukopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Thrombocytopenia	3 (2.7%)	1 (0.9%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Hyperlipidaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders/ Any Term	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Hypertension	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Investigations/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Aspartate aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood amylase increased	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**
Musculoskeletal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pain in extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**1 (0.9%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

System Organ Class and Preferred term	Placebo + Capecitabine N=112				Sorafenib + Capecitabine N=112			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
Hepatobiliary disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Hyperbilirubinaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Folliculitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	**1 (0.9%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
Cardiac arrest	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Renal failure	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Post-text Table 14.3.4 - PFS Data Set: 27 March 2009.

Table 60: Grade 3 and Higher Drug-related Treatment Emergent Adverse Events – Safety Population *(OS data)*

System Organ Class and Preferred term	Placebo + Capecitabine N=112				Sorafenib + Capecitabine N=112			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	**28 (25.0%)**	**1 (0.9%)**	**2 (1.8%)**	**31 (27.7%)**	**63 (56.3%)**	**1 (0.9%)**	**0 (0.0%)**	**64 (57.1%)**
Skin and subcutaneous tissue disorders/Any Term	**17 (15.2%)**	**0 (0.0%)**	**0 (0.0%)**	**17 (15.2%)**	**51 (45.5%)**	**0 (0.0%)**	**0 (0.0%)**	**51 (45.5%)**
Palmar-plantar erythrodysaesthesia syndrome	16 (14.3%)	0 (0.0%)	0 (0.0%)	16 (14.3%)	49 (43.8%)	0 (0.0%)	0 (0.0%)	49 (43.8%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Onycholysis	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash erythematous	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash maculo-papular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash vesicular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blister	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	**6 (5.4%)**	**0 (0.0%)**	**0 (0.0%)**	**6 (5.4%)**	**10 (8.9%)**	**0 (0.0%)**	**0 (0.0%)**	**10 (8.9%)**
Diarrhea	5 (4.5%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Vomiting	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Constipation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

System Organ Class and Preferred term	Placebo + Capecitabine N=112				Sorafenib + Capecitabine N=112			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
General disorders and administration site conditions/Any Term	**4 (3.6%)**	**1 (0.9%)**	**0 (0.0%)**	**5 (4.5%)**	**4 (3.6%)**	**0 (0.0%)**	**0 (0.0%)**	**4 (3.6%)**
Mucosal inflammation	2 (1.8%)	1 (0.9%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Fatigue	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oedema peripheral	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Nervous system disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**
Paraesthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neuropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	**5 (4.5%)**	**1 (0.9%)**	**0 (0.0%)**	**6 (5.4%)**	**6 (5.4%)**	**1 (0.9%)**	**0 (0.0%)**	**7 (6.3%)**
Neutropenia	2 (1.8%)	1 (0.9%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	5 (4.5%)
Anaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Leukopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Thrombocytopenia	3 (2.7%)	1 (0.9%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**
Anorexia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders/ Any Term	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Hypertension	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

System Organ Class and Preferred term	Placebo + Capecitabine N=112				Sorafenib + Capecitabine N=112			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
Investigations/Any Term	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**3 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**3 (2.7%)**
Aspartate aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lipase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood amylase increased	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**
Musculoskeletal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pain in extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**1 (0.9%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatobiliary disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Hyperbilirubinaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Folliculitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Cardiac arrest	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Renal failure	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Post-text Table 14.3.4 - OS Data Set: 30 June 2010.

12.2.3.3 Adverse events leading to discontinuation of any study treatment

Table 61 and Table 62 display all treatment emergent AEs leading to discontinuation of any study treatment, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 61):

A total of 9 (8.0%) patients in the placebo + capecitabine group and 15 (13.4%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of any study treatment.

The AE leading to discontinuation of any study treatment that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 10 total patients: 2 (1.8%) patients in the placebo + capecitabine group and 8 (7.1%) patients in the sorafenib + capecitabine group. The second most common AE leading to discontinuation of any study treatment was diarrhea (SOC: gastrointestinal disorders), experienced by 4 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 1 (0.9%) patients in the sorafenib + capecitabine group. The third most common AE leading to discontinuation of any study treatment was dyspnoea (SOC: respiratory, thoracic, and mediastinal disorders), experienced by 2 total patients: 0 (0.0%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 62):

A total of 11 (9.8%) patients in the placebo + capecitabine group and 22 (19.6%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of any study treatment.

The AE leading to discontinuation of any study treatment that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 13 total patients: 4 (3.6%) patients in the placebo + capecitabine group and 9 (8.0%) patients in the sorafenib + capecitabine group. The second and third most common AEs leading to discontinuation of any study were identical to those reported above for the PFS data set.

Table 61: Adverse Events Leading to Discontinuation of Any Study Treatment, by System Organ Class and Preferred Term – Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**9 (8.0%)**	**15 (13.4%)**
Skin and subcutaneous tissue disorders/Any Term	**2 (1.8%)**	**8 (7.1%)**
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	8 (7.1%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	**4 (3.6%)**	**2 (1.8%)**
Diarrhea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**2 (1.8%)**	**2 (1.8%)**
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**1 (0.9%)**	**2 (1.8%)**
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Anaemia	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	**1 (0.9%)**	**0 (0.0%)**
Septic shock	1 (0.9%)	0 (0.0%)
Investigations/Any Term	**0 (0.0%)**	**1 (0.9%)**
Alanine aminotransferase increased	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Cell death	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Musculoskeletal pain	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Abbreviations: N = number.
Source: Post-text Table 14.3.10 - PFS Data Set: 27 March 2009.

Table 62: Adverse Events Leading to Discontinuation of Any Study Treatment, by System Organ Class and Preferred Term – Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**11 (9.8%)**	**22 (19.6%)**
Skin and subcutaneous tissue disorders/Any Term	**4 (3.6%)**	**10 (8.9%)**
Palmar-plantar erythrodysaesthesia syndrome	4 (3.6%)	9 (8.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	**4 (3.6%)**	**2 (1.8%)**
Diarrhea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**1 (0.9%)**	**3 (2.7%)**
Anaemia	1 (0.9%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Neutropenia	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	**2 (1.8%)**	**2 (1.8%)**
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**1 (0.9%)**	**2 (1.8%)**
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	**1 (0.9%)**	**1 (0.9%)**
Septic shock	1 (0.9%)	1 (0.9%)
Investigations/Any Term	**0 (0.0%)**	**2 (1.8%)**
Alanine aminotransferase increased	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**1 (0.9%)**
Cell death	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**2 (1.8%)**
Arthralgia	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	**0 (0.0%)**	**1 (0.9%)**
Wound dehiscence	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Renal failure acute	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Source: Post-text Table 14.3.10 - OS Data Set: 30 June 2010.

12.2.3.4 Adverse events leading to discontinuation of sorafenib/placebo

Table 63 and Table 64 display all treatment emergent AEs leading to discontinuation of sorafenib/placebo, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 63):

A total of 8 (7.1%) patients in the placebo + capecitabine group and 14 (12.5%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of sorafenib/placebo.

The AE leading to discontinuation sorafenib/placebo that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 10 total patients: 2 (1.8%) patients in the placebo + capecitabine group and 8 (7.1%) patients in the sorafenib + capecitabine group. The second most common AE leading to discontinuation of sorafenib/placebo was diarrhea (SOC: gastrointestinal disorders), experienced by 4 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 1 (0.9%) patients in the sorafenib + capecitabine group. The third most common AE leading to discontinuation of sorafenib/placebo was dyspnoea (SOC: respiratory, thoracic, and mediastinal disorders), experienced by 2 total patients: 0 (0.0%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 64):

A total of 10 (8.9%) patients in the placebo + capecitabine group and 20 (17.9%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of sorafenib/placebo.

The AE leading to discontinuation of sorafenib/placebo that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 13 total patients: 4 (3.6%) patients in

the placebo + capecitabine group and 9 (8.0%) patients in the sorafenib + capecitabine group. The second and third most common AEs leading to discontinuation of sorafenib/placebo were identical to those reported above for the PFS data set.

Table 63: Adverse Events Leading to Discontinuation of Sorafenib/Placebo, by System Organ Class and Preferred Term – Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	8 (7.1%)	14 (12.5%)
Skin and subcutaneous tissue disorders/Any Term	2 (1.8%)	8 (7.1%)
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	8 (7.1%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	4 (3.6%)	2 (1.8%)
Diarrhea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	**1 (0.9%)**	**0 (0.0%)**
Septic shock	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Cell death	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Musculoskeletal pain	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Abbreviations: N = number.
Source: Post-text Table 14.3.11 - PFS Data Set: 27 March 2009.

Table 64: Adverse Events Leading to Discontinuation of Sorafenib/Placebo, by System Organ Class and Preferred Term – Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**10 (8.9%)**	**20 (17.9%)**
Skin and subcutaneous tissue disorders/Any Term	**4 (3.6%)**	**10 (8.9%)**
Palmar-plantar erythrodysaesthesia syndrome	4 (3.6%)	9 (8.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	**4 (3.6%)**	**2 (1.8%)**
Diarrhea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**2 (1.8%)**	**2 (1.8%)**
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**1 (0.9%)**	**2 (1.8%)**
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**0 (0.0%)**	**2 (1.8%)**
Leukocytosis	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	**1 (0.9%)**	**1 (0.9%)**
Septic shock	1 (0.9%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**1 (0.9%)**
Cell death	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**2 (1.8%)**
Arthralgia	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	**0 (0.0%)**	**1 (0.9%)**
Wound dehiscence	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Renal failure acute	0 (0.0%)	1 (0.9%)

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Reproductive system and breast disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Abbreviations: N = number.
Source: Post-text Table 14.3.11 - OS Data Set: 30 June 2010.

12.2.3.4.1 Grade 3 and higher adverse events leading to discontinuation of sorafenib/placebo

Table 65 and Table 66 display all grade 3 and higher treatment emergent AEs leading to discontinuation of sorafenib/placebo, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 65):

Grade 3 AEs leading to discontinuation of sorafenib/placebo were experienced by 4 (3.6%) patients in the placebo + capecitabine group and by 11 (9.8%) patients in the sorafenib + capecitabine group. Grade 4 AEs leading to discontinuation of sorafenib/placebo were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group. Grade 5 AEs leading to discontinuation of sorafenib/placebo were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 66):

Grade 3 AEs leading to discontinuation of sorafenib/placebo were experienced by 5 (4.5%) patients in the placebo + capecitabine group and by 11 (9.8%) patients in the sorafenib + capecitabine group. Grade 4 AEs leading to discontinuation of sorafenib/placebo were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group. Grade 5 AEs leading to discontinuation of sorafenib/placebo were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 1 (0.9%) patients in the sorafenib + capecitabine group.

Table 65: Grade 3 and Higher Adverse Events leading to Discontinuation of Sorafenib/Placebo – Safety Population *(PFS data)*

System Organ Class and Preferred term	Placebo + Capecitabine N=112			Sorafenib + Capecitabine N=112		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
All Systems/Any Term	4 (3.6%)	1 (0.9%)	1 (0.9%)	11 (9.8%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders/Any Term	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	0 (0.0%)	0 (0.0%)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	0 (0.0%)	0 (0.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	**3 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Diarrhea	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**1 (0.9%)**	**1 (0.9%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Musculoskeletal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Infections and infestations/Any Term	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Septic shock	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Cell death	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: N = number.
Source: Post-text Table 14.3.14 - PFS Data Set: 27 March 2009.

Table 66: Grade 3 and Higher Adverse Events leading to Discontinuation of Sorafenib/Placebo – Safety Population *(OS data)*

System Organ Class and Preferred term	Placebo + Capecitabine N=112			Sorafenib + Capecitabine N=112		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
All Systems/Any Term	**5 (4.5%)**	**1 (0.9%)**	**1 (0.9%)**	**11 (9.8%)**	**0 (0.0%)**	**1 (0.9%)**
Skin and subcutaneous tissue disorders/Any Term	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**6 (5.4%)**	**0 (0.0%)**	**0 (0.0%)**
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	0 (0.0%)	0 (0.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**
Leukocytosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Gastrointestinal disorders/Any Term	**3 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Diarrhea	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**1 (0.9%)**	**1 (0.9%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Bone pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations/Any Term	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Septic shock	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**
Metabolic acidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Cell death	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**
Renal failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)

Abbreviations: N = number.
Source: Post-text Table 14.3.14 - OS Data Set: 30 June 2010.

12.2.3.5 Adverse events leading to discontinuation of capecitabine

Table 67 and Table 68 display all treatment emergent AEs leading to discontinuation of capecitabine, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 67):

A total of 8 (7.1%) patients in the placebo + capecitabine group and 14 (12.5%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of capecitabine.

The AE leading to discontinuation capecitabine that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 9 total patients: 2 (1.8%) patients in the placebo + capecitabine group and 7 (6.3%) patients in the sorafenib + capecitabine group. The second most common AE leading to discontinuation of capecitabine was diarrhea (SOC: gastrointestinal disorders), experienced by 4 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 1 (0.9%) patients in the sorafenib + capecitabine group. The third most common AE leading to discontinuation of capecitabine was dyspnoea (SOC: respiratory, thoracic, and mediastinal disorders), experienced by 2 total patients: (0.0%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 68):

A total of 10 (8.9%) patients in the placebo + capecitabine group and 22 (19.6%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of capecitabine.

The AE leading to discontinuation of capecitabine that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 13 total patients: 4 (3.6%) patients in the placebo + capecitabine group and 9 (8.0%) patients in the sorafenib + capecitabine group. The second and third most common AEs leading to discontinuation of capecitabine were identical to those reported above for the PFS data set.

Table 67: Adverse Events Leading to Discontinuation of Capecitabine, by System Organ Class and Preferred Term – Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**8 (7.1%)**	**14 (12.5%)**
Skin and subcutaneous tissue disorders/Any Term	**2 (1.8%)**	**7 (6.3%)**
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	7 (6.3%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	**4 (3.6%)**	**2 (1.8%)**
Diarrhea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**2 (1.8%)**	**2 (1.8%)**
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**1 (0.9%)**	**2 (1.8%)**
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Anaemia	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	**1 (0.9%)**	**0 (0.0%)**
Septic shock	1 (0.9%)	0 (0.0%)
Investigations/Any Term	**0 (0.0%)**	**1 (0.9%)**
Alanine aminotransferase increased	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Cell death	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Musculoskeletal pain	0 (0.0%)	1 (0.9%)

Abbreviations: N = number.
Source: Post-text Table 14.3.12 - PFS Data Set: 27 March 2009.

Table 68: Adverse Events Leading to Discontinuation of Capecitabine, by System Organ Class and Preferred Term – Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**10 (8.9%)**	**22 (19.6%)**
Skin and subcutaneous tissue disorders/Any Term	**4 (3.6%)**	**10 (8.9%)**
Palmar-plantar erythrodysaesthesia syndrome	4 (3.6%)	9 (8.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	**4 (3.6%)**	**2 (1.8%)**
Diarrhea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**1 (0.9%)**	**3 (2.7%)**
Anaemia	1 (0.9%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Neutropenia	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	**2 (1.8%)**	**2 (1.8%)**
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**1 (0.9%)**	**2 (1.8%)**
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	**1 (0.9%)**	**1 (0.9%)**
Septic shock	1 (0.9%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**1 (0.9%)**
Cell death	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**2 (1.8%)**
Arthralgia	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	**0 (0.0%)**	**1 (0.9%)**
Wound dehiscence	0 (0.0%)	1 (0.9%)

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Renal and urinary disorders/Any Term	**0 (0.0%)**	**1 (0.9%)**
Renal failure acute	0 (0.0%)	1 (0.9%)

Abbreviations: N = number.
Source: Post-text Table 14.3.12 - OS Data Set: 30 June 2010.

12.2.3.5.1 Grade 3 and higher adverse events leading to discontinuation of capecitabine

Table 69 and Table 70 display all grade 3 and higher treatment emergent AEs leading to discontinuation of capecitabine, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 69):

Grade 3 AEs leading to discontinuation of capecitabine were experienced by 5 (4.5%) patients in the placebo + capecitabine group and by 10 (8.9 %) patients in the sorafenib + capecitabine group. Grade 4 AEs leading to discontinuation of capecitabine were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group. Grade 5 AEs leading to discontinuation of capecitabine were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 70):

Grade 3 AEs leading to discontinuation of capecitabine were experienced by 6 (5.4%) patients in the placebo + capecitabine group and by 12 (10.7%) patients in the sorafenib + capecitabine group. Grade 4 AEs leading to discontinuation of capecitabine were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 0 (0.0%) patients in the sorafenib + capecitabine group. Grade 5 AEs leading to discontinuation of capecitabine were experienced by 1 (0.9%) patient in the placebo + capecitabine group and by 1 (0.9%) patients in the sorafenib + capecitabine group.

Table 69: Grade 3 and Higher Adverse Events leading to Discontinuation of Capecitabine – Safety Population *(PFS data)*

System Organ Class and Preferred term	Placebo + Capecitabine N=112			Sorafenib + Capecitabine N=112		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
All Systems/Any Term	**5 (4.5%)**	**1 (0.9%)**	**1 (0.9%)**	**10 (8.9%)**	**0 (0.0%)**	**0 (0.0%)**
Skin and subcutaneous tissue disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**6 (5.4%)**	**0 (0.0%)**	**0 (0.0%)**
Palmar-plantar erythrodysaesthesia syndrome	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	0 (0.0%)	0 (0.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	**3 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Diarrhea	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**1 (0.9%)**	**1 (0.9%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Musculoskeletal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Anaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations/Any Term	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Septic shock	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Cell death	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: N = number.
Source: Post-text Table 14.3.13 - PFS Data Set: 27 March 2009.

Table 70: Grade 3 and Higher Adverse Events leading to Discontinuation of Capecitabine – Safety Population *(OS data)*

System Organ Class and Preferred term	Placebo + Capecitabine N=112			Sorafenib + Capecitabine N=112		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
All Systems/Any Term	**6 (5.4%)**	**1 (0.9%)**	**1 (0.9%)**	**12 (10.7%)**	**0 (0.0%)**	**1 (0.9%)**
Skin and subcutaneous tissue disorders/Any Term	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**	**6 (5.4%)**	**0 (0.0%)**	**0 (0.0%)**
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	0 (0.0%)	0 (0.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**
Leukocytosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Anemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	**3 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Diarrhea	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	**1 (0.9%)**	**1 (0.9%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Transaminases increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Bone pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**2 (1.8%)**	**0 (0.0%)**	**0 (0.0%)**
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations/Any Term	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**
Septic shock	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**
Metabolic acidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Cell death	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

System Organ Class and Preferred term	Placebo + Capecitabine N=112			Sorafenib + Capecitabine N=112		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Renal and urinary disorders/Any Term	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.9%)**	**0 (0.0%)**
Renal failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)

Abbreviations: N = number.
Source: Post-text Table 14.3.15 - OS Data Set: 30 June 2010.

12.2.4 Listing of adverse events by patient

Listings of AEs for each patient are available upon request.

12.3 Deaths, other serious adverse events, and other significant adverse events

12.3.1 Listing of deaths, other serious adverse events and other significant adverse events

The listing of deaths, other serious adverse events and other significant adverse events is shown in Section 14.3.2.

12.3.1.1 Deaths

Table 71 and Table 72 display a summary of the incidence of deaths, including the cause, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 71):

A total of 5 (4.5%) on-study deaths occurred in the placebo + capecitabine group and 5 (4.5%) on-study deaths occurred in the sorafenib + capecitabine group before the cutoff date for PFS data. The most common cause of death was progressive disease, which was reported for 3 (2.7%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group. One patient (0.9%) in the placebo + capecitabine had a cause of death reported as toxicity due to study treatment (with at least one AE with the outcome of death).

For the OS data set (Table 72):

A total of 65 (58.0%) on-study deaths occurred in the placebo + capecitabine group and 60 (53.6%) on-study deaths occurred in the sorafenib + capecitabine group before the cutoff date for OS data. A total of 5 (4.5%) patients in the placebo + capecitabine group and 7 (6.3%) patients in the sorafenib + capecitabine group were reported as deceased within 30 days post treatment. A total of 60 (53.6%) patients in the placebo + capecitabine group and 53 (47.3%) patients in the sorafenib + capecitabine group were reported as deceased beyond 30 days post treatment.

The most common cause of death for patients deceased within 30 days post treatment was progressive disease, which was reported for 3 (2.7%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group. The most common cause of death for patients deceased beyond 30 days post treatment was

progressive disease, which was reported for 60 (53.6%) patients in the placebo + capecitabine group and 53 (47.3%) patients in the sorafenib + capecitabine group.

Table 71: Incidence of Deaths - Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
On-study deaths	**5 (4.5%)**	**5 (4.5%)**
Cause		
Progressive disease	3 (2.7%)	2 (1.8%)
Toxicity due to study treatment (with at least one AE with the outcome of death)	1 (0.9%)	0 (0.0%)
Toxicity due to study treatment	1 (0.9%)	0 (0.0%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Other	0 (0.0%)	1 (0.9%)

Note: On-study death was defined as death that occurred during the study treatment period or within 30 days post-study treatment discontinuation.
Source: Post-text Table 14.3.7 - PFS Data Set: 27 March 2009.

Table 72: Incidence of Deaths - Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Total deaths	**65 (58.0%)**	**60 (53.6%)**
Deceased within 30 Days Post Treatment	**5 (4.5%)**	**7 (6.3%)**
Cause		
Progressive disease	3 (2.7%)	2 (1.8%)
Toxicity due to study treatment (with at least one AE with the outcome of death)	1 (0.9%)	0 (0.0%)
Toxicity due to study treatment	1 (0.9%)	0 (0.0%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Other	0 (0.0%)	3 (2.7%)
Deceased beyond 30 Days Post Treatment	**60 (53.6%)**	**53 (47.3%)**
Progressive disease	57 (50.9%)	51 (45.5%)
Other	3 (2.7%)	2 (1.8%)

Source: Post-text Table 14.3.7 - OS Data Set: 30 June 2010.

12.3.1.2 Serious adverse events

Table 73 and Table 74 display a summary of serious treatment emergent AEs occurring in ≥ 2% of either treatment group, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets.

For the PFS data set (Table 73):

A total of 30 (26.8%) patients in the placebo + capecitabine group and 36 (32.1%) patients in the sorafenib + capecitabine group reported 1 or more serious treatment emergent AEs.

The serious AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 19 total patients: 5 (4.5%) patients in the placebo + capecitabine group and 14 (12.5%) patients in the sorafenib + capecitabine group. There were two AEs that were the second most common serious AEs: pleural effusion and diarrhea were both experienced by a total of 6 patients; pleural effusion (SOC: respiratory, thoracic, and mediastinal disorders) was experienced by 2 (1.8%) patients in the placebo + capecitabine group and 4 (3.6%) patients in the sorafenib + capecitabine group; diarrhea (SOC: gastrointestinal disorders) was experienced by 4 (3.6%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group. The third most common serious AE was dyspnoea (SOC: respiratory, thoracic, and mediastinal disorders), experienced by a total of 5 patients: 2 (1.8%) patients in the placebo + capecitabine group and 3 (2.7%) patients in the sorafenib + capecitabine group.
The fourth most common serious AE was vomiting (SOC: gastrointestinal disorders), experienced by 3 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 0 (0.0%) patients in the sorafenib + capecitabine group. There were no additional serious AEs experienced by ≥ 2% of either treatment group.

For the OS data set (Table 74):

A total of 31 (27.7 %) patients in the placebo + capecitabine group and 40 (35.7%) patients in the sorafenib + capecitabine group reported 1 or more serious treatment emergent AEs.

The serious AE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 19 total patients: 5 (4.5%) patients in the placebo + capecitabine group and 14 (12.5%) patients in the sorafenib + capecitabine group. The second most common serious AE was pleural effusion (SOC: respiratory, thoracic, and mediastinal disorders), experienced by 2 (1.8%) patients in the placebo + capecitabine group and 5 (4.5%) patients in the sorafenib + capecitabine group. The third most common serious AE was diarrhea (SOC: gastrointestinal disorders), experienced by 4 (3.6%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group dyspnoea (SOC: respiratory, thoracic, and mediastinal disorders). The fourth most common serious AE was vomiting (SOC: gastrointestinal disorders), experienced by 3 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 0 (0.0%) patients in the sorafenib + capecitabine group. There were no additional serious AEs experienced by ≥ 2% of either treatment group.

Table 73: Serious Treatment Emergent Adverse Events, Occurring in ≥2% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(PFS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**30 (26.8%)**	**36 (32.1%)**
Skin and subcutaneous tissue disorders/Any Term	**5 (4.5%)**	**14 (12.5%)**
Palmar-plantar erythrodysaesthesia syndrome	5 (4.5%)	14 (12.5%)
Respiratory, thoracic and mediastinal disorders/Any Term	**5 (4.5%)**	**8 (7.1%)**
Pleural effusion	2 (1.8%)	4 (3.6%)
Dyspnoea	2 (1.8%)	3 (2.7%)
Gastrointestinal disorders/Any Term	**7 (6.3%)**	**3 (2.7%)**
Diarrhea	4 (3.6%)	2 (1.8%)
Vomiting	3 (2.7%)	0 (0.0%)

Source: Post-text Table 14.3.8 - PFS Data Set: 27 March 2009.

Table 74: Serious Treatment Emergent Adverse Events, Occurring in ≥2% of Either Treatment Group, by System Organ Class and Preferred Term – Safety Population *(OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**31 (27.7%)**	**40 (35.7%)**
Skin and subcutaneous tissue disorders/Any Term	5 (4.5%)	14 (12.5%)
Palmar-plantar erythrodysaesthesia syndrome	5 (4.5%)	14 (12.5%)
Respiratory, thoracic and mediastinal disorders/Any Term	6 (5.4%)	8 (7.1%)
Pleural effusion	2 (1.8%)	5 (4.5%)
Dyspnoea	2 (1.8%)	3 (2.7%)
Gastrointestinal disorders/Any Term	7 (6.3%)	3 (2.7%)
Diarrhea	4 (3.6%)	2 (1.8%)
Vomiting	3 (2.7%)	0 (0.0%)

Source: Post-text Table 14.3.8 - OS Data Set: 30 June 2010.

12.3.1.3 Drug-related serious adverse events

Table 75 displays a summary of all drug-related serious treatment emergent AEs, by system organ class and preferred term, based on the 224 patients in the safety population, for the PFS and OS data sets. These data were identical for the PFS and OS data sets, and thus, are presented within a single table.

Drug-related serious adverse events were those SAEs related to either sorafenib/placebo or capecitabine (including those AEs related to both).

A total of 11 (9.8%) patients in the placebo + capecitabine group and 20 (17.9%) patients in the sorafenib + capecitabine group reported 1 or more drug-related SAEs. The SOC with the greatest number of drug-related SAEs was "skin and subcutaneous tissue disorders" where drug-related SAEs were experienced by 5 (68.8%) patients in the placebo + capecitabine group and 14 (12.5%) patients in the sorafenib + capecitabine group. The SOC with the second greatest number of drug-related SAEs was "gastrointestinal disorders" where drug-related SAEs were experienced by 3 (2.7%) patients in the placebo + capecitabine group and 3 (2.7%) patients in the sorafenib + capecitabine group. The SOC with the third greatest number of drug-related SAEs was "general disorders and administrative site conditions" where drug-related SAEs were experienced by 2 (1.8%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group.

The drug-related SAE that was experienced by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders), experienced by 19 total patients: 5 (4.5%) patients in the placebo + capecitabine group and 14 (12.5%) patients in the sorafenib + capecitabine group. The second most common drug-related SAE was diarrhea (SOC: gastrointestinal disorders), experienced by 5 total patients: 3 (2.7%) patients in the placebo + capecitabine group and 2 (1.8%) patients in the sorafenib + capecitabine group. The third most common drug-related SAE was vomiting (SOC: gastrointestinal disorders), experienced by 2 total patients: 2 (1.8%) patients in the placebo + capecitabine group and 0 (0.0%) patients in the sorafenib + capecitabine group. There were no additional drug-related SAEs experienced by more than 1 patient in either treatment group.

Table 75: Drug-related Serious Treatment Emergent Adverse Events, by System Organ Class and Preferred Term – Safety Population *(PFS and OS data)*

System Organ Class and Preferred Term	Treatment Group	
	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
All Systems/Any Term	**11 (9.8%)**	**20 (17.9%)**
Skin and subcutaneous tissue disorders/Any Term	**5 (4.5%)**	**14 (12.5%)**
Palmar-plantar erythrodysaesthesia syndrome	5 (4.5%)	14 (12.5%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	**3 (2.7%)**	**3 (2.7%)**
Diarrhea	3 (2.7%)	2 (1.8%)
Vomiting	2 (1.8%)	0 (0.0%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	**2 (1.8%)**	**2 (1.8%)**
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Oedema peripheral	1 (0.9%)	0 (0.0%)
Pyrexia	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	**1 (0.9%)**	**1 (0.9%)**
Neutropenia	1 (0.9%)	1 (0.9%)
Thrombocytopenia	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	**1 (0.9%)**	**1 (0.9%)**
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	**1 (0.9%)**	**1 (0.9%)**
Dyspnoea	0 (0.0%)	1 (0.9%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Cell death	1 (0.9%)	0 (0.0%)
Renal and urinary disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Renal failure	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	**1 (0.9%)**	**0 (0.0%)**
Hypertension	1 (0.9%)	0 (0.0%)

Source: Post-text Table 14.3.9 - PFS and OS Data Sets: 27 March 2009 and 30 June 2010.

12.3.2 Narratives of deaths, other serious adverse events and other significant adverse events

Narratives of deaths, other serious adverse events and other significant adverse events are included in Section 14.5.

12.3.3 Analysis and discussion of deaths, other serious adverse events and other significant adverse events

There were no apparent differences between the treatment groups in terms of the total number of patients who died, the number of deaths within 30 days of the end of treatment, and the cause of death. Refer to Section 14.5 for the narratives, which contain detailed information regarding deaths, other serious adverse events and other significant adverse events.

Death of 1 patient in the placebo + capecitabine group was considered related to treatment: patient 16-320-1010 died 3 days after the termination of placebo + capecitabine due to a cardiac arrest (CTC Grade 5) that the investigator considered related to study drug. Death of 1 patient in the placebo + capecitabine group was considered a "toxicity due to study treatment with at least one AE with the outcome of death": patient 24-300-1011 died approximately 2 months after the termination of placebo + capecitabine due to septic shock, and had experienced Grade 4 thrombocytopenia that was considered related to study treatment on two separate occasions, both within 30 days of discontinuation of study treatment.

One or more drug-related SAEs were reported by 9.8% of patients in the placebo + capecitabine group and 17.9% of patients in the sorafenib + capecitabine group.

The drug-related SAE that was reported by the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome (SOC: skin and subcutaneous tissue disorders): reported by 4.5% of placebo + capecitabine patients and 12.5% of sorafenib + capecitabine patients. The second most common drug-related SAE was diarrhea (SOC: gastrointestinal disorders): reported by 2.7% of placebo + capecitabine patients and 1.8% of sorafenib + capecitabine patients. The third most common drug-related SAE was vomiting (SOC: gastrointestinal disorders): reported by 1.8% placebo + capecitabine patients and 0% of sorafenib + capecitabine patients. There were no additional drug-related SAEs experienced by more than 1 patient in either treatment group.

The AEs of special interest include neutrophils/granulocytes, leukocytes, platelets, hemoglobin, febrile neutropenia, sensory neuropathy, fatigue, diarrhea, nausea, mucositis, thrombus/embolism, hemorrhage/bleeding, hypertension, hand-foot skin reaction, rash/desquamation, dermatology-other, and pruritis, all of which may be associated with sorafenib use.

The AEs which occurred with notably higher frequency in the sorafenib + capecitabine group included the AEs palmar-plantar erythrodysaesthesia syndrome (also called hand foot skin reaction), alopecia, rash, diarrhea, vomiting, constipation, neutropenia, and anaemia. The AE that was reported in the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome, reported by 66.1% of placebo + capecitabine patients and 90.2% of sorafenib + capecitabine patients (OS data set). Alopecia was reported by 4.5% of placebo + capecitabine patients and 32.1% of sorafenib + capecitabine patients (OS data set). Rash was reported by 8.0% of placebo + capecitabine patients and 22.3% of sorafenib + capecitabine patients (OS data set). Diarrhea was reported by 30.4% of placebo + capecitabine patients and 58.0% of sorafenib + capecitabine patients (OS data set). Vomiting was reported by 16.1% of placebo + capecitabine patients and 25.0% of sorafenib + capecitabine patients (OS data set). Constipation was reported by 10.7% of placebo + capecitabine patients and 23.2% of sorafenib + capecitabine patients (OS data set). Neutropenia was reported by 3.6% of placebo + capecitabine patients and 12.5% of sorafenib + capecitabine patients (OS data set).

Anaemia was reported by 5.4% of placebo + capecitabine patients and 10.7% of sorafenib + capecitabine patients (OS data set).

Hand foot skin reactions (HFSR, also known as palmar plantar erythrodysaesthesia syndrome) are a known complication of both sorafinib therapy and capecitabine therapy. As expected, the incidence in the sorafinib + capecitabine arm was higher (89.3% versus 62.5% in placebo). Although the incidence was higher, the rate of discontinuation due to HFSR was not correspondingly high (8.0% in the sorafinib + capecitabine arm and 3.6% in the placebo + capecitabine arm). This indicates that the symptoms were manageable, and that most patients who experienced HFSR AEs were able to continue therapy. Thus, HSFR is an expected AE with the sorafinib + capecitabine, and should be managed with appropriate dose modifications, as indicated.

Grade 3 neutropenia was reported by 1.8% of placebo + capecitabine patients and 3.6% of sorafenib + capecitabine patients, and Grade 4 neutropenia was reported by 0.9% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients (OS data set). Grade 3 anaemia was reported by 0.9% of placebo + capecitabine patients and 1.8% of sorafenib + capecitabine patients, and Grade 4 anaemia was not reported in any patient (OS data set).

The incidence of thrombocytopenia was low overall, and a higher incidence of thrombocytopenia occurred in the placebo + capecitabine group than in the sorafenib + capecitabine group (5.4% versus 2.7%, respectively, OS data set). Grade 3 thrombocytopenia was reported 2.7% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients, and Grade 4 thrombocytopenia was reported by 0.9% of placebo + capecitabine patients and 0% sorafenib + capecitabine patients (OS data set).

Infections occurred with similar frequency in the placebo + capecitabine group (26.8%) and the sorafenib + capecitabine group (25.9%) (OS data set). Fatigue occurred in 12.5% of placebo + capecitabine patients and in 15.2% of sorafenib + capecitabine patients. Grade 3 fatigue was reported by 0.9% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients, and Grade 4 fatigue was not reported in any patient (OS data set). Nausea was experienced with similar frequency the placebo + capecitabine group (32.1%) and the sorafenib + capecitabine group (28.6%) (OS data set).

Hypertension was noted as an AE in 11.6% of placebo + capecitabine patients and in 17.9% of sorafenib + capecitabine patients (OS data set). Hypertension was noted as Grade 3 in 1.8% of placebo + capecitabine patients and in 0.9% of sorafenib + capecitabine patients, and was noted as an SAE in 0.9% of placebo + capecitabine patients and in 0% of sorafenib + capecitabine patients.

12.4 Clinical laboratory evaluation

12.4.1 Listing of individual laboratory measurements by patient and each abnormal laboratory value

Tabular listings by patient of all safety-related laboratory data and a by-patient listing of all abnormal values are available on request.

12.4.2 Laboratory parameters of CTCAE toxicity grade 3 and 4

Tabular listings by patient of all safety-related laboratory data and a by-patient listing of all abnormal values are available on request. Post-text Tables 14.4.1 and 14.4.2 summarize the actual value and change from baseline for hematology tests and chemistry tests, respectively, for all patients in the safety population.

Table 76 and

Table 77 display summaries of laboratory values of CTCAE toxicity Grades 3 and 4, based on the safety population, for the PFS and OS data sets.

For the PFS data set (Table 76):

The most commonly reported Grade 3 laboratory abnormality was lymphocytes, reported as a Grade 3 abnormality in 7/108 (6.5%) patients in the placebo + capecitabine group and in 2/103 (1.9%) patients in the sorafenib + capecitabine group. Lipase was reported as a as Grade 3 abnormality in 0/38 (0%) patients in the placebo + capecitabine group and in 3/46 (6.5%) patients in the sorafenib + capecitabine group. Amylase was reported as a as Grade 3 abnormality in 2/91 (2.2%) patients in the placebo + capecitabine group and in 1/90 (1.1%) patients in the sorafenib + capecitabine group No other Grade 3 laboratory abnormalities were reported for more than 2% of the patients in either treatment group.

The only Grade 4 laboratory abnormality was lipase, reported as a Grade 4 abnormality in 0/38 (0%) patients in the placebo + capecitabine group and in 1/46 (2.2%) patients in the sorafenib + capecitabine group.

For the OS data set (Table 77):

The most commonly reported Grade 4 laboratory abnormality was lymphocytes, reported as a Grade 3 abnormality in 9/108 (8.3%) patients in the placebo + capecitabine group and in 4/103 (3.9%) patients in the sorafenib + capecitabine group. Lipase was reported as a as Grade 3 abnormality in 0/38 (0%) patients in the placebo + capecitabine group and in 3/48 (6.3%) patients in the sorafenib + capecitabine group. Amylase was reported as a as Grade 3 abnormality in 3/91 (3.3%) patients in the placebo + capecitabine group and in 0/90 (0%) patients in the sorafenib + capecitabine group. No other Grade 3 laboratory abnormalities were reported for more than 2% of the patients in either treatment group.

The only Grade 4 laboratory abnormality was lipase, reported as a Grade 4 abnormality in 0/39 (0%) patients in the placebo + capecitabine group and in 1/48 (2.1%) patients in the sorafenib + capecitabine group.

Table 76: Laboratory Values of CTCAE Toxicity Grade 3 and 4 - Safety Population *(PFS data)*

Laboratory Test (Units)	Treatment Group			
	Placebo + Capecitabine N=112		Sorafenib + Capecitabine N=112	
	Grade 3 n/N[1] (%)	Grade 4 n/N[1] (%)	Grade 3 n/N[1] (%)	Grade 4 n/N[1] (%)
Hemoglobin (g/dL)	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
Lymphocytes	7/108 (6.5%)	0/108 (0%)	2/103 (1.9%)	0/103 (0%)
Neutrophils	0/110 (0%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Platelets	1/110 (0.9%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
WBC	1/110 (0.9%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Amylase	2/91 (2.2%)	0/91 (0%)	1/90 (1.1%)	0/90 (0%)
Lipase	0/38 (0%)	0/38 (0%)	3/46 (6.5%)	1/46 (2.2%)
Bilirubin, total	0/109 (0%)	0/109 (0%)	0/104 (0%)	0/104 (0%)
Creatinine	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
SGOT/AST	2/109 (1.8%)	0/109 (0%)	1/104 (1.0%)	0/104 (0%)
SGPT/ALT	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)

Note: Grade in this table represents the worst post-baseline grade reported for the patient.
1: n=number of patients with the grade being the worst post baseline toxicity; N=total number of patients with the laboratory measurement reported post baseline.
Source: Post-text Table 14.4.3 - PFS Data Set: 27 March 2009.

Table 77: Laboratory Values of CTCAE Toxicity Grade 3 and 4 - Safety Population *(OS data)*

Laboratory Test (Units)	Treatment Group			
	Placebo + Capecitabine N=112		Sorafenib + Capecitabine N=112	
	Grade 3 n/N[1] (%)	Grade 4 n/N[1] (%)	Grade 3 n/N[1] (%)	Grade 4 n/N[1] (%)
Hemoglobin (g/dL)	0/110 (0%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Lymphocytes	9/108 (8.3%)	0/108 (0%)	4/103 (3.9%)	0/103 (0%)
Neutrophils	0/110 (0%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Platelets	1/110 (0.9%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
WBC	1/110 (0.9%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Amylase	3/91 (3.3%)	0/91 (0%)	0/90 (0%)	0/90 (0%)
Lipase	0/39 (0%)	0/39 (0%)	3/48 (6.3%)	1/48 (2.1%)
Bilirubin, total	1/109 (0.9%)	0/109 (0%)	0/104 (0%)	0/104 (0%)
Creatinine	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
SGOT/AST	2/109 (1.8%)	0/109 (0%)	1/104 (1.0%)	0/104 (0%)
SGPT/ALT	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)

Note: Grade in this table represents the worst post-baseline grade reported for the patient.
1: n=number of patients with the grade being the worst post baseline toxicity; N=total number of patients with the laboratory measurement reported post baseline.
Source: Post-text Table 14.4.3 - OS Data Set: 30 June 2010.

12.4.2.1 Laboratory parameters: Change from baseline in CTCAE toxicity grade

Table 78 and Table 79 display summaries of change from baseline in CTCAE toxicity grade for the safety population, for the PFS and OS data sets.

For the PFS data set (Table 78):

The laboratory test with the greatest number of patients with a change from baseline in CTCAE toxicity grade was AST, which included 76 patients: 29 patients in the placebo + capecitabine group (18 patients with a +1-point change, 2 patients with a +2-point change, and 9 patients with a -1 change), and in 47 patients in the sorafenib + capecitabine group (40 patients with a +1-point change, 1 patient with a +2-point change, 1 patient with a +3-point change, and 5 patients with a -1 change).

The laboratory test with the second greatest number of patients with a change from baseline in CTCAE toxicity was total bilirubin, which included 73 patients: 30 patients in the placebo + capecitabine group (20 patients with a +1-point change, 7 patients with a +2-point change, and 3 patients with a -1 change), and in 43 patients in the sorafenib + capecitabine group (32 patients with a +1-point change, 10 patients with a +2-point change, and 1 patient with a -1 change).

The laboratory test with the third greatest number of patients with a change from baseline in CTCAE toxicity was WBC, which included 63 patients: 24 patients in the placebo + capecitabine group (19 patients with a +1-point change, 4 patients with a +2-point change, 1 patient with a +3-point change, and 1 patient with a -1 change), and in 38 patients in the

sorafenib + capecitabine group (30 patients with a +1-point change, and 8 patients with a +2-point change).

For the OS data set (Table 79):

The laboratory test with the greatest number of patients with a change from baseline in CTCAE toxicity grade was AST, which included 82 patients: 31 patients in the placebo + capecitabine group (22 patients with a +1-point change, 2 patients with a +2-point change, and 7 patients with a -1 change), and in 51 patients in the sorafenib + capecitabine group (42 patients with a +1-point change, 4 patients with a +2-point change, 1 patient with a +3--point change, and 4 patients with a -1 change).

The laboratory test with the second greatest number of patients with a change from baseline in CTCAE toxicity was total bilirubin, which included 74 patients: 30 patients in the placebo + capecitabine group (19 patients with a +1-point change, 7 patients with a +2-point change, 1 patient with a +1-point change, and 3 patients with a -1 change), and in 44 patients in the sorafenib + capecitabine group (33 patients with a +1-point change, 10 patients with a +2-point change, and 1 patient with a -1 change).

The laboratory test with the third greatest number of patients with a change from baseline in CTCAE toxicity was WBC, which included 70 patients: 26 patients in the placebo + capecitabine group (19 patients with a +1-point change, 5 patients with a +2-point change, 1 patient with a +3-point change, and 1 patient with a -1 change), and in 44 patients in the sorafenib + capecitabine group (35 patients with a +1-point change, 8 patients with a +2-point change, and 1 patient with a -1 change).

Table 78: Change from Baseline in CTCAE Toxicity Grade - Safety Population *(PFS data)*

Laboratory Test	Change in CTCAE Grade	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Amylase (U/L)	-1	3	1
	0	76	64
	1	5	12
	2	1	3
	3	1	0
	Unk	26	32
Bilirubin, total (mg/dL)	-1	3	1
	0	78	60
	1	20	32
	2	7	10
	Unk	4	9
Creatinine (mg/dL)	-1	1	2
	0	102	93
	1	4	8
	2	2	0
	Unk	3	9
Hemoglobin (g/dL)	-2	0	1
	-1	5	3
	0	76	77
	1	25	20
	2	3	2
	Unk	3	9
Lipase (U/L)	-3	1	0
	-2	0	1
	0	27	21
	1	4	5
	2	0	2
	3	0	3
	Unk	80	80
Lymphocytes absolute ct (GIGA/L)	-3	0	1
	-2	0	1
	-1	0	3
	0	80	66
	1	16	21
	2	6	8
	3	2	1
	Unk	8	11

Laboratory Test	Change in CTCAE Grade	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Neutrophils absolute ct (GIGA/L)	-1	2	2
	0	91	79
	1	14	16
	2	2	5
	3	0	1
	Unk	3	9
Platelets (GIGA/L)	0	100	74
	1	7	28
	2	2	1
	Unk	3	9
SGOT/AST (U/L)	-2	0	1
	-1	9	5
	0	79	55
	1	18	40
	2	2	1
	3	0	1
	Unk	4	9
SGPT/ALT (U/L)	-1	8	4
	0	81	63
	1	18	29
	2	2	7
	Unk	3	9
WBC (GIGA/L)	-1	1	0
	0	84	65
	1	19	30
	2	4	8
	3	1	0
	Unk	3	9

Note: Grade in this table represents the worst post-baseline grade reported for the patient.
Note: Unk=Either baseline grade or worst post baseline grade is missing.
1: n=number of patients with the grade being the worst post baseline toxicity; N=total number of patients with the laboratory measurement reported post baseline.
Source: Post-text Table 14.4.4 - PFS Data Set: 27 March 2009.

Table 79: Change from Baseline in CTCAE Toxicity Grade - Safety Population *(OS data)*

Laboratory Test	Change in CTCAE Grade	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Amylase (U/L)	-1	0	1
	-1	3	1
	0	73	63
	1	7	13
	2	1	2
	3	2	0
	Unk	26	32
Bilirubin, total (mg/dL)	-1	3	1
	0	78	59
	1	19	33
	2	7	10
	3	1	0
	Unk	4	9
Creatinine (mg/dL)	-1	1	2
	0	101	88
	1	5	13
	2	2	0
	Unk	3	9
Hemoglobin (g/dL)	-2	0	1
	-1	2	3
	0	77	70
	1	27	25
	2	3	3
	3	0	1
	Unk	3	9
Lipase (U/L)	-3	1	0
	-2	0	1
	0	27	20
	1	5	8
	2	0	2
	3	0	3
	Unk	79	78
Lymphocytes absolute ct (GIGA/L)	-3	0	1
	-2	0	1
	-1	0	5
	0	76	60
	1	19	24
	2	6	7
	3	3	3
	Unk	8	11

Laboratory Test	Change in CTCAE Grade	Placebo + Capecitabine N=112	Sorafenib + Capecitabine N=112
Neutrophils absolute ct (GIGA/L)	-1	2	2
	0	89	75
	1	16	18
	2	2	7
	3	0	1
	Unk	3	9
Platelets (GIGA/L)	0	99	70
	1	8	31
	2	2	2
	Unk	3	9
SGOT/AST (U/L)	-2	0	1
	-1	7	4
	0	77	51
	1	22	42
	2	2	4
	3	0	1
	Unk	4	9
SGPT/ALT (U/L)	-1	7	4
	0	80	57
	1	21	34
	2	1	8
	Unk	3	9
WBC (GIGA/L)	-1	1	1
	0	83	59
	1	19	35
	2	5	8
	3	1	0
	Unk	3	9

Note: Grade in this table represents the worst post-baseline grade reported for the patient.
1: n=number of patients with the grade being the worst post baseline toxicity; N=total number of patients with the laboratory measurement reported post baseline.
Source: Post-text Table 14.4.4 - OS Data Set: 30 June 2010.

12.5 Vital signs, physical findings and other observations related to safety

Post-text Table 14.4.5 provides the actual value and change from baseline vital signs for both treatment groups. There were no consistent trends over time with respect to mean change from baseline systolic or diastolic blood pressure or temperature in either treatment group. There was a consistent trend for weight loss from baseline after the start of treatment in both treatment groups.

Any clinically significant changes in vital signs were to be noted as AEs. In the PFS data set, hypertension was noted as an AE in 13 (11.6%) of the patients in the placebo + capecitabine

group and in 19 (17.0%) of the patients in the sorafenib + capecitabine group. In the OS data set, hypertension was noted as an AE in 13 (11.6%) of the patients in the placebo + capecitabine group and in 20 (17.9%) of the patients in the sorafenib + capecitabine group. Grade 3 hypertension was noted in 2 placebo + capecitabine patients and in 1 sorafenib + capecitabine patient in both data sets. Hypertension was noted as an SAE in 1 placebo + capecitabine patient and in 0 sorafenib + capecitabine patients.

12.6 Safety results

Exposure to study drug was slightly lower for sorafenib/placebo than for capecitabine between the 2 treatment groups:

For the PFS data set, the median duration of treatment for sorafenib/placebo was 18 weeks for the placebo + capecitabine group versus 22 weeks for the sorafenib + capecitabine group; the median duration of treatment for capecitabine was 6 cycles for the placebo + capecitabine group versus 7 cycles for the sorafenib + capecitabine group.

For the OS data set, the median duration of treatment for sorafenib/placebo was 19 weeks for the placebo + capecitabine group versus 26 weeks for the sorafenib + capecitabine group; the median duration of treatment for capecitabine was 6 cycles for the placebo + capecitabine group versus 9 cycles for the sorafenib + capecitabine group

The percentage of patients with dose reductions and dose interruptions was lower in the placebo + capecitabine group versus the sorafenib + capecitabine group. Most of the dose reductions and interruptions in both treatment groups were due to AEs. Dose reductions and interruptions occurred in the following percentages for the PFS and OS data sets:

For the PFS Data set: Dose reductions: Reductions of placebo were noted for 11.4% of placebo + capecitabine patients, and of sorafenib for 47.8% of sorafenib + capecitabine patients. Reductions of capecitabine were noted for 31.6% of placebo + capecitabine patients and for 78.3% of sorafenib + capecitabine patients. Dose interruptions: Interruptions of placebo were noted for 41.2% of placebo + capecitabine patients, and of sorafenib for 73.9% of sorafenib + capecitabine patients. Interruptions of capecitabine were noted for 40.4% placebo + capecitabine patients, and for 75.7% sorafenib + capecitabine patients.

For the OS Data set: Dose reductions: Reductions of placebo were noted for 14.0% of placebo + capecitabine patients, and of sorafenib for 53.0% of sorafenib + capecitabine patients. Reductions of capecitabine were noted for 33.3% of placebo + capecitabine patients, and for 78.3% of sorafenib + capecitabine patients. Dose interruptions: Interruptions of placebo were noted for 42.1% of placebo + capecitabine patients, and of sorafenib for 74.8% of sorafenib + capecitabine patients. Interruptions of capecitabine were noted for 41.2% of placebo + capecitabine patients, and for 76.5% of sorafenib + capecitabine patients.

The AE profile was relatively similar between the treatment groups in this study. A total of 109 (97.3%) patients in the placebo + capecitabine group and all patients (112 [100%]) in the sorafenib + capecitabine group reported 1 or more treatment-emergent AEs. AEs were reported as follows for the PFS and OS data sets:

For the PFS Data set: A total of 106 (94.6%) patients in the placebo + capecitabine group and 111 (99.1%) patients in the sorafenib + capecitabine group reported 1 or more treatment-emergent AEs.

For the OS Data set: A total of 109 (97.3%) patients in the placebo + capecitabine group and 112 (100%) patients in the sorafenib + capecitabine group reported 1 or more treatment-emergent AEs.

The drug-related AE profile was relatively similar between the treatment groups in this study. A total of 100 (89.3%) patients in the placebo + capecitabine group and 109 (97.3%) patients in the sorafenib + capecitabine group reported 1 or more drug-related treatment emergent AEs. Drug-related AEs were reported as follows for the PFS and OS data sets:

For the PFS data set: A total of 97 (86.6%) patients in the placebo + capecitabine group and 108 (96.4%) patients in the sorafenib + capecitabine group reported 1 or more drug-related treatment emergent AEs.

For the OS data set: A total of 100 (89.3%) patients in the placebo + capecitabine group and 109 (97.3%) patients in the sorafenib + capecitabine group reported 1 or more drug-related treatment emergent AEs.

Grade 3 or higher AEs occurred in fewer patients in the placebo + capecitabine group versus the sorafenib + capecitabine group. Grade 3 or higher AEs were reported for the PFS and OS data sets, as follows:

For the PFS data set: A total of 47 (42.0%) patients in the placebo + capecitabine group and 67 (59.8%) patients in the sorafenib + capecitabine group reported 1 or more grade 3 or higher treatment emergent AEs. The most common grade 3 or higher AEs were palmar-plantar erythrodysaesthesia syndrome (15 [13.4%] placebo + capecitabine patients and 50 [44.6%] sorafenib + capecitabine patients), diarrhea (5 [4.5%] placebo + capecitabine patients and 6 [5.4%] sorafenib + capecitabine patients), and dyspnoea (reported by 4 [3.6%] placebo + capecitabine patients and 5 [4.5%] sorafenib + capecitabine patients).

For the OS data set: A total of 51 (45.5%) patients in the placebo + capecitabine group and 70 (62.5%) patients in the sorafenib + capecitabine group reported 1 or more grade 3 or higher treatment emergent AEs. The three most common grade 3 or higher AEs were the same AEs as in the PFS data set: Palmar-plantar erythrodysaesthesia syndrome (16 [14.3%] placebo + capecitabine patients and 49 [43.8%] sorafenib + capecitabine patients), diarrhea (5 [4.5%] placebo + capecitabine patients and 7 [6.3%] sorafenib + capecitabine patients), and dyspnoea (4 [3.6%] placebo + capecitabine patients and 5 [4.5%] sorafenib + capecitabine patients).

Grade 3 drug-related AEs occurred in fewer patients in the placebo + capecitabine group versus the sorafenib + capecitabine group in both data sets. For the PFS data set, grade 3 drug-related AEs were reported by 25 (22.3%) placebo + capecitabine patients and 62 (55.4%) sorafenib + capecitabine patients. For the OS set, grade 3 drug-related AEs were reported by 28 (25.0%) placebo + capecitabine patients versus 63 (56.3%) sorafenib + capecitabine patients.

Grade 4 drug-related AEs occurred in the same number of patients (1 [0.9%]) in both treatment groups and in both data sets.

Grade 5 drug-related AEs were reported by 2 (1.8%) placebo + capecitabine patient and 0 (0%) sorafenib + capecitabine patient in the PFS and OS data sets.

AEs leading to discontinuation of any study treatment occurred in a fewer patients in the placebo + capecitabine group versus the sorafenib + capecitabine group in both data sets. For the PFS data set, 9 (8.0%) patients in the placebo + capecitabine group and 15 (13.4%) patients in the sorafenib + capecitabine group reported AEs leading to discontinuation of any study treatment. For the OS data set, 11 (9.8%) patients in the placebo + capecitabine group and 22 (19.6%) patients in the sorafenib + capecitabine group experienced AEs leading to discontinuation of any study treatment.

The SAE profile was also relatively similar between the treatment groups in this study. For the PFS data set, SAEs were reported by 30 (26.8%) patients in the placebo + capecitabine group and 36 (32.1%) patients in the sorafenib + capecitabine group, and for the OS data set, SAEs were reported by 31 (27.7 %) patients in the placebo + capecitabine group and 40 (35.7%) patients in the sorafenib + capecitabine group. The most common SAE was palmar-plantar erythrodysaesthesia syndrome, reported in both the PFS and OS data sets by 5 (4.5%) placebo + capecitabine patients and 14 (12.5%) sorafenib + capecitabine patients.

Drug-related SAEs occurred in fewer patients in the placebo + capecitabine group versus the sorafenib + capecitabine group; data in the PFS and OS data sets were identical. A total of 11 (9.8%) patients in the placebo + capecitabine group and 20 (17.9%) patients in the sorafenib + capecitabine group reported 1 or more drug-related SAEs. The most common drug-related SAE was palmar-plantar erythrodysaesthesia syndrome, reported 5 (4.5%) patients in the placebo + capecitabine group and 14 (12.5%) patients in the sorafenib + capecitabine group.

There were no apparent differences between the treatment groups in terms of the total number of patients who died, the number of deaths within 30 days of the end of treatment, and the cause of death. Death, including death within 30 days of end of treatment and death more than 30 days after the end of treatment, occurred in 65 (58.0%) patients in the placebo + capecitabine group and 60 (53.6%) patients in the sorafenib + capecitabine group.

Death of 1 patient in the placebo + capecitabine group was considered related to treatment: patient 16-320-1010 died 3 days after the termination of placebo + capecitabine due to a cardiac arrest (CTC Grade 5). Death of 1 patient in the placebo + capecitabine group was considered a "toxicity due to study treatment with at least one AE with the outcome of death": patient 24-300-1011 died approximately 2 months after the termination of placebo + capecitabine due to septic shock, and had experienced Grade 4 thrombocytopenia that was considered related to study treatment on two separate occasions, both within 30 days of discontinuation of study treatment.

The AEs of special interest include neutrophils/granulocytes, leukocytes, platelets, hemoglobin, febrile neutropenia, sensory neuropathy, fatigue, diarrhea, nausea, mucositis, thrombus/embolism, hemorrhage/bleeding, hypertension, hand-foot skin reaction, rash/desquamation, dermatology-other, and pruritus, all of which may be associated with sorafenib use.

The AEs which occurred with notably higher frequency in the sorafenib + capecitabine group included the AEs palmar-plantar erythrodysaesthesia syndrome (also frequently called hand foot skin reaction [HFSR]), alopecia, rash, diarrhea, vomiting, constipation, neutropenia, and

anaemia. The AE that was reported in the greatest number of patients was palmar-plantar erythrodysaesthesia syndrome, reported by 66.1% of placebo + capecitabine patients and 90.2% of sorafenib + capecitabine patients (OS data set).

Grade 3 palmar-plantar erythrodysaesthesia syndrome [HSFR] was reported by 13.4% of placebo + capecitabine patients and 46.4% of sorafenib + capecitabine patients. No HSFR events were Grade 4 or 5. Grade 3 neutropenia was reported by 1.8% of placebo + capecitabine patients and 3.6% of sorafenib + capecitabine patients, and Grade 4 neutropenia was reported by 0.9% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients (OS data set). Grade 3 anaemia was reported by 0.9% of placebo + capecitabine patients and 1.8% of sorafenib + capecitabine patients (OS data set).

The incidence of thrombocytopenia was low overall, and a higher incidence of thrombocytopenia occurred in the placebo + capecitabine group than in the sorafenib + capecitabine group (5.4% versus 2.7%, respectively, OS data set). Grade 3 thrombocytopenia was reported 2.7% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients, and Grade 4 thrombocytopenia was reported by 0.9% of placebo + capecitabine patients and 0% sorafenib + capecitabine patients (OS data set).

Infections occurred with similar frequency in the placebo + capecitabine group (26.8%) and the sorafenib + capecitabine group (25.9%) (OS data set). Fatigue occurred in 12.5% of placebo + capecitabine patients and in 15.2% of sorafenib + capecitabine patients (OS data set). Grade 3 fatigue was reported by 0.9% of placebo + capecitabine patients and 0.9% of sorafenib + capecitabine patients (OS data set). Nausea was experienced with similar frequency the placebo + capecitabine group (32.1%) and the sorafenib + capecitabine group (28.6%) (OS data set).

Hypertension was noted as an AE in 11.6% of placebo + capecitabine patients and in 17.9% of sorafenib + capecitabine patients (OS data set). Hypertension was noted as Grade 3 in 1.8% of placebo + capecitabine patients and in 0.9% of sorafenib + capecitabine patients, and was noted as an SAE in 0.9% of placebo + capecitabine patients and in 0% of sorafenib + capecitabine patients.

There were no laboratory tests for which the treatment groups differed by more than 3% regarding the incidence of Grade 3, 4 toxicity.

Most AEs were tolerable and manageable, and did not result in increased hospitalization.

12.7 Pharmacokinetics

Blood samples for PK were collected from a subset of enrolled patients in the study who were willing to participate in PK data collection. Approximately one-third of enrolled patients participated in PK assessment. In these patients, three samples were collected at 1, 4, and 8 hours post-capecitabine-dose on Day 14 of Cycle 1 and evaluated to measure plasma capecitabine and 5-FU levels. Since the study design permitted only point estimates at these selected time points, PK parameters such exposure (AUC), Cmax, and Tmax were not computed. The context for the point estimates in this study was provided by comparison with results obtained from previous studies with comprehensive PK evaluation (REFMAL-122, Bayer Study 10955).

Capecitabine and 5-FU plasma concentrations were measured by NorthEast Bioanalytical Laboratories, Hamden, CT, using a validated LC/MS/MS assay [NEBA MET064].

Descriptive statistics: Geometric mean and geometric coefficient of variation (%) for concentrations at 1 and 4 hours post capecitabine dose administration were used for the PK comparisons. Geometric mean was calculated as the n-th root of the product of n numbers: values below the limit of quantitation were denoted with letters and were excluded from the mean. At least 2/3rds of the values had to be numerical for this calculation.

The 8 hr time point did not provide evaluable data for the placebo group because capecitabine is rapidly absorbed and has a short plasma half-life (< 1h), therefore, plasma concentrations at 8 hours were for mostly below LLOQ. However, the majority of patients in the sorafenib treated group had measurable capecitabine concentrations at 8 hours. Therefore, the mean and confidence interval was calculated for the sorafenib treated group.

12.7.1 Pharmacokinetics: Study population

Blood samples were obtained from 60 patients in the study. Some patients were excluded from analysis because either they did not take sorafenib on the day of PK sampling or had a dose reduction. While records indicated that all the patients had been administered capecitabine, 4 patients were excluded from the PK evaluation because the plasma concentrations of capecitabine and 5-FU in these patient were below or close to the lower limit of quantitation for all the time points. This is implausible based on the observed PK of capecitabine from previous studies (REFMAL-122, Bayer Study 10955).

Excluded patient IDs grouped by treatment and reason for exclusion are shown below:

Group	Patient ID	Reason for Exclusion
Sorafenib	24-300-1001	Implausible PK
Sorafenib	24-300-1002	No sorafenib on PK date
Sorafenib	24-300-1005	No sorafenib on PK date
Sorafenib	24-300-1006	No sorafenib on PK date
Sorafenib	24-305-1001	Dose Reduced 800-400mg
Sorafenib	50-330-1004	No sorafenib on PK date
Sorafenib	50-332-1006	No sorafenib on PK date
Sorafenib	50-332-1012	No sorafenib & capecitabine on PK date
Sorafenib	50-332-1019	Implausible PK
Placebo	24-302-1001	No placebo on PK date
Placebo	50-332-1008	Implausible PK
Placebo	50-332-1013	Implausible PK

Statistical tables, located in Section 14.4, are presented both with inclusion and exclusion of patients with implausible PK to assess the effect of exclusion.

There were 21 evaluable patients in the sorafenib group and 28 patients in the placebo group.

The data shows that the blood samples were obtained primarily from Caucasian females with a median age of 54-59 years, median body weight of 65–69 kg, and an ECOG score of either 0 or 1. There were no significant differences in demographic characteristics between the placebo and sorafenib treated patients.

12.7.2 Pharmacokinetics: Dose analysis

Patients in the analyzed groups took 14 days of the capecitabine (BID). If a dose day was missed the cycle was extended by additional days to make up for the missed dose. Dosing

data was examined to ensure patients took the full capecitabine dose on the previous day of PK sampling. Data was also examined to ensure that patients took sorafenib/placebo for the previous 7 days and including the day of PK sampling. Patients who did not meet this criterion were excluded from PK analysis. The mean dose and variation in the administered capecitabine dose on day of PK sampling (morning/AM dose) for the two groups are summarized below:

	Capecitabine AM Dose (mg)
Sorafenib	Mean (1619.0), CV% (10.2)
Placebo	Mean (1650.0), CV% (11.4)

The data shows that the sorafenib treated and the placebo treated groups were similar in terms of dose administered prior to PK sampling.

12.7.3 Pharmacokinetics: Elapsed time analysis

The PK data shows that, on average, in both groups sampling times were close to the scheduled sampling time. There was however a larger number of patients with significant deviations at the 1-hour time point, particularly in the placebo group. Since capecitabine has a very short half life, these deviations could have a high impact on the computation of the mean concentration at each time point. Therefore, the mean concentration data for the two groups is presented both with inclusion, and exclusion, of time points with a deviation greater than 20% from the scheduled time (Section 14.4).

12.7.4 Pharmacokinetics: Plasma concentration time

The data indicate that both capecitabine and 5-FU plasma mean plasma concentrations were higher in the sorafenib treated group compared to the placebo treated group at all of the time points examined. At 8 hours post morning dose the majority of patients in the sorafenib treated group (15/21) had measurable concentrations of capecitabine, whereas, only 2 patients (2/28) in the placebo group had measurable capecitabine concentrations at that time point.

At 4 hours the sorafenib treated group had 4.7 times plasma capecitabine concentration compared to the placebo treated group. The higher concentration and the longer duration of capecitabine and 5-FU concentrations in circulation could be significant for capecitabine, which is a prodrug with a very short half-life requiring enzymatic conversion to 5-fluorouracil in the tumor.

Since these data represent only point estimates at selected times it is not possible to infer conclusions about key PK parameters (AUC) exposure, (C_{max}) maximal plasma concentration and (T_{max}) time at maximal plasma concentration.

To obtain a better understanding of the observed increase in plasma concentration after coadministration with sorafenib was compared with data from previous studies (REFMAL-122, Bayer-10955) which had similar dosing schedules. The comparison of plasma concentrations from the current study SOLTI-0701, and the previous studies REFMAL-122 and Bayer-10955, revealed similar concentrations for capecitabine and 5-FU at the 1 and 4-hour time points.

12.7.5 Pharmacokinetic results

- Capecitabine and 5-FU plasma concentrations were observed to be higher at 1h and 4h when capecitabine was co-administered with sorafenib as compared to placebo.
- At 8 hours, there were measurable concentrations of capecitabine for the majority of patients in the sorafenib treated group however, plasma concentrations were mostly below the limit of quantitation for the placebo group. This is indicative of a sustained exposure to the drug in the sorafenib treated group.
- Plasma 5-FU concentrations were not quantifiable in either treatment group at 8 hours postdose.
- The increase in plasma capecitabine and 5-FU concentrations at the 1 and 4 hours postdose observed in this Phase 2b study are consistent with results observed in previous studies (REFMAL-122 and Bayer-10955).

13. Overall conclusions and discussion

The SOLTI 0701 trial was one of a series of trials, known as the TIES program, designed to assess the potential activity of sorafenib in the treatment of breast cancer.

The trial analyzed progression free survival in patients treated with the combination of sorafenib and capecitabine compared to capecitabine alone for locally advanced or metastatic breast cancer. Limitation of the eligible patient population to those who had failed prior therapy with taxanes and an anthracycline regimen or for whom an anthracycline was not indicated was consistent with the approved prescription for capecitabine and current treatment practices. Assessments of overall survival, the objective response rate, time to progression, safety and tolerability were among the secondary objectives.

The trial conduct was of high quality and the results robust and consistent with previous reports of the activity of anti-angiogenic therapies (e.g., bevacizumab) used for the treatment of breast carcinoma.

The SOLTI trial demonstrated a significant improvement in the PFS for patients treated with the combination of sorafenib and capecitabine compared to those treated with capecitabine alone. Subjects in the sorafenib arm were 42.4% (HR=0.576) less likely to progress than their counterparts on the placebo arm (ITT population). This finding was further corroborated by most of the planned and exploratory subgroup analyses, the per protocol analysis and sensitivity analyses.

In the cases where the subgroup analysis was not significantly in favor of the sorafenib treated arm (subjects < 40, those without prior anthracycline use, progesterone receptor positive, and those without visceral or measurable disease) the hazard ratio was less than 0.72, indicating a trend in favor of the sorafenib arm. The only exception was the subgroup of patients aged <40 years in which the HR was 0.836 (P=0.3719) but once again of the analysis favored the sorafenib arm. The number of patients in the < 40-yr subgroup was small, N=18, which likely played a part in the result. The HR for the subgroup of patients aged up to 40 years, N= 211, was 0.569 (P=0.0007). This result was among the strongest trends observed in the trial.

Groups showing a significant treatment effect in favor of sorafenib included those without prior chemotherapy (HR=0.498), those with visceral disease (HR=0.532) and those with ER positive or PR positive hormonal status (HR=0.615). Patients with ER negative and PR negative disease had an HR=0.596, which was not statistically significant but trended strongly in favor of sorafenib treatment. These findings suggest that the activity conferred by sorafenib is broad occurring in patients with good and poor prognosis.

The significant improvement in PFS observed in patients treated with the combination of sorafenib and capecitabine did not translate into a significant improvement in overall survival (HR = 0.864; P=0.2075). At the time of the final analysis (27 March 2009), 57% of the subjects on the placebo arm had died. Fewer subjects, 52%, on the sorafenib and capecitabine arm had died. No further OS data is being collected so the impact of further data maturity will remain unknown.

None of the planned or exploratory subgroup analyses of OS demonstrated a significant difference between the treatment arms. The groups with the largest trends favoring sorafenib

were those without prior chemotherapy (HR = 0.666; *P*=0.0567); those treated in France or Spain (HR = 0.757; *P*=0.1469); and those with visceral disease (HR =0.834; *P*=0.1881). In the exploratory analyses the subgroups with the largest OS trend were those subjects without prior anthracycline (HR= 0.301; *P*=0.0613); those treated in France (HR = 0.543; *P*=0.0770); and subjects with 3 or more metastatic sites (HR = 0.596; *P*=0.0381). Based upon the overall OS result of the trial, the value of the information obtained in these subset analyses is limited. At most, these data should be utilized for hypothesis generation.

The remaining secondary efficacy variables assessed in this trial were TTP, objective response rate, and duration of response. The results favored sorafenib treatment. The improvement in TTP was statistically significant, but the increases in the overall response rate and the objective response rate were slight and not statistically significant. The TTP result is consistent with the PFS result of the trial while the other secondary results are consistent with previous reports of anti-angiogenic agents in breast carcinoma. The duration of objective response was slightly in favor of sorafenib + capecitabine, and the median duration of objective response was 105 days longer for the sorafenib + capecitabine group (*P*=0.0533).

The combined administration of sorafenib and capecitabine in this trial was tolerable with clinically manageable toxicities despite the overlapping toxicity profile of the sorafenib and capecitabine. Serious adverse events were reported for less than one-third of patients in the treatment and placebo arms of the PFS data set. Drug-related SAEs were reported more frequently in the sorafenib-treated arm. The most common of these were palmar-plantar erythrodysaesthesia and diarrhea.

Hypertension is among the known adverse events for sorafenib. However, the incidence of grade 3 hypertension was low occurring in 0.9% of the patients treated with the combination of sorafenib and capecitabine. Infections and fatigue are common in patients with breast cancer during chemotherapy. Importantly, the incidence of these adverse events was balanced between arms, as was the incidence of the remaining serious adverse events indicating that these were not sorafenib+capecitabine-specific.

Only 1 grade 4 event (neutropenia) and no grade 5 events occurred in the sorafenib treated arm compared to 3 events (1 grade 4 and 2 grade 5) in the placebo arm. The incidence of serious adverse events in sorafenib treated subjects did not change with the increased follow-up performed with the OS data set.

The incidence of AEs leading to drug discontinuation was less than 15% in each of the arms. However, AEs leading to dose reductions, interruptions and discontinuation of any study treatment occurred in fewer patients in the placebo and capecitabine group relative to the sorafenib and capecitabine group.

Notably, no differences between the treatment groups were apparent in regard to the total number of patients who died, the number of deaths within 30 days of the end of treatment, and the cause of death suggesting that sorafenib treatment did not contribute to the deaths of subjects enrolled in the trial.

14. Tables and figures referred to but not included in the text

14.1 Demographic data summary tables

Progression-free Survival Dataset

Overall Survival Dataset

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects Enrolled	Randomized	Treated
Overall	Overall	07AUG2007	27MAR2009	Placebo	114	114	112
				Sorafenib	115	115	112
				Not Randomized	44	0	0
France	Hôpital Jean Minjoz	28JAN2008	31DEC2008	Placebo	1	1	1
				Sorafenib	1	1	1
				Not Randomized	0	0	0
France	Hôpital Saint Louis	24OCT2007	23MAR2009	Placebo	2	2	2
				Sorafenib	5	5	4
				Not Randomized	0	0	0
France	Institut Claudius Regaud	22NOV2007	26MAR2009	Placebo	15	15	15
				Sorafenib	10	10	10
				Not Randomized	0	0	0

[1] Date of death or date of last contact alive

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Enrolled	Randomized	Treated
France	Institut Jean Godinot	13OCT2008	27MAR2009	Placebo	0	0	0
				Sorafenib	3	3	3
				Not Randomized	0	0	0
Spain	Hospital Clinico Univ. De Santiago De Compostela	16JUN2008	26MAR2009	Placebo	2	2	2
				Sorafenib	1	1	1
				Not Randomized	0	0	0
Spain	Hospital Clinico Universitario De Valencia	15FEB2008	25MAR2009	Placebo	6	6	6
				Sorafenib	8	8	8
				Not Randomized	0	0	0
Spain	Hospital De La Santa Creu I Sant Pau	12JUN2008	27MAR2009	Placebo	2	2	2
				Sorafenib	0	0	0
				Not Randomized	0	0	0

[1] Date of death or date of last contact alive

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Enrolled	Randomized	Treated
Spain	Hospital Mutua De Terrassa	01JUL2008	12JAN2009	Placebo	0	0	0
				Sorafenib	1	1	1
				Not Randomized	0	0	0
Spain	Hospital Universitario 12 De Octubre	18DEC2007	27MAR2009	Placebo	14	14	14
				Sorafenib	7	7	6
				Not Randomized	2	0	0
Spain	Hospital Universitario Arnau De Vilanova	09OCT2007	25MAR2009	Placebo	5	5	5
				Sorafenib	5	5	5
				Not Randomized	0	0	0
Spain	Hospital Universitario Vall D'Hebron	07AUG2007	12MAR2009	Placebo	7	7	7
				Sorafenib	8	8	8
				Not Randomized	0	0	0

[1] Date of death or date of last contact alive

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Enrolled	Randomized	Treated
Spain	ICO Hospital Dr. Josep Trueta	08JUL2008	07JAN2009	Placebo	1	1	1
				Sorafenib	0	0	0
				Not Randomized	0	0	0
Spain	Instituto Catalan De Oncologia	30NOV2007	20MAR2009	Placebo	1	1	1
				Sorafenib	3	3	3
				Not Randomized	0	0	0
Spain	Instituto Valenciano De Oncologia	28JAN2008	20MAR2009	Placebo	5	5	5
				Sorafenib	4	4	3
				Not Randomized	0	0	0
Brazil	Centro de Pesquisa em Hematologia e Oncologia da Faculdade de Medicina do ABC - CEPHO	17DEC2007	27MAR2009	Placebo	14	14	14
				Sorafenib	13	13	13
				Not Randomized	15	0	0

[1] Date of death or date of last contact alive

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Enrolled	Randomized	Treated
Brazil	Fundação Dr. Amaral Carvalho	26OCT2007	26MAR2009	Placebo	5	5	5
				Sorafenib	10	10	10
				Not Randomized	3	0	0
Brazil	Hospital Português da Bahia	27FEB2008	27MAR2009	Placebo	5	5	4
				Sorafenib	1	1	1
				Not Randomized	1	0	0
Brazil	Hospital São Lucas PUCRS	19DEC2007	27MAR2009	Placebo	6	6	6
				Sorafenib	6	6	6
				Not Randomized	4	0	0
Brazil	Hospital das Clínicas - HCFMUSP	11DEC2007	25MAR2009	Placebo	5	5	4
				Sorafenib	4	4	4
				Not Randomized	5	0	0

[1] Date of death or date of last contact alive

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Enrolled	Randomized	Treated
Brazil	Instituto de Oncologia Clínica de Piracicaba S/S Ltda	21DEC2007	23MAR2009	Placebo	5	5	5
				Sorafenib	2	2	2
				Not Randomized	1	0	0
Brazil	Instituto do Cancer Arnaldo Vieira de Carvalho	19DEC2007	26MAR2009	Placebo	7	7	7
				Sorafenib	8	8	8
				Not Randomized	5	0	0
Brazil	Instituto do Câncer do Ceará - ICC	18FEB2008	24MAR2009	Placebo	2	2	2
				Sorafenib	3	3	3
				Not Randomized	0	0	0
Brazil	Santa Casa de Misericórdia de Belo Horizonte	05MAR2008	27MAR2009	Placebo	4	4	4
				Sorafenib	12	12	12
				Not Randomized	8	0	0

[1] Date of death or date of last contact alive

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Table 14.1.2 Subject Disposition

	Placebo	Sorafenib	Total
Number of subjects screened			273
Number of subjects not randomized[1]			44 (16.1%)
Reasons for subject not randomized[1]			
Inclusion/exclusion criteria violation			35 (12.8%)
Unknown			9 (3.3%)
Number of subjects randomized[1]	114	115	229 (83.9%)
Number of subjects randomized but not treated[2]	2 (1.8%)	3 (2.6%)	5 (2.2%)
Reasons for subject randomized but not treated[2]			
Consent withdrawn	0 (0%)	2 (1.7%)	2 (0.9%)
Death	0 (0%)	1 (0.9%)	1 (0.4%)
Investigator decision	1 (0.9%)	0 (0%)	1 (0.4%)
Other	1 (0.9%)	0 (0%)	1 (0.4%)
Number of subjects treated[2]	112 (98.2%)	112 (97.4%)	224 (97.8%)
Number of subjects discontinuing active treatment[2]	90 (78.9%)	75 (65.2%)	165 (72.1%)

[1] Denominator is the number of patients screened and informed consent signed
[2] Denominator is the number of patients randomized

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Table 14.1.2 Subject Disposition

	Placebo	Sorafenib	Total
Reasons for subject discontinuing active treatment[2]			
Adverse event	8 (7.0%)	17 (14.8%)	25 (10.9%)
Consent withdrawn	1 (0.9%)	1 (0.9%)	2 (0.9%)
Death	1 (0.9%)	0 (0%)	1 (0.4%)
Disease progression, recurrence or relapse	75 (65.8%)	52 (45.2%)	127 (55.5%)
Investigator decision	1 (0.9%)	1 (0.9%)	2 (0.9%)
Subject requested to stop study drug administration	2 (1.8%)	2 (1.7%)	4 (1.7%)
Other	2 (1.8%)	2 (1.7%)	4 (1.7%)
Number of subjects discontinuing follow-up[2]	25 (21.9%)	22 (19.1%)	47 (20.5%)
Reasons for subjects discontinuing follow-up[2]			
Deceased during or within 30 days post treatment	5 (4.4%)	5 (4.3%)	10 (4.4%)
Deceased beyond 30 days post treatment	19 (16.7%)	15 (13.0%)	34 (14.8%)
Lost to follow-up	1 (0.9%)	2 (1.7%)	3 (1.3%)
Number of subjects ongoing in study[2]	87 (76.3%)	90 (78.3%)	177 (77.3%)
Active treatment	22 (19.3%)	37 (32.2%)	59 (25.8%)
Follow-up	65 (57.0%)	53 (46.1%)	118 (51.5%)

[1] Denominator is the number of patients screened and informed consent signed
[2] Denominator is the number of patients randomized

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Table 14.1.3 Subject Status at Analysis
(ITT Population)

Subject Status	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Alive progression free	25 (21.9%)	44 (38.3%)	69 (30.1%)
Alive post progression	61 (53.5%)	44 (38.3%)	105 (45.9%)
Death without progression	1 (0.9%)	1 (0.9%)	2 (0.9%)
Death post progression	20 (17.5%)	16 (13.9%)	36 (15.7%)
Lost to follow-up	7 (6.1%)	10 (8.7%)	17 (7.4%)

Note: Subjects with no adequate post-baseline tumor assessment and/or survival status unknown are counted in lost to follow-up.

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Table 14.1.4 Subject Disposition by Randomization Strata
(ITT Population)

	Visceral Disease	Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Number of subjects randomized[1]	Yes	84 (73.7%)	87 (75.7%)	171 (74.7%)
	No	30 (26.3%)	28 (24.3%)	58 (25.3%)
	Total	114 (100.0%)	115 (100.0%)	229 (100.0%)
Number of subjects treated[2]	Yes	82 (73.2%)	84 (75.0%)	166 (74.1%)
	No	30 (26.8%)	28 (25.0%)	58 (25.9%)
	Total	112 (100.0%)	112 (100.0%)	224 (100.0%)

[1] Denominator is the number of patients randomized
[2] Denominator is the number of patients treated

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Table 14.1.5 Subject Disposition by Cycle
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Duration of treatment (cycles)	Not treated	2 (1.8%)	3 (2.6%)	5 (2.2%)
	1	4 (3.5%)	9 (7.8%)	13 (5.7%)
	2	15 (13.2%)	9 (7.8%)	24 (10.5%)
	3	15 (13.2%)	7 (6.1%)	22 (9.6%)
	4	11 (9.6%)	9 (7.8%)	20 (8.7%)
	5	6 (5.3%)	5 (4.3%)	11 (4.8%)
	>=6	61 (53.5%)	73 (63.5%)	134 (58.5%)
Duration of treatment (weeks)[1]	N	112	112	224
	Mean	19.8	23.3	21.5
	SD	13.0	14.1	13.6
	Median	18	22	19
	Min	1	1	1
	Max	59	60	60

[1] Stop date of Sorafenib/placebo or Capecitabine (whichever is later) - start date of Sorafenib/placebo or Capecitabine (whichever is earlier) + 1; For subjects in treatment period, the data cutoff date is used as the stop date.

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Table 14.1.6 Summary of Major Protocol Violations
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Subjects with any major protocol violations	15 (13.2%)	15 (13.0%)	30 (13.1%)
Classification of major protocol violations			
Receipt of protocol-prohibited concomitant therapy before discontinuation of study treatment	3 (2.6%)	0 (0.0%)	3 (1.3%)
Receipt of study treatment different from treatment randomized	1 (0.9%)	1 (0.9%)	2 (0.9%)
Scheduled tumor assessment skipped	10 (8.8%)	9 (7.8%)	19 (8.3%)
Significant inclusion/exclusion criteria violation	3 (2.6%)	5 (4.3%)	8 (3.5%)
Unblinding randomization code prior to pfs event	1 (0.9%)	0 (0.0%)	1 (0.4%)

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Table 14.1.7 Demographics
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Age at enrollment (yrs)			
N	114	115	229
Mean	55.4	55.1	55.2
Sd	11.9	11.3	11.6
Median	56	54	55
Min	30	29	29
Max	80	79	80
Age at enrollment category (yrs)			
<40	11 (9.6%)	7 (6.1%)	18 (7.9%)
40-64	76 (66.7%)	81 (70.4%)	157 (68.6%)
65-74	19 (16.7%)	23 (20.0%)	42 (18.3%)
>=75	8 (7.0%)	4 (3.5%)	12 (5.2%)

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Table 14.1.7 Demographics
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Gender			
Male	1 (0.9%)	0 (0.0%)	1 (0.4%)
Female	113 (99.1%)	115 (100%)	228 (99.6%)
Race			
Caucasian	98 (86.0%)	98 (85.2%)	196 (85.6%)
Black	7 (6.1%)	5 (4.3%)	12 (5.2%)
Asian	0 (0.0%)	2 (1.7%)	2 (0.9%)
American Indian or Native Alaskan	1 (0.9%)	0 (0.0%)	1 (0.4%)
Mestizo	7 (6.1%)	6 (5.2%)	13 (5.7%)
Mulatto	0 (0.0%)	4 (3.5%)	4 (1.7%)
Other	1 (0.9%)	0 (0.0%)	1 (0.4%)

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Weight (kg)	N	112	114	226
	Mean	67.3	66.6	66.9
	SD	12.6	13.4	13.0
	Median	66	65	66
	Min	37	42	37
	Max	116	103	116
BSA (m^2)	N	111	113	224
	Mean	1.7	1.7	1.7
	SD	0.1	0.2	0.2
	Median	1.7	1.7	1.7
	Min	1.2	1.3	1.2
	Max	2.1	2.2	2.2

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
ECOG performance status	0	77 (67.5%)	79 (68.7%)	156 (68.1%)
	1	34 (29.8%)	34 (29.6%)	68 (29.7%)
	>= 2	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Missing	2 (1.8%)	1 (0.9%)	3 (1.3%)
Stage of disease at initial diagnosis	Stage I	9 (7.9%)	8 (7.0%)	17 (7.4%)
	Stage II	42 (36.8%)	48 (41.7%)	90 (39.3%)
	Stage III	47 (41.2%)	49 (42.6%)	96 (41.9%)
	Stage IV	14 (12.3%)	10 (8.7%)	24 (10.5%)
	Missing	2 (1.8%)	0 (0%)	2 (0.9%)

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Stage of disease at enrollment	Stage IIIB or IIIC	9 (7.9%)	11 (9.6%)	20 (8.7%)
	Stage IV	104 (91.2%)	104 (90.4%)	208 (90.8%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Months since initial diagnosis	N	113	115	228
	Mean	63.9	71.0	67.5
	SD	58.6	52.6	55.6
	Median	44	57	48
	Min	1	6	1
	Max	278	231	278

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_1_08_BC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Months since metastatic diagnosis	N	113	115	228
	Mean	23.1	19.4	21.3
	SD	31.3	22.2	27.1
	Median	13	10	12
	Min	0	0	0
	Max	176	113	176
	0 - 12 Months	56 (49.1%)	61 (53.0%)	117 (51.1%)
	>12 - <24 Months	21 (18.4%)	15 (13.0%)	36 (15.7%)
	>=24 Months	36 (31.6%)	39 (33.9%)	75 (32.8%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Months from adjuvant treatment to recurrence or metastatic diagnosis	0 - 12 Months	50 (43.9%)	37 (32.2%)	87 (38.0%)
	>12 - <24 Months	15 (13.2%)	16 (13.9%)	31 (13.5%)
	>=24 Months	45 (39.5%)	57 (49.6%)	102 (44.5%)
	Missing	4 (3.5%)	5 (4.3%)	9 (3.9%)

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Sites of metastasis	Ascites	1 (0.9%)	0 (0%)	1 (0.4%)
	Bone	67 (58.8%)	66 (57.4%)	133 (58.1%)
	Breast	10 (8.8%)	11 (9.6%)	21 (9.2%)
	CNS (brain)	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Chest wall	9 (7.9%)	7 (6.1%)	16 (7.0%)
	Liver	39 (34.2%)	41 (35.7%)	80 (34.9%)
	Lung	42 (36.8%)	53 (46.1%)	95 (41.5%)
	Lymph node	49 (43.0%)	38 (33.0%)	87 (38.0%)
	Pleural effusion	3 (2.6%)	12 (10.4%)	15 (6.6%)
	Skin	11 (9.6%)	16 (13.9%)	27 (11.8%)
	Other	5 (4.4%)	6 (5.2%)	11 (4.8%)
Location of metastatic sites	Non-visceral	30 (26.3%)	28 (24.3%)	58 (25.3%)
	Visceral	84 (73.7%)	87 (75.7%)	171 (74.7%)

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Measurable disease	Yes	96 (84.2%)	95 (82.6%)	191 (83.4%)
	No	17 (14.9%)	20 (17.4%)	37 (16.2%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Number of metastatic sites	1	34 (29.8%)	31 (27.0%)	65 (28.4%)
	2	45 (39.5%)	41 (35.7%)	86 (37.6%)
	3	23 (20.2%)	36 (31.3%)	59 (25.8%)
	>3	11 (9.6%)	7 (6.1%)	18 (7.9%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Brain metastases	Yes	1 (0.9%)	1 (0.9%)	2 (0.9%)
	No	112 (98.2%)	114 (99.1%)	226 (98.7%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Estrogen receptor	Positive	77 (67.5%)	91 (79.1%)	168 (73.4%)
	Negative	35 (30.7%)	23 (20.0%)	58 (25.3%)
	Unknown	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Progesterone receptor	Positive	51 (44.7%)	66 (57.4%)	117 (51.1%)
	Negative	60 (52.6%)	43 (37.4%)	103 (45.0%)
	Unknown	2 (1.8%)	6 (5.2%)	8 (3.5%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Hormone receptor status[1]	ER-, PgR-	33 (28.9%)	20 (17.4%)	53 (23.1%)
	ER+, PgR-	27 (23.7%)	23 (20.0%)	50 (21.8%)
	ER-, PgR+	2 (1.8%)	3 (2.6%)	5 (2.2%)
	ER+, PgR+	49 (43.0%)	63 (54.8%)	112 (48.9%)
	Unknown	2 (1.8%)	6 (5.2%)	8 (3.5%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Histology	Infiltrating ductal NOS	99 (86.8%)	101 (87.8%)	200 (87.3%)
	Inflammatory breast cancer	0 (0%)	1 (0.9%)	1 (0.4%)
	Lobular invasive	9 (7.9%)	11 (9.6%)	20 (8.7%)
	Mucinous	1 (0.9%)	0 (0%)	1 (0.4%)
	Papillary	2 (1.8%)	0 (0%)	2 (0.9%)
	Other	2 (1.8%)	2 (1.7%)	4 (1.7%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Menopausal status	Pre-menopausal	20 (17.5%)	25 (21.7%)	45 (19.7%)
	Post-menopausal	92 (80.7%)	90 (78.3%)	182 (79.5%)
	N/A (Male)	1 (0.9%)	0 (0%)	1 (0.4%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
FACT-B total score	N	108	109	217
	Mean	99.9	97.1	98.5
	SD	16.7	21.0	19.0
	Median	100	99	100
	Min	62	40	40
	Max	136	130	136
FACT-B breast cancer subscale score	N	110	110	220
	Mean	23.2	22.6	22.9
	SD	5.2	6.1	5.7
	Median	24	23	23
	Min	12	6	6
	Max	35	36	36

Note: For vital signs and ECOG, the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated is used as baseline.
Note: Measurable disease defined as having at least one target lesion at baseline.
[1] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.9 Prior Therapy for Non-Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Prior surgery	Yes	95 (83.3%)	100 (87.0%)	195 (85.2%)
	No	18 (15.8%)	15 (13.0%)	33 (14.4%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior radiotherapy	Yes	76 (66.7%)	83 (72.2%)	159 (69.4%)
	No	37 (32.5%)	32 (27.8%)	69 (30.1%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior endocrine therapy	Yes	58 (50.9%)	67 (58.3%)	125 (54.6%)
	No	55 (48.2%)	48 (41.7%)	103 (45.0%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior chemotherapy	Yes	89 (78.1%)	93 (80.9%)	182 (79.5%)
	No	24 (21.1%)	22 (19.1%)	46 (20.1%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)

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Table 14.1.9 Prior Therapy for Non-Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Type of prior chemotherapy	N	89 (100%)	93 (100%)	182 (100%)
	Adjuvant	70 (78.7%)	73 (78.5%)	143 (78.6%)
	Neo-adjuvant	39 (43.8%)	44 (47.3%)	83 (45.6%)
	Taxane	41 (46.1%)	36 (38.7%)	77 (42.3%)
	Anthracycline	80 (89.9%)	80 (86.0%)	160 (87.9%)
Anthracycline dose (mg/m^2)	N	74	80	154
	Mean	330.9	340.3	335.7
	SD	177.8	176.0	176.4
	Median	300	300	300
	Min	60	36	36
	Max	876	800	876

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Table 14.1.10 Prior Therapy for Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Prior surgery	Yes	23 (20.2%)	15 (13.0%)	38 (16.6%)
	No	90 (78.9%)	100 (87.0%)	190 (83.0%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior radiotherapy	Yes	31 (27.2%)	31 (27.0%)	62 (27.1%)
	No	82 (71.9%)	84 (73.0%)	166 (72.5%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior endocrine therapy	Yes	66 (57.9%)	67 (58.3%)	133 (58.1%)
	No	47 (41.2%)	48 (41.7%)	95 (41.5%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior chemotherapy	Yes	51 (44.7%)	65 (56.5%)	116 (50.7%)
	No	62 (54.4%)	50 (43.5%)	112 (48.9%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)

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Table 14.1.10 Prior Therapy for Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Number of prior chemotherapy regimens	0	62 (54.4%)	50 (43.5%)	112 (48.9%)
	1	51 (44.7%)	65 (56.5%)	116 (50.7%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Type of prior chemotherapy	N	51 (100%)	65 (100%)	116 (100%)
	Taxane	28 (54.9%)	40 (61.5%)	68 (58.6%)
	Anthracycline	28 (54.9%)	31 (47.7%)	59 (50.9%)
Anthracycline dose (mg/mg^2)	N	28	30	58
	Mean	326.8	311.0	318.6
	SD	186.1	178.5	180.8
	Median	300	300	300
	Min	75	60	60
	Max	960	900	960

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Planned daily dose		800 mg	800 mg
Duration of treatment[1] (weeks)	N	112	112
	Mean	19.6	23.2
	SD	12.9	14.1
	Median	18	22
	Min	1	1
	Max	59	60
Duration of treatment (weeks)	Not treated	2 (1.8%)	3 (2.6%)
	<=3 weeks	4 (3.5%)	6 (5.2%)
	> 3 - 6 weeks	10 (8.8%)	10 (8.7%)
	> 6 - 9 weeks	18 (15.8%)	5 (4.3%)
	> 9 -12 weeks	7 (6.1%)	6 (5.2%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)
>12 -15 weeks	7 (6.1%)	8 (7.0%)
>15 -18 weeks	12 (10.5%)	5 (4.3%)
>18 -21 weeks	12 (10.5%)	13 (11.3%)
>21 -24 weeks	6 (5.3%)	11 (9.6%)
>24 -27 weeks	3 (2.6%)	5 (4.3%)
>27 -30 weeks	11 (9.6%)	8 (7.0%)
>30 -33 weeks	2 (1.8%)	4 (3.5%)
>33 -36 weeks	4 (3.5%)	9 (7.8%)
>36 -39 weeks	4 (3.5%)	2 (1.7%)
>39 -42 weeks	3 (2.6%)	5 (4.3%)
>42 -45 weeks	4 (3.5%)	8 (7.0%)
>45 -48 weeks	4 (3.5%)	2 (1.7%)
>48 weeks	1 (0.9%)	5 (4.3%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Average daily dose[2] (mg)	N	112	112
	Mean	748.7	602.7
	SD	104.6	178.4
	Median	800	659
	Min	213	235
	Max	800	800
Percentage of cycles[3] with >90% compliant with dosing	0-20%[4]	0 (0.0%)	1 (0.9%)
	20-40%[4]	1 (0.9%)	0 (0.0%)
	40-60%[4]	3 (2.6%)	0 (0.0%)
	60-80%[4]	4 (3.5%)	9 (7.8%)
	80-100%[4]	102 (89.5%)	102 (88.7%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Subjects with dose reduction	n (%)	13 (11.4%)	55 (47.8%)
Reason for dose reduction			
Adverse Event(s)	n (%)	13 (11.4%)	55 (47.8%)
Number of dose reduction per subject	0	99 (86.8%)	57 (49.6%)
	1	10 (8.8%)	38 (33.0%)
	2	3 (2.6%)	17 (14.8%)
Subjects with dose re-escalation	n (%)	1 (0.9%)	1 (0.9%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Subjects with dose interruption	n (%)	47 (41.2%)	85 (73.9%)
Reason for dose interruption			
Adverse Event(s)	n (%)	44 (38.6%)	84 (73.0%)
Site Error	n (%)	0 (0.0%)	2 (1.7%)
Investigator or subject decision	n (%)	4 (3.5%)	6 (5.2%)
Number of dose interruption per subject	0	65 (57.0%)	27 (23.5%)
	1	31 (27.2%)	28 (24.3%)
	2	9 (7.9%)	20 (17.4%)
	>=3	7 (6.1%)	37 (32.2%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

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Table 14.1.11.2 Study Medication : Sorafenib / Placebo
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)
1	112	106 (94.6%)	106 (94.6%)	781	112	69 (61.6%)	69 (61.6%)	700
2	108	96 (88.9%)	95 (88.0%)	769	103	57 (55.3%)	54 (52.4%)	620
3	93	79 (84.9%)	79 (84.9%)	751	94	62 (66.0%)	48 (51.1%)	633
4	78	64 (82.1%)	58 (74.4%)	716	87	61 (70.1%)	41 (47.1%)	588
5	67	60 (89.6%)	56 (83.6%)	739	78	62 (79.5%)	35 (44.9%)	566
6	61	56 (91.8%)	50 (82.0%)	727	73	59 (80.8%)	28 (38.4%)	525
7	48	46 (95.8%)	42 (87.5%)	753	59	51 (86.4%)	19 (32.2%)	507
8	38	36 (94.7%)	32 (84.2%)	732	50	43 (86.0%)	18 (36.0%)	503
9	33	32 (97.0%)	27 (81.8%)	726	43	37 (86.0%)	12 (27.9%)	469
10	27	26 (96.3%)	21 (77.8%)	712	34	30 (88.2%)	11 (32.4%)	503
11	22	19 (86.4%)	15 (68.2%)	667	30	29 (96.7%)	11 (36.7%)	490
12	18	15 (83.3%)	10 (55.6%)	633	23	21 (91.3%)	7 (30.4%)	454
13	14	13 (92.9%)	9 (64.3%)	614	21	20 (95.2%)	6 (28.6%)	443
14	10	9 (90.0%)	5 (50.0%)	568	14	13 (92.9%)	3 (21.4%)	426
15	6	5 (83.3%)	3 (50.0%)	549	8	7 (87.5%)	2 (25.0%)	462

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_1_11_2_expdbcyc.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.11.2 Study Medication : Sorafenib / Placebo
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)
16	2	2 (100%)	0 (0.0%)	282	6	6 (100%)	2 (33.3%)	500
17	1	1 (100%)	0 (0.0%)	400	2	2 (100%)	0 (0.0%)	300
18	1	1 (100%)	0 (0.0%)	400	1	1 (100%)	0 (0.0%)	400
19	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	400

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_1_11_2_expdbcyc.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Planned daily dose		2000 mg/m^2 for 14 days followed by 7 day rest period	2000 mg/m^2 for 14 days followed by 7 day rest period
Duration of treatment[1] (cycles)	N	112	112
	Mean	6.6	7.5
	SD	4.2	4.5
	Median	6	7
	Min	1	1
	Max	18	19
Duration of treatment (cycles)	Not treated	2 (1.8%)	3 (2.6%)
	<=1 cycle	5 (4.4%)	9 (7.8%)
	> 1 - 2 cycles	15 (13.2%)	11 (9.6%)
	> 2 - 3 cycles	15 (13.2%)	6 (5.2%)
	> 3 - 4 cycles	11 (9.6%)	9 (7.8%)
	> 4 - 5 cycles	5 (4.4%)	5 (4.3%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)
> 5 - 6 cycles	12 (10.5%)	12 (10.4%)
> 6 - 7 cycles	10 (8.8%)	9 (7.8%)
> 7 - 8 cycles	5 (4.4%)	8 (7.0%)
> 8 - 9 cycles	6 (5.3%)	9 (7.8%)
> 9 -10 cycles	5 (4.4%)	4 (3.5%)
>10 -11 cycles	6 (5.3%)	8 (7.0%)
>11 -12 cycles	3 (2.6%)	1 (0.9%)
>12 -13 cycles	5 (4.4%)	7 (6.1%)
>13 -14 cycles	3 (2.6%)	6 (5.2%)
>14 -15 cycles	4 (3.5%)	2 (1.7%)
>15 -16 cycles	1 (0.9%)	4 (3.5%)
>16 -17 cycles	0 (0.0%)	1 (0.9%)
>17 -18 cycles	1 (0.9%)	0 (0.0%)
>18 cycles	0 (0.0%)	1 (0.9%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_1_12_1_expcm.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Percentage of cycles[2] with >90% compliant with dosing	0-20%[3]	9 (7.9%)	7 (6.1%)
	20-40%[3]	5 (4.4%)	5 (4.3%)
	40-60%[3]	10 (8.8%)	9 (7.8%)
	60-80%[3]	5 (4.4%)	12 (10.4%)
	80-100%[3]	83 (72.8%)	79 (68.7%)
Subjects with dose reduction	n (%)	36 (31.6%)	90 (78.3%)
Reason for dose reduction			
Adverse Event(s)	n (%)	35 (30.7%)	90 (78.3%)
Investigator or subject decision	n (%)	2 (1.8%)	1 (0.9%)
Number of dose reduction per subject	0	76 (66.7%)	22 (19.1%)
	1	27 (23.7%)	55 (47.8%)
	2	9 (7.9%)	34 (29.6%)
	>=3	0 (0.0%)	1 (0.9%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Subjects with dose escalation/ re-escalation	n (%)	6 (5.3%)	2 (1.7%)
Subjects with dose interruption	n (%)	46 (40.4%)	87 (75.7%)
Reason for dose interruption			
Adverse Event(s)	n (%)	42 (36.8%)	87 (75.7%)
Subject withdrawn from the study	n (%)	2 (1.8%)	0 (0.0%)
Investigator or subject decision	n (%)	5 (4.4%)	4 (3.5%)
Number of dose interruption per subject	0	66 (57.9%)	25 (21.7%)
	1	27 (23.7%)	32 (27.8%)
	2	14 (12.3%)	24 (20.9%)
	>=3	5 (4.4%)	31 (27.0%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_1_12_1_expcm.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.12.2 Study Medication : Capecitabine
(ITT Population)

	Placebo (N = 114)			Sorafenib (N = 115)		
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption
1	112	105 (93.8%)	104 (92.9%)	112	72 (64.3%)	66 (58.9%)
2	107	96 (89.7%)	82 (76.6%)	103	61 (59.2%)	41 (39.8%)
3	92	78 (84.8%)	67 (72.8%)	92	64 (69.6%)	21 (22.8%)
4	77	64 (83.1%)	47 (61.0%)	86	62 (72.1%)	11 (12.8%)
5	66	57 (86.4%)	38 (57.6%)	77	62 (80.5%)	7 (9.1%)
6	61	58 (95.1%)	34 (55.7%)	72	58 (80.6%)	5 (6.9%)
7	49	47 (95.9%)	30 (61.2%)	60	52 (86.7%)	3 (5.0%)
8	39	36 (92.3%)	23 (59.0%)	51	46 (90.2%)	2 (3.9%)
9	34	33 (97.1%)	18 (52.9%)	43	37 (86.0%)	2 (4.7%)
10	28	27 (96.4%)	16 (57.1%)	34	30 (88.2%)	2 (5.9%)
11	23	20 (87.0%)	10 (43.5%)	30	29 (96.7%)	2 (6.7%)
12	17	15 (88.2%)	5 (29.4%)	22	19 (86.4%)	2 (9.1%)
13	14	14 (100%)	3 (21.4%)	21	19 (90.5%)	2 (9.5%)
14	9	8 (88.9%)	1 (11.1%)	14	13 (92.9%)	2 (14.3%)
15	6	5 (83.3%)	0 (0.0%)	8	7 (87.5%)	1 (12.5%)

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.
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Table 14.1.12.2 Study Medication : Capecitabine
(ITT Population)

	Placebo (N = 114)			Sorafenib (N = 115)		
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption
16	2	2 (100%)	0 (0.0%)	6	6 (100%)	2 (33.3%)
17	1	1 (100%)	0 (0.0%)	2	2 (100%)	1 (50.0%)
18	1	1 (100%)	0 (0.0%)	1	1 (100%)	0 (0.0%)
19	0	0 (0.0%)	0 (0.0%)	1	1 (100%)	0 (0.0%)

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_1_12_2_expcmcyc.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.13 Concomitant Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Therapy (non-medication)	3 (2.7%)	
Radiotherapy	3 (2.7%)	
Medication classified by WHO-DD		
ATC code		
Preferred drug name		
Any ATC code	0 (0.0%)	0 (0.0%)
Any drug	0 (0.0%)	0 (0.0%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication anytime during the study treatment.
Note: Therapy with medications classified by WHO-DD are only included under "Medication Classified by WHO-DD".

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\T_14_1_13_cmeds.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Therapy (non-medication)	4 (3.6%)	5 (4.5%)
Radiotherapy	4 (3.6%)	5 (4.5%)
Surgery	0 (0.0%)	1 (0.9%)
Medication Classified by WHO-DD		
ATC code		
Preferred drug name		
Any ATC code	34 (30.4%)	31 (27.7%)
Any drug	34 (30.4%)	31 (27.7%)
Antineoplastic and immunomodulating agents; anthracyclines and related substances	1 (0.9%)	1 (0.9%)
Mitoxantrone	0 (0.0%)	1 (0.9%)
Myocet [doxorubicin]	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; anti-estrogens	1 (0.9%)	3 (2.7%)
Faslodex [fulvestrant]	0 (0.0%)	1 (0.9%)
Fulvestrant	1 (0.9%)	1 (0.9%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\T_14_1_14_cmedpst.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Tamoxifen	0 (0.0%)	1 (0.9%)
Antineoplastic and immunomodulating agents; enzyme inhibitors	4 (3.6%)	3 (2.7%)
Anastrozole	2 (1.8%)	2 (1.8%)
Arimidex [anastrozole]	1 (0.9%)	0 (0.0%)
Exemestane	0 (0.0%)	1 (0.9%)
Letrozole	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; ethylene imines	2 (1.8%)	1 (0.9%)
Thiotepa	2 (1.8%)	1 (0.9%)
Antineoplastic and immunomodulating agents; folic acid analogues	1 (0.9%)	1 (0.9%)
Methotrexate	1 (0.9%)	1 (0.9%)
Antineoplastic and immunomodulating agents; monoclonal antibodies	5 (4.5%)	1 (0.9%)
Avastin [bevacizumab]	3 (2.7%)	0 (0.0%)
Bevacizumab	1 (0.9%)	1 (0.9%)
Trastuzumab	1 (0.9%)	0 (0.0%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\T_14_1_14_cmedpst.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Antineoplastic and immunomodulating agents; nitrogen mustard analogues	2 (1.8%)	2 (1.8%)
Cyclophosphamide	2 (1.8%)	2 (1.8%)
Antineoplastic and immunomodulating agents; platinum compounds	10 (8.9%)	1 (0.9%)
Carboplatin	3 (2.7%)	1 (0.9%)
Cisplatin	8 (7.1%)	0 (0.0%)
Antineoplastic and immunomodulating agents; pyrimidine analogues	18 (16.1%)	10 (8.9%)
5-fu [flurouracil]	0 (0.0%)	1 (0.9%)
Capecitabine	6 (5.4%)	7 (6.3%)
Gemcitabine	9 (8.0%)	2 (1.8%)
Gemzar [gemcitabine]	4 (3.6%)	0 (0.0%)
Antineoplastic and immunomodulating agents; taxanes	18 (16.1%)	14 (12.5%)
Docetaxel	6 (5.4%)	2 (1.8%)
Paclitaxel	7 (6.3%)	8 (7.1%)
Taxol [paclitaxel]	4 (3.6%)	5 (4.5%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Taxotere [docetaxel]	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; vinca alkaloids and analogues	2 (1.8%)	5 (4.5%)
Navelbine [vinorelbine]	2 (1.8%)	3 (2.7%)
Vinorelbine	0 (0.0%)	2 (1.8%)
Various; detoxifying agents for antineoplastic treatment	0 (0.0%)	1 (0.9%)
Leucovorin [calcium folinate]	0 (0.0%)	1 (0.9%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\T_14_1_14_cmedpst.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Screened	Randomized	Treated
Overall	Overall	07AUG2007	30JUN2010	Placebo	114	114	112
				Sorafenib	115	115	112
				Not Randomized	44	0	0
France	All Centers	24OCT2007	30JUN2010	Placebo	18	18	18
				Sorafenib	19	19	18
				Not Randomized	0	0	0
Spain	All Centers	07AUG2007	30JUN2010	Placebo	43	43	43
				Sorafenib	37	37	35
				Not Randomized	2	0	0
Brazil	All Centers	26OCT2007	30JUN2010	Placebo	53	53	51
				Sorafenib	59	59	59
				Not Randomized	42	0	0

[1] Date of last death or date of last contact alive, whichever is later.

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Screened	Randomized	Treated
France	Institut Claudius Regaud	22NOV2007	30JUN2010	Placebo	15	15	15
				Sorafenib	10	10	10
				Not Randomized	0	0	0
	Hôpital Jean Minjoz	28JAN2008	22JUN2010	Placebo	1	1	1
				Sorafenib	1	1	1
				Not Randomized	0	0	0
	Hôpital Saint Louis	24OCT2007	28JUN2010	Placebo	2	2	2
				Sorafenib	5	5	4
				Not Randomized	0	0	0
	Institut Jean Godinot	13OCT2008	23JUN2010	Placebo	0	0	0
				Sorafenib	3	3	3
				Not Randomized	0	0	0

[1] Date of last death or date of last contact alive, whichever is later.

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Screened	Randomized	Treated
Spain	Hospital Universitario Vall D'Hebron	07AUG2007	29JUN2010	Placebo	7	7	7
				Sorafenib	8	8	8
				Not Randomized	0	0	0
	Hospital Clinico Universitario De Valencia	15FEB2008	29JUN2010	Placebo	6	6	6
				Sorafenib	8	8	8
				Not Randomized	0	0	0
	Hospital Universitario 12 De Octubre	18DEC2007	30JUN2010	Placebo	14	14	14
				Sorafenib	7	7	6
				Not Randomized	2	0	0
	Instituto Valenciano De Oncologia	28JAN2008	30JUN2010	Placebo	5	5	5
				Sorafenib	4	4	3
				Not Randomized	0	0	0

[1] Date of last death or date of last contact alive, whichever is later.

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Screened	Randomized	Treated
Spain	Hospital Universitario Arnau De Vilanova	09OCT2007	30JUN2010	Placebo	5	5	5
				Sorafenib	5	5	5
				Not Randomized	0	0	0
	Hospital Mutua De Terrassa	01JUL2008	04DEC2009	Placebo	0	0	0
				Sorafenib	1	1	1
				Not Randomized	0	0	0
	Instituto Catalan De Oncologia	30NOV2007	30JUN2010	Placebo	1	1	1
				Sorafenib	3	3	3
				Not Randomized	0	0	0
	Hospital De La Santa Creu I Sant Pau	12JUN2008	29JUN2010	Placebo	2	2	2
				Sorafenib	0	0	0
				Not Randomized	0	0	0

[1] Date of last death or date of last contact alive, whichever is later.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_01_SumCC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Screened	Randomized	Treated
Spain	ICO Hospital Dr. Josep Trueta	08JUL2008	21JUN2010	Placebo	1	1	1
				Sorafenib	0	0	0
				Not Randomized	0	0	0
	Hospital Clinico Univ. De Santiago De Compostela	16JUN2008	03SEP2009	Placebo	2	2	2
				Sorafenib	1	1	1
				Not Randomized	0	0	0
Brazil	Fundação Dr. Amaral Carvalho	26OCT2007	29JUN2010	Placebo	5	5	5
				Sorafenib	10	10	10
				Not Randomized	3	0	0
	Hospital das Clínicas - HCFMUSP	11DEC2007	22JUN2010	Placebo	5	5	4
				Sorafenib	4	4	4
				Not Randomized	5	0	0

[1] Date of last death or date of last contact alive, whichever is later.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_01_SumCC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_SumCC.sas (Run Date: 24SEP2010 9:54)

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Screened	Randomized	Treated
Brazil	Instituto do Cancer Arnaldo Vieira de Carvalho	19DEC2007	30JUN2010	Placebo	7	7	7
				Sorafenib	8	8	8
				Not Randomized	5	0	0
	Centro de Pesquisa em Hematologia e Oncologia da Faculdade de Medicina do ABC - CEPHO	17DEC2007	30JUN2010	Placebo	14	14	14
				Sorafenib	13	13	13
				Not Randomized	15	0	0
	Hospital Português da Bahia	27FEB2008	22JUN2010	Placebo	5	5	4
				Sorafenib	1	1	1
				Not Randomized	1	0	0
	Instituto do Câncer do Ceará - ICC	18FEB2008	29JUN2010	Placebo	2	2	2
				Sorafenib	3	3	3
				Not Randomized	0	0	0

[1] Date of last death or date of last contact alive, whichever is later.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_01_SumCC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_SumCC.sas (Run Date: 24SEP2010 9:54)

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Table 14.1.1 Study Periods and Sample Sizes by Country and Study Center

Country	Study Center	Start of Enrollment	Date of Last Visit [1]	Treatment Group	Number of Subjects		
					Screened	Randomized	Treated
Brazil	Santa Casa de Misericórdia de Belo Horizonte	05MAR2008	21JUN2010	Placebo	4	4	4
				Sorafenib	12	12	12
				Not Randomized	8	0	0
	Hospital São Lucas PUCRS	19DEC2007	23JUN2010	Placebo	6	6	6
				Sorafenib	6	6	6
				Not Randomized	4	0	0
	Instituto de Oncologia Clínica de Piracicaba S/S Ltda	21DEC2007	29JUN2010	Placebo	5	5	5
				Sorafenib	2	2	2
				Not Randomized	1	0	0

[1] Date of last death or date of last contact alive, whichever is later.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_01_SumCC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_SumCC.sas (Run Date: 24SEP2010 9:54)

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Table 14.1.2 Subject Disposition

	Placebo	Sorafenib	Total
Number of subjects screened			273
Number of subjects not randomized[1]			44 (16.1%)
Reasons for subjects not randomized[1]			
Inclusion/exclusion criteria violation			35 (12.8%)
Unknown			9 (3.3%)
Number of subjects randomized[1]	114	115	229 (83.9%)
Number of subjects randomized but not treated[2]	2 (1.8%)	3 (2.6%)	5 (2.2%)
Reasons for subjects randomized but not treated[2]			
Consent withdrawn	0 (0%)	2 (1.7%)	2 (0.9%)
Death	0 (0%)	1 (0.9%)	1 (0.4%)
Investigator decision	1 (0.9%)	0 (0%)	1 (0.4%)
Mis-randomization	1 (0.9%)	0 (0%)	1 (0.4%)
Number of subjects treated[2]	112 (98.2%)	112 (97.4%)	224 (97.8%)
Number of subjects discontinuing active treatment[2]	112 (98.2%)	104 (90.4%)	216 (94.3%)

[1] Denominator is the number of patients screened and informed consent signed
[2] Denominator is the number of patients randomized
Note: Subjects who discontinued study treatment due to death, consent withdrawn or lost to follow-up are also counted in subjects discontinuing follow-up.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_02_Disp.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_Disp.sas (Run Date: 24SEP2010 11:26)

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Table 14.1.2 Subject Disposition

	Placebo	Sorafenib	Total
Reasons for subjects discontinuing active treatment[2]			
Adverse event	10 (8.8%)	23 (20.0%)	33 (14.4%)
Consent withdrawn	1 (0.9%)	1 (0.9%)	2 (0.9%)
Death	1 (0.9%)	0 (0%)	1 (0.4%)
Disease progression, recurrence or relapse	93 (81.6%)	73 (63.5%)	166 (72.5%)
Investigator decision	2 (1.8%)	1 (0.9%)	3 (1.3%)
Subject requested to stop study drug administration	3 (2.6%)	3 (2.6%)	6 (2.6%)
Other	2 (1.8%)	3 (2.6%)	5 (2.2%)
Number of subjects discontinuing follow-up[2]	68 (59.6%)	65 (56.5%)	133 (58.1%)
Reasons for subjects discontinuing follow-up[2]			
Deceased during or within 30 days post treatment	5 (4.4%)	7 (6.1%)	12 (5.2%)
Deceased beyond 30 days post treatment	60 (52.6%)	53 (46.1%)	113 (49.3%)
Consent withdrawn	1 (0.9%)	1 (0.9%)	2 (0.9%)
Lost to follow-up	2 (1.8%)	4 (3.5%)	6 (2.6%)

[1] Denominator is the number of patients screened and informed consent signed
[2] Denominator is the number of patients randomized
Note: Subjects who discontinued study treatment due to death, consent withdrawn or lost to follow-up are also counted in subjects discontinuing follow-up.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_02_Disp.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_Disp.sas (Run Date: 24SEP2010 11:26)

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Table 14.1.2 Subject Disposition

	Placebo	Sorafenib	Total
Number of subjects ongoing in study[2]	44 (38.6%)	47 (40.9%)	91 (39.7%)
Active treatment	0 (0%)	8 (7.0%)	8 (3.5%)
Follow-up	44 (38.6%)	39 (33.9%)	83 (36.2%)

[1] Denominator is the number of patients screened and informed consent signed
[2] Denominator is the number of patients randomized
Note: Subjects who discontinued study treatment due to death, consent withdrawn or lost to follow-up are also counted in subjects discontinuing follow-up.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_02_Disp.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_Disp.sas (Run Date: 24SEP2010 11:26)

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Table 14.1.3 Subject Status at Analysis
(ITT Population)

Subject Status	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Alive	46 (40.4%)	47 (40.9%)	93 (40.6%)
Dead	65 (57.0%)	61 (53.0%)	126 (55.0%)
Lost to follow-up	3 (2.6%)	7 (6.1%)	10 (4.4%)

Note: Subjects with treatment or follow-up discontinued due to consent withdrawn or lost to follow-up are counted in lost to follow-up.
Note: Subjects who randomized but not treated due to reasons other than death, disease progression, consent withdrawn or lost to follow-up are counted in alive.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_03_status.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_status.sas (Run Date: 24SEP2010 9:54)

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Table 14.1.4 Subject Disposition by Randomization Strata
(ITT Population)

	Visceral Disease	Placebo	Sorafenib	Total
Number of subjects randomized[1]	Yes	84 (73.7%)	87 (75.7%)	171 (74.7%)
	No	30 (26.3%)	28 (24.3%)	58 (25.3%)
	Total	114 (100.0%)	115 (100.0%)	229 (100.0%)
Number of subjects treated[2]	Yes	82 (73.2%)	84 (75.0%)	166 (74.1%)
	No	30 (26.8%)	28 (25.0%)	58 (25.9%)
	Total	112 (100.0%)	112 (100.0%)	224 (100.0%)

[1] Denominator is the number of patients randomized
[2] Denominator is the number of patients treated
Visceral disease Yes=With at least one visceral metastatic site; No=Only with non-visceral metastatic sites.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_04_DispR.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_DispR.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.5 Subject Disposition by Cycle
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Duration of treatment (cycles)	Not treated	2 (1.8%)	3 (2.6%)	5 (2.2%)
	1	4 (3.5%)	9 (7.8%)	13 (5.7%)
	2	15 (13.2%)	9 (7.8%)	24 (10.5%)
	3	15 (13.2%)	7 (6.1%)	22 (9.6%)
	4	10 (8.8%)	9 (7.8%)	19 (8.3%)
	5	5 (4.4%)	2 (1.7%)	7 (3.1%)
	>=6	63 (55.3%)	76 (66.1%)	139 (60.7%)
Duration of treatment (weeks)[1]	N	112	112	224
	Mean	22.7	33.9	28.3
	SD	16.7	28.5	23.9
	Median	19	27	22
	Min	1	1	1
	Max	78	126	126

[1] [Stop date of Sorafenib/placebo or Capecitabine (whichever is later) -start date of Sorafenib/placebo or Capecitabine (whichever is earlier) + 1] /7;
For subjects in treatment period, the data cutoff date is used as the last dose date.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_05_DispC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_DispC.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.6 Summary of Major Protocol Deviations
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Subjects with any major protocol deviations	15 (13.2%)	15 (13.0%)	30 (13.1%)
Classification of major protocol deviations			
Receipt of protocol-prohibited concomitant therapy before discontinuation of study treatment	3 (2.6%)	0 (0.0%)	3 (1.3%)
Receipt of study treatment different from treatment randomized	1 (0.9%)	1 (0.9%)	2 (0.9%)
Scheduled tumor assessment skipped[1]	10 (8.8%)	9 (7.8%)	19 (8.3%)
Significant inclusion/exclusion criteria violation	3 (2.6%)	5 (4.3%)	8 (3.5%)
Unblinding randomization code prior to PFS event[1]	1 (0.9%)	0 (0.0%)	1 (0.4%)

1: Applied only up to data cutoff time for primary PFS analysis.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_06_protdev.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_protdev.sas (Run Date: 24SEP2010 9:53)

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Table 14.1.7 Demographics
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Age at enrollment (yrs)			
N	114	115	229
Mean	55.4	55.1	55.2
Sd	11.9	11.3	11.6
Median	56	54	55
Min	30	29	29
Max	80	79	80
Age at enrollment category (yrs)			
<40	11 (9.6%)	7 (6.1%)	18 (7.9%)
40-64	76 (66.7%)	81 (70.4%)	157 (68.6%)
65-74	19 (16.7%)	23 (20.0%)	42 (18.3%)
>=75	8 (7.0%)	4 (3.5%)	12 (5.2%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_07_demo.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_demo.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.7 Demographics
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Gender			
Male	1 (0.9%)	0 (0.0%)	1 (0.4%)
Female	113 (99.1%)	115 (100%)	228 (99.6%)
Race			
Caucasian	98 (86.0%)	98 (85.2%)	196 (85.6%)
Black	7 (6.1%)	5 (4.3%)	12 (5.2%)
Asian	0 (0.0%)	2 (1.7%)	2 (0.9%)
American Indian or Native Alaskan	1 (0.9%)	0 (0.0%)	1 (0.4%)
Mestizo	7 (6.1%)	6 (5.2%)	13 (5.7%)
Mulatto	0 (0.0%)	4 (3.5%)	4 (1.7%)
Other	1 (0.9%)	0 (0.0%)	1 (0.4%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_07_demo.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Weight[1] (kg)	N	112	114	226
	Mean	67.3	66.6	66.9
	SD	12.6	13.4	13.0
	Median	66	65	66
	Min	37	42	37
	Max	116	103	116
BSA[1] (m^2)	N	111	113	224
	Mean	1.7	1.7	1.7
	SD	0.1	0.2	0.2
	Median	1.7	1.7	1.7
	Min	1.2	1.3	1.2
	Max	2.1	2.2	2.2

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
ECOG performance status[1]	0	77 (67.5%)	79 (68.7%)	156 (68.1%)
	1	34 (29.8%)	34 (29.6%)	68 (29.7%)
	>= 2	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Missing	2 (1.8%)	1 (0.9%)	3 (1.3%)
Stage of disease at initial diagnosis	Stage I	9 (7.9%)	8 (7.0%)	17 (7.4%)
	Stage II	42 (36.8%)	48 (41.7%)	90 (39.3%)
	Stage III	47 (41.2%)	49 (42.6%)	96 (41.9%)
	Stage IV	14 (12.3%)	10 (8.7%)	24 (10.5%)
	Missing	2 (1.8%)	0 (0%)	2 (0.9%)

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Stage of disease at enrollment	Stage IIIB or IIIC	10 (8.8%)	11 (9.6%)	21 (9.2%)
	Stage IV	103 (90.4%)	104 (90.4%)	207 (90.4%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Months since initial diagnosis	N	113	115	228
	Mean	63.9	71.0	67.5
	SD	58.6	52.6	55.6
	Median	44	57	48
	Min	1	6	1
	Max	278	231	278

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Months since metastatic diagnosis	N	113	115	228
	Mean	23.1	19.4	21.3
	SD	31.3	22.2	27.1
	Median	13	10	12
	Min	0	0	0
	Max	176	113	176
	0 - 12 Months	56 (49.1%)	61 (53.0%)	117 (51.1%)
	>12 - <24 Months	21 (18.4%)	15 (13.0%)	36 (15.7%)
	>=24 Months	36 (31.6%)	39 (33.9%)	75 (32.8%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Months from adjuvant treatment to recurrence or metastatic diagnosis	0 - 12 Months	50 (43.9%)	37 (32.2%)	87 (38.0%)
	>12 - <24 Months	15 (13.2%)	16 (13.9%)	31 (13.5%)
	>=24 Months	45 (39.5%)	57 (49.6%)	102 (44.5%)
	Missing	4 (3.5%)	5 (4.3%)	9 (3.9%)

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Sites of metastasis	Ascites	1 (0.9%)	0 (0%)	1 (0.4%)
	Bone	67 (58.8%)	67 (58.3%)	134 (58.5%)
	Breast	10 (8.8%)	11 (9.6%)	21 (9.2%)
	CNS (brain)	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Chest wall	9 (7.9%)	7 (6.1%)	16 (7.0%)
	Liver	39 (34.2%)	41 (35.7%)	80 (34.9%)
	Lung	42 (36.8%)	53 (46.1%)	95 (41.5%)
	Lymph node	49 (43.0%)	38 (33.0%)	87 (38.0%)
	Pleural effusion	3 (2.6%)	12 (10.4%)	15 (6.6%)
	Skin	11 (9.6%)	16 (13.9%)	27 (11.8%)
	Other	5 (4.4%)	6 (5.2%)	11 (4.8%)
Location of metastatic sites[2]	Non-visceral	30 (26.3%)	28 (24.3%)	58 (25.3%)
	Visceral	84 (73.7%)	87 (75.7%)	171 (74.7%)

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Measurable disease[3]	Yes	96 (84.2%)	95 (82.6%)	191 (83.4%)
	No	17 (14.9%)	20 (17.4%)	37 (16.2%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Number of metastatic sites	1	34 (29.8%)	31 (27.0%)	65 (28.4%)
	2	45 (39.5%)	40 (34.8%)	85 (37.1%)
	3	23 (20.2%)	37 (32.2%)	60 (26.2%)
	>3	11 (9.6%)	7 (6.1%)	18 (7.9%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Brain metastases	Yes	1 (0.9%)	1 (0.9%)	2 (0.9%)
	No	112 (98.2%)	114 (99.1%)	226 (98.7%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Estrogen receptor	Positive	77 (67.5%)	91 (79.1%)	168 (73.4%)
	Negative	35 (30.7%)	23 (20.0%)	58 (25.3%)
	Unknown	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Progesterone receptor	Positive	51 (44.7%)	66 (57.4%)	117 (51.1%)
	Negative	60 (52.6%)	43 (37.4%)	103 (45.0%)
	Unknown	2 (1.8%)	6 (5.2%)	8 (3.5%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Hormone receptor status[4]	ER-, PgR-	33 (28.9%)	20 (17.4%)	53 (23.1%)
	ER+, PgR-	27 (23.7%)	23 (20.0%)	50 (21.8%)
	ER-, PgR+	2 (1.8%)	3 (2.6%)	5 (2.2%)
	ER+, PgR+	49 (43.0%)	63 (54.8%)	112 (48.9%)
	Unknown	2 (1.8%)	6 (5.2%)	8 (3.5%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_08_BC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_BC.sas (Run Date: 24SEP2010 9:49)

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Table 14.1.8 Baseline Characteristics
(ITT Population)

		Placebo (N=114)	Sorafenib (N=115)	Total (N=229)
Histology	Infiltrating ductal NOS	99 (86.8%)	102 (88.7%)	201 (87.8%)
	Lobular invasive	9 (7.9%)	11 (9.6%)	20 (8.7%)
	Mucinous	1 (0.9%)	0 (0%)	1 (0.4%)
	Papillary	2 (1.8%)	0 (0%)	2 (0.9%)
	Other	2 (1.8%)	2 (1.7%)	4 (1.7%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)
Menopausal status	Pre-menopausal	20 (17.5%)	25 (21.7%)	45 (19.7%)
	Post-menopausal	92 (80.7%)	90 (78.3%)	182 (79.5%)
	N/A (Male)	1 (0.9%)	0 (0%)	1 (0.4%)
	Missing	1 (0.9%)	0 (0%)	1 (0.4%)

[1] Baseline is the last measurement prior to study treatment start for subjects treated and the last measurement prior to randomization date for subjects untreated.
[2] Non-visceral=Only with non-visceral metastatic sites. Visceral=With at least one visceral metastatic site.
[3] Measurable disease defined as having at least one target lesion at baseline.
[4] ER = Estrogen Receptor, PgR = Progesterone Receptor, Unknown = Either estrogen receptor status or progesterone receptor status unknown.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_08_BC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_BC.sas (Run Date: 24SEP2010 9:49)

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Table 14.1.9 Prior Therapy for Non-Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Prior surgery	Yes	95 (83.3%)	100 (87.0%)	195 (85.2%)
	No	18 (15.8%)	15 (13.0%)	33 (14.4%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior radiotherapy	Yes	76 (66.7%)	83 (72.2%)	159 (69.4%)
	No	37 (32.5%)	32 (27.8%)	69 (30.1%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior endocrine therapy	Yes	58 (50.9%)	67 (58.3%)	125 (54.6%)
	No	55 (48.2%)	48 (41.7%)	103 (45.0%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior chemotherapy	Yes	89 (78.1%)	93 (80.9%)	182 (79.5%)
	No	24 (21.1%)	22 (19.1%)	46 (20.1%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_09_pthnm.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_pthnm.sas (Run Date: 24SEP2010 9:54)

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Table 14.1.9 Prior Therapy for Non-Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Type of prior chemotherapy	N	89 (100%)	93 (100%)	182 (100%)
	Adjuvant	70 (78.7%)	73 (78.5%)	143 (78.6%)
	Neo-adjuvant	39 (43.8%)	44 (47.3%)	83 (45.6%)
	Taxane	42 (47.2%)	36 (38.7%)	78 (42.9%)
	Anthracycline	80 (89.9%)	80 (86.0%)	160 (87.9%)
Anthracycline dose (mg/m^2)	N	74	80	154
	Mean	330.9	340.3	335.7
	SD	177.8	176.0	176.4
	Median	300	300	300
	Min	60	36	36
	Max	876	800	876

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_09_pthnm.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_pthnm.sas (Run Date: 24SEP2010 9:54)

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Table 14.1.10 Prior Therapy for Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Prior surgery	Yes	23 (20.2%)	15 (13.0%)	38 (16.6%)
	No	90 (78.9%)	100 (87.0%)	190 (83.0%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior radiotherapy	Yes	32 (28.1%)	31 (27.0%)	63 (27.5%)
	No	81 (71.1%)	84 (73.0%)	165 (72.1%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior endocrine therapy	Yes	66 (57.9%)	67 (58.3%)	133 (58.1%)
	No	47 (41.2%)	48 (41.7%)	95 (41.5%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Prior chemotherapy	Yes	51 (44.7%)	65 (56.5%)	116 (50.7%)
	No	62 (54.4%)	50 (43.5%)	112 (48.9%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_10_pthmt.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_pthmt.sas (Run Date: 24SEP2010 9:53)

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Table 14.1.10 Prior Therapy for Metastatic Disease
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)	Total (N = 229)
Number of prior chemotherapy regimens	0	62 (54.4%)	50 (43.5%)	112 (48.9%)
	1	51 (44.7%)	65 (56.5%)	116 (50.7%)
	Missing	1 (0.9%)	0 (0.0%)	1 (0.4%)
Type of prior chemotherapy	N	51 (100%)	65 (100%)	116 (100%)
	Taxane	28 (54.9%)	40 (61.5%)	68 (58.6%)
	Anthracycline	28 (54.9%)	31 (47.7%)	59 (50.9%)
Anthracycline dose (mg/mg^2)	N	28	30	58
	Mean	326.8	311.0	318.6
	SD	186.1	178.5	180.8
	Median	300	300	300
	Min	75	60	60
	Max	960	900	960

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_10_pthmt.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_pthmt.sas (Run Date: 24SEP2010 9:53)

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Planned daily dose		800 mg	800 mg
Duration of treatment[1] (weeks)	N	112	112
	Mean	22.5	33.8
	SD	16.6	28.5
	Median	19	26
	Min	1	1
	Max	77	126
Duration of treatment (weeks)	Not treated	2 (1.8%)	3 (2.6%)
	<=3 weeks	4 (3.5%)	6 (5.2%)
	>3 - 6 weeks	10 (8.8%)	10 (8.7%)
	>6 - 9 weeks	18 (15.8%)	5 (4.3%)
	>9 - 12 weeks	7 (6.1%)	6 (5.2%)
	>12 - 15 weeks	6 (5.3%)	8 (7.0%)
	>15 - 18 weeks	8 (7.0%)	3 (2.6%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_1_expdb.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

	Placebo (N = 114)	Sorafenib (N = 115)
>18 - 21 weeks	10 (8.8%)	11 (9.6%)
>21 - 24 weeks	3 (2.6%)	4 (3.5%)
>24 - 27 weeks	4 (3.5%)	4 (3.5%)
>27 - 30 weeks	11 (9.6%)	5 (4.3%)
>30 - 33 weeks	4 (3.5%)	2 (1.7%)
>33 - 36 weeks	5 (4.4%)	9 (7.8%)
>36 - 39 weeks	3 (2.6%)	1 (0.9%)
>39 - 42 weeks	2 (1.8%)	5 (4.3%)
>42 - 45 weeks	5 (4.4%)	2 (1.7%)
>45 - 48 weeks	5 (4.4%)	1 (0.9%)
>48 - 52 weeks	0 (0.0%)	5 (4.3%)
>52 - 78 weeks	7 (6.1%)	15 (13.0%)
>78 - 104 weeks	0 (0.0%)	6 (5.2%)
>104 weeks	0 (0.0%)	4 (3.5%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_1_expdb.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Average daily dose[2] (mg)	N	112	112
	Mean	745.1	583.9
	SD	108.7	190.2
	Median	800	611
	Min	213	220
	Max	800	800
Percentage of cycles[3] with >90% compliant with dosing	80-100%[4]	101 (88.6%)	103 (89.6%)
	60-80%[4]	5 (4.4%)	8 (7.0%)
	40-60%[4]	3 (2.6%)	0 (0.0%)
	20-40%[4]	1 (0.9%)	0 (0.0%)
	0-20%[4]	0 (0.0%)	1 (0.9%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_1_expdb.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Subjects with dose reduction	n (%)	16 (14.0%)	61 (53.0%)
Reason for dose reduction			
Adverse Event(s)	n (%)	16 (14.0%)	61 (53.0%)
Number of dose reduction per subject	0	96 (84.2%)	51 (44.3%)
	1	13 (11.4%)	38 (33.0%)
	2	3 (2.6%)	22 (19.1%)
	>=3	0 (0.0%)	1 (0.9%)
Subjects with dose re-escalation	n (%)	1 (0.9%)	1 (0.9%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_1_expdb.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.1 Study Medication : Sorafenib / Placebo
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Subjects with dose interruption	n (%)	48 (42.1%)	86 (74.8%)
Reason for dose interruption			
Adverse Event(s)	n (%)	45 (39.5%)	84 (73.0%)
Site Error	n (%)	0 (0.0%)	2 (1.7%)
Investigator or subject decision	n (%)	4 (3.5%)	7 (6.1%)
Number of dose interruption per subject	0	64 (56.1%)	26 (22.6%)
	1	31 (27.2%)	25 (21.7%)
	2	9 (7.9%)	17 (14.8%)
	>=3	8 (7.0%)	44 (38.3%)

1: Only treated subjects are included.
2: Average of intended daily dose.
3: A cycle is defined as 3 weeks when there is no interruption.
4: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_1_expdb.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.2 Study Medication : Sorafenib / Placebo by Cycle
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)
1	112	106 (94.6%)	106 (94.6%)	781	112	69 (61.6%)	69 (61.6%)	700
2	108	96 (88.9%)	95 (88.0%)	769	103	57 (55.3%)	54 (52.4%)	620
3	93	79 (84.9%)	79 (84.9%)	751	94	62 (66.0%)	48 (51.1%)	633
4	78	64 (82.1%)	58 (74.4%)	716	87	61 (70.1%)	41 (47.1%)	588
5	68	61 (89.7%)	57 (83.8%)	740	78	62 (79.5%)	35 (44.9%)	565
6	63	58 (92.1%)	52 (82.5%)	730	76	62 (81.6%)	30 (39.5%)	530
7	53	51 (96.2%)	45 (84.9%)	742	64	55 (85.9%)	21 (32.8%)	503
8	44	42 (95.5%)	36 (81.8%)	723	60	53 (88.3%)	21 (35.0%)	499
9	41	40 (97.6%)	33 (80.5%)	721	56	48 (85.7%)	16 (28.6%)	474
10	36	35 (97.2%)	28 (77.8%)	712	50	46 (92.0%)	16 (32.0%)	490
11	29	26 (89.7%)	21 (72.4%)	686	45	42 (93.3%)	14 (31.1%)	482
12	25	22 (88.0%)	16 (64.0%)	663	40	36 (90.0%)	14 (35.0%)	485
13	20	19 (95.0%)	14 (70.0%)	640	36	32 (88.9%)	10 (27.8%)	459
14	17	15 (88.2%)	10 (58.8%)	616	34	33 (97.1%)	9 (26.5%)	446
15	13	12 (92.3%)	7 (53.8%)	577	31	30 (96.8%)	9 (29.0%)	461

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_2_expdbcyc.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdbcyc.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.11.2 Study Medication : Sorafenib / Placebo by Cycle
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)
16	7	7 (100%)	2 (28.6%)	481	30	27 (90.0%)	9 (30.0%)	452
17	7	6 (85.7%)	1 (14.3%)	412	25	23 (92.0%)	8 (32.0%)	430
18	6	6 (100%)	2 (33.3%)	500	20	20 (100%)	5 (25.0%)	400
19	4	4 (100%)	2 (50.0%)	600	19	18 (94.7%)	5 (26.3%)	403
20	3	3 (100%)	1 (33.3%)	533	17	16 (94.1%)	5 (29.4%)	406
21	3	3 (100%)	1 (33.3%)	533	15	13 (86.7%)	4 (26.7%)	399
22	2	2 (100%)	1 (50.0%)	600	14	13 (92.9%)	4 (28.6%)	411
23	2	2 (100%)	1 (50.0%)	600	13	13 (100%)	4 (30.8%)	431
24	1	1 (100%)	0 (0.0%)	400	11	11 (100%)	4 (36.4%)	455
25	1	1 (100%)	0 (0.0%)	400	10	8 (80.0%)	2 (20.0%)	381
26	1	0 (0.0%)	0 (0.0%)	333	10	10 (100%)	2 (20.0%)	380
27	0	0 (0.0%)	0 (0.0%)	-	10	8 (80.0%)	2 (20.0%)	369
28	0	0 (0.0%)	0 (0.0%)	-	9	9 (100%)	2 (22.2%)	378
29	0	0 (0.0%)	0 (0.0%)	-	9	7 (77.8%)	2 (22.2%)	357

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_2_expdbcyc.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdbcyc.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.11.2 Study Medication : Sorafenib / Placebo by Cycle
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose (mg)
30	0	0 (0.0%)	0 (0.0%)	-	7	7 (100%)	0 (0.0%)	229
31	0	0 (0.0%)	0 (0.0%)	-	6	6 (100%)	0 (0.0%)	233
32	0	0 (0.0%)	0 (0.0%)	-	5	4 (80.0%)	0 (0.0%)	230
33	0	0 (0.0%)	0 (0.0%)	-	5	5 (100%)	0 (0.0%)	240
34	0	0 (0.0%)	0 (0.0%)	-	4	4 (100%)	0 (0.0%)	250
35	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	400
36	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	400
37	0	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	150
38	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	200
39	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	200

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_2_expdbcyc.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdbcyc.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.11.3 Study Medication : Sorafenib / Placebo
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
Planned daily dose		800 mg	800 mg
Duration of treatment (weeks)	N	112	112
	Mean	22.5	33.8
	SD	16.6	28.5
	Median	19	26
	Min	1	1
	Max	77	126
Duration of treatment (weeks)	<=3 weeks	4 (3.6%)	6 (5.4%)
	>3 - 6 weeks	10 (8.9%)	10 (8.9%)
	>6 - 9 weeks	18 (16.1%)	5 (4.5%)
	>9 - 12 weeks	7 (6.3%)	6 (5.4%)
	>12 - 15 weeks	6 (5.4%)	8 (7.1%)

1: Average of intended daily dose.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_3_expdb2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb2.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.3 Study Medication : Sorafenib / Placebo
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
	>15 - 18 weeks	8 (7.1%)	3 (2.7%)
	>18 - 21 weeks	10 (8.9%)	11 (9.8%)
	>21 - 24 weeks	3 (2.7%)	4 (3.6%)
	>24 - 27 weeks	4 (3.6%)	4 (3.6%)
	>27 - 30 weeks	11 (9.8%)	5 (4.5%)
	>30 - 33 weeks	4 (3.6%)	2 (1.8%)
	>33 - 36 weeks	5 (4.5%)	9 (8.0%)
	>36 - 39 weeks	3 (2.7%)	1 (0.9%)
	>39 - 42 weeks	2 (1.8%)	5 (4.5%)
	>42 - 45 weeks	5 (4.5%)	2 (1.8%)
	>45 - 48 weeks	5 (4.5%)	1 (0.9%)
	>48 - 52 weeks	0 (0.0%)	5 (4.5%)
	>52 - 78 weeks	7 (6.3%)	15 (13.4%)
	>78 - 104 weeks	0 (0.0%)	6 (5.4%)
	>104 weeks	0 (0.0%)	4 (3.6%)

1: Average of intended daily dose.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_3_expdb2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb2.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.3 Study Medication : Sorafenib / Placebo
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
Average daily dose[1] (mg)	N	112	112
	Mean	745.1	583.9
	SD	108.7	190.2
	Median	800	611
	Min	213	220
	Max	800	800
Percentage of cycles[2] with >90% compliant with dosing	80-100%[3]	101 (90.2%)	103 (92.0%)
	60-80%[3]	5 (4.5%)	8 (7.1%)
	40-60%[3]	3 (2.7%)	0 (0.0%)
	20-40%[3]	1 (0.9%)	0 (0.0%)
	0-20%[3]	0 (0.0%)	1 (0.9%)

1: Average of intended daily dose.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_3_expdb2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb2.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.3 Study Medication : Sorafenib / Placebo
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
Subjects with dose reduction	n (%)	16 (14.3%)	61 (54.5%)
Reason for dose reduction			
Adverse Event(s)	n (%)	16 (14.3%)	61 (54.5%)
Number of dose reduction per subject	0	96 (85.7%)	51 (45.5%)
	1	13 (11.6%)	38 (33.9%)
	2	3 (2.7%)	22 (19.6%)
	>=3	0 (0.0%)	1 (0.9%)
Subjects with dose re-escalation	n (%)	1 (0.9%)	1 (0.9%)

1: Average of intended daily dose.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_3_expdb2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb2.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.3 Study Medication : Sorafenib / Placebo
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
Subjects with dose interruption	n (%)	48 (42.9%)	86 (76.8%)
Reason for dose interruption			
Adverse Event(s)	n (%)	45 (40.2%)	84 (75.0%)
Site Error	n (%)	0 (0.0%)	2 (1.8%)
Investigator or subject decision	n (%)	4 (3.6%)	7 (6.3%)
Number of dose interruption per subject	0	64 (57.1%)	26 (23.2%)
	1	31 (27.7%)	25 (22.3%)
	2	9 (8.0%)	17 (15.2%)
	>=3	8 (7.1%)	44 (39.3%)

1: Average of intended daily dose.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_3_expdb2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdb2.sas (Run Date: 24SEP2010 9:50)

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Table 14.1.11.4 Study Medication : Sorafenib / Placebo by Cycle
(Safety Population)

	Placebo (N = 112)					Sorafenib (N = 112)				
Cycle	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose (mg)	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose (mg)
1	112	0 (0.0%)	5 (4.5%)	1 (0.9%)	781	112	0 (0.0%)	42 (37.5%)	1 (0.9%)	700
2	108	1 (0.9%)	12 (11.1%)	0 (0.0%)	769	103	1 (1.0%)	37 (35.9%)	9 (8.7%)	620
3	93	0 (0.0%)	12 (12.9%)	2 (2.2%)	751	94	8 (8.5%)	28 (29.8%)	4 (4.3%)	633
4	78	3 (3.8%)	14 (17.9%)	0 (0.0%)	716	87	7 (8.0%)	21 (24.1%)	5 (5.7%)	588
5	68	1 (1.5%)	7 (10.3%)	0 (0.0%)	740	78	10 (12.8%)	13 (16.7%)	3 (3.8%)	565
6	63	2 (3.2%)	5 (7.9%)	0 (0.0%)	730	76	8 (10.5%)	13 (17.1%)	1 (1.3%)	530
7	53	2 (3.8%)	1 (1.9%)	1 (1.9%)	742	64	5 (7.8%)	7 (10.9%)	2 (3.1%)	503
8	44	0 (0.0%)	2 (4.5%)	0 (0.0%)	723	60	3 (5.0%)	7 (11.7%)	0 (0.0%)	499
9	41	1 (2.4%)	1 (2.4%)	0 (0.0%)	721	56	2 (3.6%)	7 (12.5%)	1 (1.8%)	474
10	36	0 (0.0%)	1 (2.8%)	0 (0.0%)	712	50	2 (4.0%)	4 (8.0%)	0 (0.0%)	490
11	29	0 (0.0%)	3 (10.3%)	0 (0.0%)	686	45	1 (2.2%)	3 (6.7%)	0 (0.0%)	482
12	25	1 (4.0%)	3 (12.0%)	0 (0.0%)	663	40	1 (2.5%)	4 (10.0%)	0 (0.0%)	485
13	20	1 (5.0%)	1 (5.0%)	0 (0.0%)	640	36	1 (2.8%)	4 (11.1%)	0 (0.0%)	459

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_4_expdbcyc2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdbcyc2.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.11.4 Study Medication : Sorafenib / Placebo by Cycle
(Safety Population)

	Placebo (N = 112)					Sorafenib (N = 112)				
Cycle	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose (mg)	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose (mg)
14	17	0 (0.0%)	2 (11.8%)	0 (0.0%)	616	34	2 (5.9%)	0 (0.0%)	1 (2.9%)	446
15	13	2 (15.4%)	1 (7.7%)	0 (0.0%)	577	31	0 (0.0%)	1 (3.2%)	0 (0.0%)	461
16	7	1 (14.3%)	0 (0.0%)	0 (0.0%)	481	30	1 (3.3%)	3 (10.0%)	0 (0.0%)	452
17	7	0 (0.0%)	1 (14.3%)	0 (0.0%)	412	25	2 (8.0%)	1 (4.0%)	1 (4.0%)	430
18	6	0 (0.0%)	0 (0.0%)	0 (0.0%)	500	20	0 (0.0%)	0 (0.0%)	0 (0.0%)	400
19	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	600	19	0 (0.0%)	1 (5.3%)	0 (0.0%)	403
20	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	533	17	1 (5.9%)	1 (5.9%)	0 (0.0%)	406
21	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	533	15	0 (0.0%)	2 (13.3%)	0 (0.0%)	399
22	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	600	14	0 (0.0%)	1 (7.1%)	0 (0.0%)	411
23	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	600	13	0 (0.0%)	0 (0.0%)	0 (0.0%)	431
24	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	400	11	0 (0.0%)	0 (0.0%)	0 (0.0%)	455
25	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	400	10	0 (0.0%)	2 (20.0%)	0 (0.0%)	381
26	1	0 (0.0%)	1 (100%)	0 (0.0%)	333	10	1 (10.0%)	0 (0.0%)	0 (0.0%)	380

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_4_expdbcyc2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdbcyc2.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.11.4 Study Medication : Sorafenib / Placebo by Cycle
(Safety Population)

	Placebo (N = 112)					Sorafenib (N = 112)				
Cycle	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose (mg)	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose (mg)
27	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	10	0 (0.0%)	2 (20.0%)	0 (0.0%)	369
28	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	9	0 (0.0%)	0 (0.0%)	0 (0.0%)	378
29	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	9	0 (0.0%)	2 (22.2%)	0 (0.0%)	357
30	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	7	1 (14.3%)	0 (0.0%)	0 (0.0%)	229
31	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	6	0 (0.0%)	0 (0.0%)	0 (0.0%)	233
32	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	5	0 (0.0%)	1 (20.0%)	0 (0.0%)	230
33	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	240
34	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	250
35	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	400
36	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	400
37	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	1 (100%)	150
38	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	200
39	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	200

Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Note: A cycle is defined as 3 weeks when there is no interruption.
Note: Average daily dose is average of intended daily dose.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_11_4_expdbcyc2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expdbcyc2.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Planned daily dose		2000 mg/m^2 for 14 days followed by 7 day rest period	2000 mg/m^2 for 14 days followed by 7 day rest period
Duration of treatment[1] (cycles)	N	112	112
	Mean	7.4	10.7
	SD	5.3	9.0
	Median	6	9
	Min	1	1
	Max	26	39
Duration of treatment (cycles)	Not treated	2 (1.8%)	3 (2.6%)
	<=1 cycle	5 (4.4%)	9 (7.8%)
	> 1 - 2 cycles	15 (13.2%)	11 (9.6%)
	> 2 - 3 cycles	15 (13.2%)	6 (5.2%)
	> 3 - 4 cycles	10 (8.8%)	9 (7.8%)
	> 4 - 5 cycles	4 (3.5%)	3 (2.6%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_1_expcm.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
	> 5 - 6 cycles	9 (7.9%)	9 (7.8%)
	> 6 - 7 cycles	9 (7.9%)	4 (3.5%)
	> 7 - 8 cycles	3 (2.6%)	5 (4.3%)
	> 8 - 9 cycles	6 (5.3%)	6 (5.2%)
	> 9 -10 cycles	6 (5.3%)	5 (4.3%)
	>10 -11 cycles	7 (6.1%)	6 (5.2%)
	>11 -12 cycles	3 (2.6%)	4 (3.5%)
	>12 -13 cycles	3 (2.6%)	2 (1.7%)
	>13 -14 cycles	5 (4.4%)	2 (1.7%)
	>14 -15 cycles	5 (4.4%)	2 (1.7%)
	>15 -16 cycles	0 (0.0%)	6 (5.2%)
	>16 -17 cycles	1 (0.9%)	3 (2.6%)
	>17 -26 cycles	6 (5.3%)	10 (8.7%)
	>26 -34 cycles	0 (0.0%)	9 (7.8%)
	>34 cycles	0 (0.0%)	1 (0.9%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_1_expcm.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Average intended daily dose (mg/m^2)	N	112	112
	Mean	1839.3	1460.7
	SD	265.8	326.9
	Median	2000	1441
	Min	951	683
	Max	2375	2000
Percentage of cycles[2] with >90% compliant with dosing	80-100%[3]	83 (72.8%)	81 (70.4%)
	60-80%[3]	5 (4.4%)	15 (13.0%)
	40-60%[3]	10 (8.8%)	6 (5.2%)
	20-40%[3]	5 (4.4%)	3 (2.6%)
	0-20%[3]	9 (7.9%)	7 (6.1%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_1_expcm.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Subjects with dose reduction	n (%)	38 (33.3%)	90 (78.3%)
Reason for dose reduction			
Adverse Event(s)	n (%)	37 (32.5%)	90 (78.3%)
Investigator or subject decision	n (%)	2 (1.8%)	2 (1.7%)
Number of dose reduction per subject	0	74 (64.9%)	22 (19.1%)
	1	28 (24.6%)	48 (41.7%)
	2	10 (8.8%)	40 (34.8%)
	>=3	0 (0.0%)	2 (1.7%)
Subjects with dose escalation/ re-escalation	n (%)	6 (5.3%)	2 (1.7%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_1_expcm.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.1 Study Medication : Capecitabine
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Subjects with dose interruption	n (%)	47 (41.2%)	88 (76.5%)
Reason for dose interruption			
Adverse Event(s)	n (%)	43 (37.7%)	87 (75.7%)
Subject withdrawn from the study	n (%)	2 (1.8%)	0 (0.0%)
Investigator or subject decision	n (%)	6 (5.3%)	7 (6.1%)
Number of dose interruption per subject	0	65 (57.0%)	24 (20.9%)
	1	26 (22.8%)	28 (24.3%)
	2	15 (13.2%)	17 (14.8%)
	>=3	6 (5.3%)	43 (37.4%)

1: Only treated subjects are included.
2: A cycle is defined as 3 weeks when there is no interruption.
3: The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_1_expcm.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.2 Study Medication : Capecitabine by Cycle
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose Level (mg/m^2)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose Level (mg/m^2)
1	112	105 (93.8%)	104 (92.9%)	1951	112	71 (63.4%)	65 (58.0%)	1812
2	107	96 (89.7%)	82 (76.6%)	1937	103	61 (59.2%)	41 (39.8%)	1573
3	92	78 (84.8%)	67 (72.8%)	1879	92	63 (68.5%)	21 (22.8%)	1508
4	77	64 (83.1%)	47 (61.0%)	1803	86	62 (72.1%)	11 (12.8%)	1399
5	67	58 (86.6%)	39 (58.2%)	1753	77	62 (80.5%)	7 (9.1%)	1358
6	63	60 (95.2%)	35 (55.6%)	1757	74	60 (81.1%)	5 (6.8%)	1339
7	54	52 (96.3%)	31 (57.4%)	1794	65	56 (86.2%)	3 (4.6%)	1277
8	45	42 (93.3%)	25 (55.6%)	1741	61	56 (91.8%)	2 (3.3%)	1310
9	42	40 (95.2%)	21 (50.0%)	1748	56	48 (85.7%)	2 (3.6%)	1236
10	36	34 (94.4%)	18 (50.0%)	1712	50	45 (90.0%)	2 (4.0%)	1290
11	30	27 (90.0%)	13 (43.3%)	1649	45	40 (88.9%)	2 (4.4%)	1254
12	23	20 (87.0%)	8 (34.8%)	1582	39	33 (84.6%)	2 (5.1%)	1229
13	20	20 (100%)	6 (30.0%)	1650	35	30 (85.7%)	2 (5.7%)	1163
14	17	16 (94.1%)	2 (11.8%)	1508	33	32 (97.0%)	2 (6.1%)	1202
15	12	10 (83.3%)	0 (0.0%)	1377	31	29 (93.5%)	1 (3.2%)	1186

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_2_expcmcyc.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcmcyc.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.2 Study Medication : Capecitabine by Cycle
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose Level (mg/m^2)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose Level (mg/m^2)
16	7	7 (100%)	0 (0.0%)	1357	29	26 (89.7%)	2 (6.9%)	1205
17	7	6 (85.7%)	0 (0.0%)	1241	23	21 (91.3%)	2 (8.7%)	1193
18	6	6 (100%)	0 (0.0%)	1333	20	20 (100%)	2 (10.0%)	1200
19	4	4 (100%)	0 (0.0%)	1375	19	17 (89.5%)	2 (10.5%)	1194
20	3	3 (100%)	0 (0.0%)	1333	17	16 (94.1%)	2 (11.8%)	1186
21	3	3 (100%)	0 (0.0%)	1333	15	13 (86.7%)	1 (6.7%)	1132
22	2	2 (100%)	0 (0.0%)	1250	13	12 (92.3%)	2 (15.4%)	1244
23	2	2 (100%)	0 (0.0%)	1250	13	12 (92.3%)	2 (15.4%)	1239
24	1	1 (100%)	0 (0.0%)	1000	11	11 (100%)	2 (18.2%)	1318
25	1	1 (100%)	0 (0.0%)	1000	10	8 (80.0%)	1 (10.0%)	1225
26	1	1 (100%)	0 (0.0%)	1000	10	10 (100%)	1 (10.0%)	1250
27	0	0 (0.0%)	0 (0.0%)	-	10	8 (80.0%)	1 (10.0%)	1148
28	0	0 (0.0%)	0 (0.0%)	-	9	9 (100%)	1 (11.1%)	1171
29	0	0 (0.0%)	0 (0.0%)	-	9	7 (77.8%)	0 (0.0%)	1087

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_2_expcmcyc.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcmcyc.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.2 Study Medication : Capecitabine by Cycle
(ITT Population)

	Placebo (N = 114)				Sorafenib (N = 115)			
Cycle	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose Level (mg/m^2)	Number Of Subjects Completed Cycle	Number Of Subjects Completed Cycle Without Interruption	Number of subjects completed cycle without dose reduction /interruption	Average Daily Dose Level (mg/m^2)
30	0	0 (0.0%)	0 (0.0%)	-	7	7 (100%)	0 (0.0%)	1000
31	0	0 (0.0%)	0 (0.0%)	-	6	6 (100%)	0 (0.0%)	1000
32	0	0 (0.0%)	0 (0.0%)	-	5	4 (80.0%)	0 (0.0%)	933
33	0	0 (0.0%)	0 (0.0%)	-	5	5 (100%)	0 (0.0%)	1000
34	0	0 (0.0%)	0 (0.0%)	-	4	4 (100%)	0 (0.0%)	1000
35	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	1000
36	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	1000
37	0	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	667
38	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	1000
39	0	0 (0.0%)	0 (0.0%)	-	1	1 (100%)	0 (0.0%)	1000

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_2_expcmcyc.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcmcyc.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.3 Study Medication : Capecitabine
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
Planned daily dose		2000 mg/m^2 for 14 days followed by 7 day rest period	2000 mg/m^2 for 14 days followed by 7 day rest period
Duration of treatment (cycles)	N	112	112
	Mean	7.4	10.7
	SD	5.3	9.0
	Median	6	9
	Min	1	1
	Max	26	39
Duration of treatment (cycles)	<=1 cycle	5 (4.5%)	9 (8.0%)
	> 1 - 2 cycles	15 (13.4%)	11 (9.8%)
	> 2 - 3 cycles	15 (13.4%)	6 (5.4%)
	> 3 - 4 cycles	10 (8.9%)	9 (8.0%)
	> 4 - 5 cycles	4 (3.6%)	3 (2.7%)
	> 5 - 6 cycles	9 (8.0%)	9 (8.0%)

[1] A cycle is defined as 3 weeks when there is no interruption.
[2] The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_3_expcm2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm2.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.3 Study Medication : Capecitabine
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
	> 6 - 7 cycles	9 (8.0%)	4 (3.6%)
	> 7 - 8 cycles	3 (2.7%)	5 (4.5%)
	> 8 - 9 cycles	6 (5.4%)	6 (5.4%)
	> 9 -10 cycles	6 (5.4%)	5 (4.5%)
	>10 -11 cycles	7 (6.3%)	6 (5.4%)
	>11 -12 cycles	3 (2.7%)	4 (3.6%)
	>12 -13 cycles	3 (2.7%)	2 (1.8%)
	>13 -14 cycles	5 (4.5%)	2 (1.8%)
	>14 -15 cycles	5 (4.5%)	2 (1.8%)
	>15 -16 cycles	0 (0.0%)	6 (5.4%)
	>16 -17 cycles	1 (0.9%)	3 (2.7%)
	>17 -26 cycles	6 (5.4%)	10 (8.9%)
	>26 -34 cycles	0 (0.0%)	9 (8.0%)
	>34 cycles	0 (0.0%)	1 (0.9%)

[1] A cycle is defined as 3 weeks when there is no interruption.
[2] The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_3_expcm2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm2.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.3 Study Medication : Capecitabine
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
Average intended daily dose (mg/m^2)	N	112	112
	Mean	1839.3	1460.7
	SD	265.8	326.9
	Median	2000	1441
	Min	951	683
	Max	2375	2000
Percentage of cycles[1] with >90% compliant with dosing	80-100%[2]	83 (74.1%)	81 (72.3%)
	60-80%[2]	5 (4.5%)	15 (13.4%)
	40-60%[2]	10 (8.9%)	6 (5.4%)
	20-40%[2]	5 (4.5%)	3 (2.7%)
	0-20%[2]	9 (8.0%)	7 (6.3%)
Subjects with dose reduction	n (%)	38 (33.9%)	90 (80.4%)
Reason for dose reduction			
Adverse Event(s)	n (%)	37 (33.0%)	90 (80.4%)
Investigator or subject decision	n (%)	2 (1.8%)	2 (1.8%)

[1] A cycle is defined as 3 weeks when there is no interruption.
[2] The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_3_expcm2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_expcm2.sas (Run Date: 24SEP2010 9:51)

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Table 14.1.12.3 Study Medication : Capecitabine
(Safety Population)

		Placebo (N = 112)	Sorafenib (N = 112)
Number of dose reduction per subject	0	74 (66.1%)	22 (19.6%)
	1	28 (25.0%)	48 (42.9%)
	2	10 (8.9%)	40 (35.7%)
	>=3	0 (0.0%)	2 (1.8%)
Subjects with dose escalation/ re-escalation	n (%)	6 (5.4%)	2 (1.8%)
Subjects with dose interruption	n (%)	47 (42.0%)	88 (78.6%)
Reason for dose interruption			
Adverse Event(s)	n (%)	43 (38.4%)	87 (77.7%)
Subject withdrawn from the study	n (%)	2 (1.8%)	0 (0.0%)
Investigator or subject decision	n (%)	6 (5.4%)	7 (6.3%)
Number of dose interruption per subject	0	65 (58.0%)	24 (21.4%)
	1	26 (23.2%)	28 (25.0%)
	2	15 (13.4%)	17 (15.2%)
	>=3	6 (5.4%)	43 (38.4%)

[1] A cycle is defined as 3 weeks when there is no interruption.
[2] The denominator is the number of cycles for which >90% compliance was checked either yes or no. The numerator is the number of cycles for which >90% compliance is checked yes.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_3_expcm2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.12.4 Study Medication : Capecitabine by Cycle
(Safety Population)

	Placebo (N = 112)					Sorafenib (N = 112)				
Cycle	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose Level (mg/m^2)	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose Level (mg/m^2)
1	112	0 (0.0%)	7 (6.3%)	0 (0.0%)	1951	112	1 (0.9%)	40 (35.7%)	1 (0.9%)	1812
2	107	2 (1.9%)	9 (8.4%)	2 (1.9%)	1937	103	15 (14.6%)	30 (29.1%)	12 (11.7%)	1573
3	92	4 (4.3%)	10 (10.9%)	4 (4.3%)	1879	92	23 (25.0%)	18 (19.6%)	11 (12.0%)	1508
4	77	5 (6.5%)	12 (15.6%)	1 (1.3%)	1803	86	15 (17.4%)	19 (22.1%)	5 (5.8%)	1399
5	67	7 (10.4%)	7 (10.4%)	2 (3.0%)	1753	77	14 (18.2%)	13 (16.9%)	2 (2.6%)	1358
6	63	6 (9.5%)	3 (4.8%)	0 (0.0%)	1757	74	3 (4.1%)	12 (16.2%)	2 (2.7%)	1339
7	54	0 (0.0%)	2 (3.7%)	0 (0.0%)	1794	65	8 (12.3%)	8 (12.3%)	1 (1.5%)	1277
8	45	0 (0.0%)	2 (4.4%)	1 (2.2%)	1741	61	2 (3.3%)	5 (8.2%)	0 (0.0%)	1310
9	42	3 (7.1%)	2 (4.8%)	0 (0.0%)	1748	56	3 (5.4%)	7 (12.5%)	1 (1.8%)	1236
10	36	1 (2.8%)	2 (5.6%)	0 (0.0%)	1712	50	0 (0.0%)	5 (10.0%)	0 (0.0%)	1290
11	30	2 (6.7%)	3 (10.0%)	0 (0.0%)	1649	45	3 (6.7%)	5 (11.1%)	0 (0.0%)	1254
12	23	1 (4.3%)	2 (8.7%)	1 (4.3%)	1582	39	2 (5.1%)	6 (15.4%)	0 (0.0%)	1229
13	20	1 (5.0%)	0 (0.0%)	0 (0.0%)	1650	35	3 (8.6%)	3 (8.6%)	2 (5.7%)	1163

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_4_expcmcyc2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.12.4 Study Medication : Capecitabine by Cycle
(Safety Population)

	Placebo (N = 112)					Sorafenib (N = 112)				
Cycle	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose Level (mg/m^2)	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose Level (mg/m^2)
14	17	1 (5.9%)	1 (5.9%)	0 (0.0%)	1508	33	0 (0.0%)	1 (3.0%)	0 (0.0%)	1202
15	12	0 (0.0%)	2 (16.7%)	0 (0.0%)	1377	31	1 (3.2%)	2 (6.5%)	0 (0.0%)	1186
16	7	2 (28.6%)	0 (0.0%)	0 (0.0%)	1357	29	0 (0.0%)	3 (10.3%)	0 (0.0%)	1205
17	7	0 (0.0%)	1 (14.3%)	0 (0.0%)	1241	23	0 (0.0%)	2 (8.7%)	0 (0.0%)	1193
18	6	0 (0.0%)	0 (0.0%)	0 (0.0%)	1333	20	1 (5.0%)	0 (0.0%)	0 (0.0%)	1200
19	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1375	19	0 (0.0%)	2 (10.5%)	0 (0.0%)	1194
20	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1333	17	0 (0.0%)	1 (5.9%)	0 (0.0%)	1186
21	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1333	15	0 (0.0%)	2 (13.3%)	0 (0.0%)	1132
22	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1250	13	0 (0.0%)	1 (7.7%)	0 (0.0%)	1244
23	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1250	13	0 (0.0%)	1 (7.7%)	0 (0.0%)	1239
24	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000	11	0 (0.0%)	0 (0.0%)	0 (0.0%)	1318
25	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000	10	0 (0.0%)	2 (20.0%)	0 (0.0%)	1225
26	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000	10	1 (10.0%)	0 (0.0%)	0 (0.0%)	1250

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_4_expcmcyc2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.12.4 Study Medication : Capecitabine by Cycle
(Safety Population)

	Placebo (N = 112)					Sorafenib (N = 112)				
Cycle	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose Level (mg/m^2)	Subjects Completed Cycle	Subjects with Dose Reduction Only	Subjects with Dose Interruption Only	Subjects with Dose Interruption and Reduction	Average Daily Dose Level (mg/m^2)
27	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	10	0 (0.0%)	2 (20.0%)	0 (0.0%)	1148
28	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	9	1 (11.1%)	0 (0.0%)	0 (0.0%)	1171
29	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	9	0 (0.0%)	2 (22.2%)	0 (0.0%)	1087
30	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	7	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000
31	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	6	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000
32	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	5	0 (0.0%)	1 (20.0%)	0 (0.0%)	933
33	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000
34	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000
35	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000
36	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000
37	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	1 (100%)	0 (0.0%)	667
38	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000
39	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1000

Note: A cycle is defined as 3 weeks when there is no interruption.
Note: The denominator in percentage calculation is the number of subjects completed the cycle.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_12_4_expcmcyc2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.13 Concomitant Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Therapy (non-medication)	3 (2.7%)	
Radiotherapy	3 (2.7%)	
Medication classified by WHO-DD		
ATC code		
Preferred drug name		
Any ATC code	0 (0.0%)	0 (0.0%)
Any drug	0 (0.0%)	0 (0.0%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication anytime during the study treatment period.
Note: Therapy with medications classified by WHO-DD are only included under "Medication Classified by WHO-DD".

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\T_14_1_13_cmeds.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_cmeds.sas (Run Date: 24SEP2010 9:49)

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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Therapy (non-medication)	5 (4.5%)	8 (7.1%)
Radiotherapy	5 (4.5%)	8 (7.1%)
Surgery	0 (0.0%)	1 (0.9%)
Medication Classified by WHO-DD		
ATC code		
Preferred drug name		
Any ATC code	49 (43.8%)	50 (44.6%)
Any drug	49 (43.8%)	50 (44.6%)
Antineoplastic and immunomodulating agents; podophyllotoxin derivatives	1 (0.9%)	0 (0.0%)
Vepesid (etoposide)	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; anthracyclines and related substances	5 (4.5%)	2 (1.8%)
Adriablastina (doxorubicin)	1 (0.9%)	0 (0.0%)
Adriamycin (doxorubicin)	1 (0.9%)	0 (0.0%)
Doxorubicin	1 (0.9%)	0 (0.0%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_14_cmedpst.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Mitoxantrone	0 (0.0%)	2 (1.8%)
Myocet [doxorubicin]	1 (0.9%)	0 (0.0%)
Novantrone (mitoxantrone)	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; anti-estrogens	4 (3.6%)	5 (4.5%)
Faslodex [fulvestrant]	3 (2.7%)	2 (1.8%)
Fulvestrant	1 (0.9%)	1 (0.9%)
Tamoxifen	0 (0.0%)	2 (1.8%)
Antineoplastic and immunomodulating agents; enzyme inhibitors	9 (8.0%)	11 (9.8%)
Anastrozole	3 (2.7%)	3 (2.7%)
Arimidex [anastrozole]	4 (3.6%)	5 (4.5%)
Aromasine (exemestane)	1 (0.9%)	0 (0.0%)
Exemestane	0 (0.0%)	2 (1.8%)
Letrozole	1 (0.9%)	1 (0.9%)
Antineoplastic and immunomodulating agents; ethylene imines	2 (1.8%)	2 (1.8%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_14_cmedpst.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_cmedpst.sas (Run Date: 24SEP2010 9:49)

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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Thiotepa	2 (1.8%)	2 (1.8%)
Antineoplastic and immunomodulating agents; folic acid analogues	5 (4.5%)	2 (1.8%)
Methotrexate	5 (4.5%)	2 (1.8%)
Antineoplastic and immunomodulating agents; monoclonal antibodies	6 (5.4%)	2 (1.8%)
Avastin [bevacizumab]	3 (2.7%)	0 (0.0%)
Bevacizumab	2 (1.8%)	2 (1.8%)
Trastuzumab	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; nitrogen mustard analogues	8 (7.1%)	3 (2.7%)
Cyclophosphamide	7 (6.3%)	3 (2.7%)
Genuxal (cyclophosphamide)	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; other cytotoxic antibiotics	1 (0.9%)	0 (0.0%)
Mitocin (mitomycin)	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; platinum compounds	16 (14.3%)	5 (4.5%)
Carboplatin	4 (3.6%)	3 (2.7%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_14_cmedpst.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Cisplatin	14 (12.5%)	2 (1.8%)
Oxaliplatin	1 (0.9%)	0 (0.0%)
Antineoplastic and immunomodulating agents; progestogens	1 (0.9%)	3 (2.7%)
Megestat (megestrol)	1 (0.9%)	3 (2.7%)
Antineoplastic and immunomodulating agents; pyrimidine analogues	28 (25.0%)	21 (18.8%)
5-fu [flurouracil]	4 (3.6%)	3 (2.7%)
Ara-c (cytarabine)	0 (0.0%)	1 (0.9%)
Capecitabine	6 (5.4%)	7 (6.3%)
Gemcitabine	14 (12.5%)	8 (7.1%)
Gemzar [gemcitabine]	9 (8.0%)	2 (1.8%)
Antineoplastic and immunomodulating agents; taxanes	30 (26.8%)	24 (21.4%)
Docetaxel	7 (6.3%)	4 (3.6%)
Paclitaxel	11 (9.8%)	11 (9.8%)
Taxol [paclitaxel]	8 (7.1%)	7 (6.3%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_14_cmedpst.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_cmedpst.sas (Run Date: 24SEP2010 9:49)

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Table 14.1.14 Post-Treatment Anti-Cancer Therapy/Medication
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Taxotere [docetaxel]	8 (7.1%)	4 (3.6%)
Antineoplastic and immunomodulating agents; vinca alkaloids and analogues	9 (8.0%)	12 (10.7%)
Navelbine [vinorelbine]	8 (7.1%)	7 (6.3%)
Vinorelbine	1 (0.9%)	5 (4.5%)
Systemic hormonal preparations, excl. sex hormones and insulins; glucocorticoids	0 (0.0%)	1 (0.9%)
Dexamethasone	0 (0.0%)	1 (0.9%)
Various; detoxifying agents for antineoplastic treatment	0 (0.0%)	1 (0.9%)
Leucovorin [calcium folinate]	0 (0.0%)	1 (0.9%)

Note: A frequency in this table represents the number of subjects who took the corresponding therapy/medication after discontinuation of study treatment.
Note: Therapy with medications classified by WHO-DD are only included under “Medication Classified by WHO-DD”.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_1_14_cmedpst.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_cmedpst.sas (Run Date: 24SEP2010 9:49)

14.2 Efficacy Data Summary Tables and Figures

14.2.1 Efficacy Tables

Progression-free Survival Dataset

Overall Survival Dataset

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Table 14.2.1-1 Progression-Free Survival
(ITT Population)

		Placebo	Sorafenib
Progression-free survival (days) (1-sided p-value=0.0006)	N	114	115
	Number of events (progression/death)	80 (70.2%)	62 (53.9%)
	Number of censored	34 (29.8%)	53 (46.1%)
	Hazard ratio (95% CI) sorafenib/placebo		0.576 (0.410,0.809)
	25^{th} percentile (95% CI)	63 (43,83)	92 (83,126)
	Median (95% CI)	126 (93,169)	194 (161,237)
	75^{th} percentile (95% CI)	230 (189,244)	297 (281,357)
	Progression-free survival rate at day 90 (95% CI)	0.606 (0.504,0.693)	0.770 (0.676,0.839)
	Rate difference (95% CI) sorafenib-placebo		0.164 (0.039,0.288)
	Progression-free survival rate at day 180 (95% CI)	0.363 (0.263,0.463)	0.531 (0.424,0.628)
	Rate difference (95% CI) sorafenib-placebo		0.169 (0.024,0.313)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_01_1_pfs.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfs.sas (Run Date: 17JUL2009 14:22)

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Table 14.2.1-1 Progression-Free Survival
(ITT Population)

	Placebo	Sorafenib
Progression-free survival rate at day 270 (95% CI)	0.130 (0.064,0.222)	0.363 (0.253,0.475)
Rate difference (95% CI) sorafenib-placebo		0.233 (0.095,0.371)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_01_1_pfs.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfs.sas (Run Date: 17JUL2009 14:22)

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Table 14.2.1-2 Progression-Free Survival
(Per Protocol Population)

		Placebo	Sorafenib
Progression-free survival (days) (1-sided p-value=0.0005)	N	99	100
	Number of events (progression/death)	71 (71.7%)	54 (54.0%)
	Number of censored	28 (28.3%)	46 (46.0%)
	Hazard ratio (95% CI) sorafenib/placebo		0.541 (0.374,0.784)
	25th percentile (95% CI)	53 (42,75)	92 (80,126)
	Median (95% CI)	121 (85,160)	183 (133,234)
	75th percentile (95% CI)	230 (179,249)	311 (237,357)
	Progression-free survival rate at day 90 (95% CI)	0.564 (0.456,0.659)	0.768 (0.666,0.842)
	Rate difference (95% CI) sorafenib-placebo		0.204 (0.069,0.338)
	Progression-free survival rate at day 180 (95% CI)	0.347 (0.243,0.453)	0.511 (0.394,0.617)
	Rate difference (95% CI) sorafenib-placebo		0.164 (0.010,0.319)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_01_2_pfspp.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfspp.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.1-2 Progression-Free Survival
(Per Protocol Population)

	Placebo	Sorafenib
Progression-free survival rate at day 270 (95% CI)	0.120 (0.052,0.220)	0.331 (0.215,0.452)
Rate difference (95% CI) sorafenib-placebo		0.211 (0.063,0.359)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_01_2_pfspp.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfspp.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.2 Event Types of Progression-Free Survival
(ITT Population)

	Placebo	Sorafenib
Number of events	80	62
Radiological progression (RECIST)	69 (86.3%)	54 (87.1%)
Clinical progression	6 (7.5%)	3 (4.8%)
Death without progression	5 (6.3%)	5 (8.1%)
Number censored	34	53

Note: Only uncensored progression or death (without progression) are counted as events.
Note: Denominator in percentage calculation is the number of events.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_02_pfstyp.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfstyp.sas (Run Date: 17JUL2009 14:22)

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Table 14.2.3-1: Subgroup Analysis of Progression-Free Survival
(ITT Population)

Subgroup		N	# Events (%)	# Censored (%)	Hazard Ratio Sorafenib/Placebo		P-value	Median (Days)	
					Estimate	95% CI	(1-sided)	Placebo	Sorafenib
Prior chemotherapy for metastatic breast cancer	Yes	116	73 (62.9%)	43 (37.1%)	0.652	(0.410,1.037)	0.0339	126	175
	No	112	69 (61.6%)	43 (38.4%)	0.498	(0.304,0.816)	0.0022	126	232
Hormon receptor status	ER+ or PgR+	173	100 (57.8%)	73 (42.2%)	0.615	(0.415,0.912)	0.0071	169	232
	ER- and PgR-	53	42 (79.2%)	11 (20.8%)	0.596	(0.311,1.141)	0.0546	77	130
Visceral disease	Yes	171	102 (59.6%)	69 (40.4%)	0.532	(0.357,0.792)	0.0008	151	219
	No	58	40 (69.0%)	18 (31.0%)	0.713	(0.373,1.363)	0.1492	90	130

Note: ER = Estrogen Receptor, PgR = Progesterone Receptor
Note: P-value is from log-rank test within each subgroup. Hazard ratio is from Cox regression within each subgroup.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_03_1_pfssub1.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfssub1.sas (Run Date: 17JUL2009 14:22)

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Table 14.2.3-2: Exploratory Analysis: Subgroup Analysis of Progression-Free Survival
(ITT Population)

Subgroup		N	# Events (%)	# Censored (%)	Hazard Ratio Sorafenib/Placebo		P-value	Median (Days)	
					Estimate	95% CI	(1-sided)	Placebo	Sorafenib
Age	< 40	18	15 (83.3%)	3 (16.7%)	0.836	(0.284,2.463)	0.3719	105	121
	>=40	211	127 (60.2%)	84 (39.8%)	0.569	(0.400,0.809)	0.0007	126	207
Age	< 65	175	113 (64.6%)	62 (35.4%)	0.606	(0.416,0.881)	0.0038	126	183
	>=65	54	29 (53.7%)	25 (46.3%)	0.503	(0.227,1.112)	0.0408	126	281
Prior use of anthracycline	Yes	202	132 (65.3%)	70 (34.7%)	0.594	(0.421,0.839)	0.0013	126	177
	No	25	9 (36.0%)	16 (64.0%)	0.263	(0.052,1.321)	0.0403	230	356
Prior use of taxane	Yes	135	87 (64.4%)	48 (35.6%)	0.616	(0.404,0.941)	0.0113	106	175
	No	91	54 (59.3%)	37 (40.7%)	0.559	(0.321,0.972)	0.0178	167	232
Estrogen receptor	Positive	168	97 (57.7%)	71 (42.3%)	0.634	(0.425,0.946)	0.0119	169	232
	Negative	58	45 (77.6%)	13 (22.4%)	0.527	(0.281,0.987)	0.0195	77	130
Progesterone receptor	Positive	117	65 (55.6%)	52 (44.4%)	0.711	(0.435,1.163)	0.0854	169	232
	Negative	103	74 (71.8%)	29 (28.2%)	0.490	(0.301,0.798)	0.0015	106	172
Measurable disease[1]	Yes	191	120 (62.8%)	71 (37.2%)	0.558	(0.388,0.803)	0.0007	126	194
	No	37	22 (59.5%)	15 (40.5%)	0.678	(0.290,1.583)	0.1829	121	177

1: Measurable disease defined as having at least one target lesion at baseline. Subjects with no baseline tumor assessment were excluded.
Note: P-value is from log-rank test within each subgroup. Hazard ratio is from Cox regression within each subgroup.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_03_2_pfssub2.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfssub2.sas (Run Date: 21JUL2009 13:32)

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Table 14.2.4: Sensitivity Analysis of Progression-Free Survival
(ITT Population)

Analysis	Treatment Group	N	# Events (%)	# Censored (%)	Median (Days)	Hazard Ratio Sorafenib/Placebo		P-value
						Estimate	95% CI	(1-sided)
Primary	Placebo	114	80 (70.2%)	34 (29.8%)	126	0.576	(0.410,0.809)	0.0006
	Sorafenib	115	62 (53.9%)	53 (46.1%)	194			
Un-stratified analysis	Placebo	114	80 (70.2%)	34 (29.8%)	126	0.573	(0.410,0.799)	0.0004
	Sorafenib	115	62 (53.9%)	53 (46.1%)	194			
NPT considered as PFS event	Placebo	114	91 (79.8%)	23 (20.2%)	121	0.599	(0.438,0.819)	0.0005
	Sorafenib	115	73 (63.5%)	42 (36.5%)	177			
NPT neither considered as PFS event nor used to censor PFS	Placebo	114	85 (74.6%)	29 (25.4%)	126	0.614	(0.443,0.851)	0.0015
	Sorafenib	115	65 (56.5%)	50 (43.5%)	194			

Note: NPT= protocol prohibited new anti-cancer treatment or surgery of a curative intent.
Note: Primary analysis uses stratified Cox regression and stratified log-rank test on the PFS calculated using primary censoring rules. Primary censoring rules of PFS include censoring PFS at last adequate tumor assessment before NPT if NPT is prior to first documented PD or death.
Note: P-value is from un-stratified log-rank test for "Un-stratified analysis". P-value is from stratified log-rank test for all other analyses. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_04_pfssa.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_pfssa.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.5: Summary of Response and Response Rate
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Best response	CR	1 (0.9%)	2 (1.7%)
	PR	34 (29.8%)	42 (36.5%)
	SD	43 (37.7%)	50 (43.5%)
	PD	27 (23.7%)	12 (10.4%)
	NE	3 (2.6%)	1 (0.9%)
Overall response rate (1-sided p value=0.1229)	Estimate (95% CI[1])	30.7% (22.4%,40.0%)	38.3% (29.4%,47.8%)
Objective response[2]	CR	1 (0.9%)	2 (1.7%)
	PR	24 (21.1%)	27 (23.5%)
Objective response rate (1-sided p value=0.2914)	Estimate (95% CI[1])	21.9% (14.7%,30.6%)	25.2% (17.6%,34.2%)

Note: CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not estimable or not assessable.
Note: P-value is from Cochran-Mantel-Hanszel test for treatment group difference. Visceral disease status is stratification factor.
1: Exact 95% confidence interval from binomial distribution
2: Only confirmed responses are summarized

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_05_rsp.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_rsp.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.6: Time to Progression
(ITT Population)

		Placebo	Sorafenib
Time to progression (days) (1-sided p-value=0.0005)	N	114	115
	Number of events (progression)	75 (65.8%)	57 (49.6%)
	Number of censored	39 (34.2%)	58 (50.4%)
	Hazard ratio (95% CI) sorafenib/placebo		0.562 (0.394,0.799)
	25th percentile (95% CI)	63 (43,85)	121 (85,130)
	Median (95% CI)	126 (105,179)	207 (167,253)
	75th percentile (95% CI)	231 (196,249)	311 (285,357)
	Progression-free rate at day 90 (95% CI)	0.619 (0.515,0.706)	0.790 (0.696,0.858)
	Rate difference (95% CI) sorafenib-placebo		0.171 (0.046,0.296)
	Progression-free rate at day 180 (95% CI)	0.386 (0.281,0.489)	0.551 (0.440,0.649)
	Rate difference (95% CI) sorafenib-placebo		0.166 (0.017,0.315)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_06_ttp.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ttp.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.6: Time to Progression
(ITT Population)

	Placebo	Sorafenib
Progression-free rate at day 270 (95% CI)	0.139 (0.068,0.235)	0.371 (0.255,0.487)
Rate difference (95% CI) sorafenib-placebo		0.232 (0.087,0.377)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_06_ttp.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ttp.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.7-1: Duration of Response
(ITT Population)

		Placebo	Sorafenib
Duration of response (days) (1-sided p-value=0.0477)	N	114	115
	Number of censored	14 (12.3%)	25 (21.7%)
	Number of events	100 (87.7%)	90 (78.3%)
	Number of non-responders	79 (69.3%)	71 (61.7%)
	Number of events from responders	21 (18.4%)	19 (16.5%)
	Hazard ratio (95% CI) sorafenib/placebo		0.846 (0.635,1.127)
	Quartiles of DOR of responders		
	N	35	44
	25^{th} percentile (95% CI)	85 (81,116)	89 (49,147)
	Median (95% CI)	124 (88,189)	188 (93,255)
	75^{th} percentile (95% CI)	189 (127,249)	255 (232,316)

1: Measurable disease defined as having at least one target lesion at baseline.
Note: Duration of response is the time from the first documented CR or PR until the first documented PD or death (if before progression). For the subjects with no documented CR or PR, duration of response is not censored and assigned 0 day.
Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_07_1_dorr.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.2.7-1: Duration of Response
(ITT Population)

		Placebo	Sorafenib
Subgroup: subjects with measurable disease[1]			
Duration of response (days) (1-sided p-value=0.0336)	N	96	95
	Number of censored	14 (14.6%)	25 (26.3%)
	Number of events	82 (85.4%)	70 (73.7%)
	Number of non-responders	61 (63.5%)	51 (53.7%)
	Number of events from responders	21 (21.9%)	19 (20.0%)
	Hazard ratio (95% CI) sorafenib/placebo		0.799 (0.579,1.102)
	Quartiles of DOR of responders		
	N	35	44
	25th percentile (95% CI)	85 (81,116)	89 (49,147)
	Median (95% CI)	124 (88,189)	188 (93,255)
	75th percentile (95% CI)	189 (127,249)	255 (232,316)

1: Measurable disease defined as having at least one target lesion at baseline.
Note: Duration of response is the time from the first documented CR or PR until the first documented PD or death (if before progression). For the subjects with no documented CR or PR, duration of response is not censored and assigned 0 day.
Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_07_1_dorr.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_dorr.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.7-2: Duration of Objective Response
(ITT Population)

		Placebo	Sorafenib
Duration of objective response (days) (1-sided p-value=0.0533)	N	114	115
	Number of censored	9 (7.9%)	17 (14.8%)
	Number of events	105 (92.1%)	98 (85.2%)
	Number of non-responders	89 (78.1%)	86 (74.8%)
	Number of events from responders	16 (14.0%)	12 (10.4%)
	Hazard ratio (95% CI) sorafenib/placebo		0.877 (0.665,1.158)
	Quartiles of DOR of responders		
	N	25	29
	25^{th} percentile (95% CI)	85 (83,116)	129 (89,232)
	Median (95% CI)	127 (87,189)	232 (147,255)
	75^{th} percentile (95% CI)	231 (127,260)	255 (232,316)

1: Measurable disease defined as having at least one target lesion at baseline.
Note: Duration of objective response is the time from the first documented CR or PR for confirmed responses until the first documented PD or death (if before progression). For the subjects with no documented confirmed CR or PR, duration of objective response is not censored and assigned 0 day.
Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_07_2_dorr2.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_dorr2.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.7-2: Duration of Objective Response
(ITT Population)

		Placebo	Sorafenib
Subgroup: subjects with measurable disease[1]			
Duration of objective response (days) (1-sided p-value=0.0417)	N	96	95
	Number of censored	9 (9.4%)	17 (17.9%)
	Number of events	87 (90.6%)	78 (82.1%)
	Number of non-responders	71 (74.0%)	66 (69.5%)
	Number of events from responders	16 (16.7%)	12 (12.6%)
	Hazard ratio (95% CI) sorafenib/placebo		0.843 (0.619,1.147)
	Quartiles of DOR of responders		
	N	25	29
	25th percentile (95% CI)	85 (83,116)	129 (89,232)
	Median (95% CI)	127 (87,189)	232 (147,255)
	75th percentile (95% CI)	231 (127,260)	255 (232,316)

1: Measurable disease defined as having at least one target lesion at baseline.
Note: Duration of objective response is the time from the first documented CR or PR for confirmed responses until the first documented PD or death (if before progression). For the subjects with no documented confirmed CR or PR, duration of objective response is not censored and assigned 0 day.
Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_07_2_dorr2.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_dorr2.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.8: Change of ECOG Performance Status From Baseline
(ITT Population)

		Placebo (N = 114)	Sorafenib (N = 115)
Change from baseline in performance status at the visit at which the best overall response was first documented	Missing	26 (22.8%)	38 (33.0%)
	-1	13 (11.4%)	5 (4.3%)
	0	58 (50.9%)	65 (56.5%)
	1	16 (14.0%)	6 (5.2%)
	2	1 (0.9%)	1 (0.9%)
Change from baseline in performance status at the visit at the end of treatment	Missing	3 (2.6%)	4 (3.5%)
	-2	1 (0.9%)	0
	-1	7 (6.1%)	4 (3.5%)
	0	72 (63.2%)	75 (65.2%)
	1	26 (22.8%)	21 (18.3%)
	2	4 (3.5%)	5 (4.3%)
	3	1 (0.9%)	6 (5.2%)

Note: The last performance status before end of study treatment is used if end of study treatment performance status is not available.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_2_08_ECOG.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ECOG.sas (Run Date: 17JUL2009 14:23)

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Table 14.2.1.1 Overall Survival
(ITT Population)

		Placebo	Sorafenib
Overall survival (days) (1-sided p-value=0.2075)	N	114	115
	Number of events (death)	65 (57.0%)	60 (52.2%)
	Number of censored	49 (43.0%)	55 (47.8%)
	Hazard ratio (95% CI) sorafenib/placebo		0.864 (0.608,1.228)
	25^{th} percentile (95% CI)	310 (258,404)	398 (281,464)
	Median (95% CI)	637 (489,734)	675 (550,812)
	75^{th} percentile (95% CI)	NR (740,NE)	NR (812,NE)
	Overall survival rate at day 360 (95% CI)	0.712 (0.618,0.787)	0.769 (0.680,0.837)
	Rate difference (95% CI) sorafenib-placebo		0.057 (-0.058,0.172)
	Overall survival rate at day 540 (95% CI)	0.541 (0.444,0.628)	0.593 (0.495,0.678)
	Rate difference (95% CI) sorafenib-placebo		0.052 (-0.079,0.182)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_2_01_1_os.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_os.sas (Run Date: 24SEP2010 9:53)

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Table 14.2.1.1 Overall Survival
(ITT Population)

	Placebo	Sorafenib
Overall survival rate at day 720 (95% CI)	0.436 (0.335,0.534)	0.473 (0.373,0.567)
Rate difference (95% CI) sorafenib-placebo		0.037 (-0.103,0.177)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_2_01_1_os.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_os.sas (Run Date: 24SEP2010 9:53)

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Table 14.2.1.2 Overall Survival
(Per Protocol Population)

		Placebo	Sorafenib
Overall survival (days) (1-sided p-value=0.3029)	N	97	97
	Number of events (death)	57 (58.8%)	54 (55.7%)
	Number of censored	40 (41.2%)	43 (44.3%)
	Hazard ratio (95% CI) sorafenib/placebo		0.906 (0.623,1.317)
	25^{th} percentile (95% CI)	333 (259,415)	398 (280,475)
	Median (95% CI)	637 (489,734)	605 (537,769)
	75^{th} percentile (95% CI)	NR (740,NE)	NR (769,NE)
	Overall survival rate at day 360 (95% CI)	0.719 (0.618,0.798)	0.770 (0.672,0.842)
	Rate difference (95% CI) sorafenib-placebo		0.051 (-0.073,0.174)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Note: Per-protocol population consists of subjects in safety population without major protocol deviations.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_2_01_2_os2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_os2.sas (Run Date: 24SEP2010 9:53)

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Table 14.2.1.2 Overall Survival
(Per Protocol Population)

		Placebo	Sorafenib
	Overall survival rate at day 540 (95% CI)	0.542 (0.437,0.635)	0.586 (0.479,0.678)
	Rate difference (95% CI) sorafenib-placebo		0.044 (-0.098,0.185)
	Overall survival rate at day 720 (95% CI)	0.418 (0.307,0.524)	0.446 (0.339,0.548)
	Rate difference (95% CI) sorafenib-placebo		0.029 (-0.124,0.181)

Note: P-value is from stratified log-rank test. Hazard ratio is from stratified Cox regression. Visceral disease status is stratification factor.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Note: Per-protocol population consists of subjects in safety population without major protocol deviations.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_2_01_2_os2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_os2.sas (Run Date: 24SEP2010 9:53)

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Table 14.2.2 Subgroup Analysis of Overall Survival
(ITT Population)

Subgroup		N	# Events (%)	# Censored (%)	Hazard Ratio Sorafenib/Placebo		P-value	Median (Days)	
					Estimate	95% CI	(1-sided)	Placebo (95% CI)	Sorafenib (95% CI)
Hormon receptor status	ER+ or PgR+	173	86 (49.7%)	87 (50.3%)	0.935	(0.612,1.430)	0.3790	729 (567, NE)	742 (565, NE)
	ER- and PgR-	53	38 (71.7%)	15 (28.3%)	0.977	(0.504,1.894)	0.4755	489 (310, 685)	534 (174, 694)
Visceral disease	Yes	171	96 (56.1%)	75 (43.9%)	0.834	(0.558,1.246)	0.1881	557 (404, 725)	593 (494, NE)
	No	58	29 (50.0%)	29 (50.0%)	0.970	(0.468,2.011)	0.4671	740 (482, NE)	694 (557, NE)
Region	Brazil	112	67 (59.8%)	45 (40.2%)	0.953	(0.590,1.539)	0.4227	557 (482, 740)	573 (432, NE)
	France or Spain	117	58 (49.6%)	59 (50.4%)	0.757	(0.450,1.274)	0.1469	692 (404, NE)	742 (565, NE)
Prior chemotherapy for metastatic breast cancer	Yes	116	62 (53.4%)	54 (46.6%)	1.076	(0.651,1.779)	0.3868	713 (404, NE)	578 (440, NE)
	No	112	63 (56.3%)	49 (43.8%)	0.666	(0.401,1.105)	0.0567	557 (448, 740)	694 (550, NE)

Note: ER = Estrogen Receptor, PgR = Progesterone Receptor
Note: P-value is from log-rank test within each subgroup. Hazard ratio is from Cox regression within each subgroup.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
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Table 14.2.2 Subgroup Analysis of Overall Survival
(ITT Population)

Subgroup					Hazard Ratio Sorafenib/Placebo		P-value	Median (Days)	
		N	# Events (%)	# Censored (%)	Estimate	95% CI	(1-sided)	Placebo (95% CI)	Sorafenib (95% CI)
Prior anthracycline and taxane	Yes	133	80 (60.2%)	53 (39.8%)	0.877	(0.565,1.361)	0.2801	526 (448, 729)	633 (494, 769)
	No	93	44 (47.3%)	49 (52.7%)	0.879	(0.486,1.589)	0.3343	725 (423, NE)	NR (537, NE)

Note: ER = Estrogen Receptor, PgR = Progesterone Receptor
Note: P-value is from log-rank test within each subgroup. Hazard ratio is from Cox regression within each subgroup.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_2_02_ossub1.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ossub1.sas (Run Date: 24SEP2010 9:53)

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Table 14.2.3 Exploratory Analysis: Subgroup Analysis of Overall Survival
(ITT Population)

Subgroup		N	# Events (%)	# Censored (%)	Hazard Ratio Sorafenib/Placebo		P-value	Median (Days)	
					Estimate	95% CI	(1-sided)	Placebo (95% CI)	Sorafenib (95% CI)
Age	< 40	18	12 (66.7%)	6 (33.3%)	1.420	(0.448,4.498)	0.2745	504 (399, NE)	424 (106, NE)
	>=40	211	113 (53.6%)	98 (46.4%)	0.834	(0.576,1.206)	0.1669	679 (482, 734)	694 (555, NE)
Age	< 65	175	93 (53.1%)	82 (46.9%)	0.818	(0.544,1.229)	0.1664	635 (482, 734)	742 (540, NE)
	>=65	54	32 (59.3%)	22 (40.7%)	0.962	(0.478,1.934)	0.4584	692 (404, 839)	578 (398, NE)
Country	Brazil	112	67 (59.8%)	45 (40.2%)	0.953	(0.590,1.539)	0.4227	557 (482, 740)	573 (432, NE)
	France	37	22 (59.5%)	15 (40.5%)	0.543	(0.231,1.274)	0.0770	363 (225, 734)	694 (540, NE)
	Spain	80	36 (45.0%)	44 (55.0%)	0.916	(0.474,1.772)	0.3984	729 (423, NE)	742 (550, NE)
Prior use of anthracycline	Yes	202	116 (57.4%)	86 (42.6%)	0.924	(0.642,1.330)	0.3359	637 (482, 729)	593 (524, 769)
	No	25	8 (32.0%)	17 (68.0%)	0.301	(0.060,1.510)	0.0613	839 (306, 839)	NR (NE, NE)
Prior use of taxane	Yes	136	80 (58.8%)	56 (41.2%)	0.857	(0.552,1.331)	0.2475	539 (448, 729)	675 (509, 812)
	No	90	44 (48.9%)	46 (51.1%)	0.915	(0.506,1.655)	0.3843	725 (423, NE)	593 (524, NE)
Estrogen receptor	Positive	168	84 (50.0%)	84 (50.0%)	1.019	(0.663,1.566)	0.4666	734 (635, NE)	675 (557, NE)
	Negative	58	40 (69.0%)	18 (31.0%)	0.761	(0.395,1.466)	0.2084	460 (302, 539)	550 (214, 747)

1: Measurable disease defined as having at least one target lesion at baseline. Subjects with no baseline tumor assessment were excluded.
Note: P-value is from log-rank test within each subgroup. Hazard ratio is from Cox regression within each subgroup.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_2_03_ossub2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ossub2.sas (Run Date: 24SEP2010 9:53)

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Table 14.2.3 Exploratory Analysis: Subgroup Analysis of Overall Survival
(ITT Population)

Subgroup		N	# Events (%)	# Censored (%)	Hazard Ratio Sorafenib/Placebo		P-value	Median (Days)	
					Estimate	95% CI	(1-sided)	Placebo (95% CI)	Sorafenib (95% CI)
Progesterone receptor	Positive	117	58 (49.6%)	59 (50.4%)	1.000	(0.595,1.682)	0.4999	740 (482, NE)	675 (565, NE)
	Negative	103	63 (61.2%)	40 (38.8%)	0.815	(0.489,1.359)	0.2165	513 (434, 713)	555 (457, NE)
Measurable disease[1]	Yes	191	104 (54.5%)	87 (45.5%)	0.789	(0.536,1.161)	0.1139	567 (434, 734)	694 (555, NE)
	No	37	21 (56.8%)	16 (43.2%)	1.319	(0.553,3.146)	0.2654	679 (504, NE)	540 (414, NE)
Number of metastatic sites	< 3	150	78 (52.0%)	72 (48.0%)	0.966	(0.618,1.508)	0.4399	713 (539, 839)	694 (550, NE)
	>=3	78	47 (60.3%)	31 (39.7%)	0.596	(0.334,1.063)	0.0381	384 (262, 567)	578 (440, NE)
Months from adjuvant treatment to recurrence or metastatic diagnosis	<= 12 months	87	59 (67.8%)	28 (32.2%)	1.043	(0.622,1.750)	0.4366	509 (342, 679)	475 (388, 633)
	> 12 months	133	59 (44.4%)	74 (55.6%)	0.871	(0.522,1.454)	0.2998	734 (635, NE)	812 (573, NE)

1: Measurable disease defined as having at least one target lesion at baseline. Subjects with no baseline tumor assessment were excluded.
Note: P-value is from log-rank test within each subgroup. Hazard ratio is from Cox regression within each subgroup.
Note: Subjects who died, but the date of death is unknown has been censored at the date of the last contact alive before data cutoff.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_2_03_ossub2.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ossub2.sas (Run Date: 24SEP2010 9:53)

14.2.2 Efficacy Figures

Progression-free Survival Dataset

Overall Survival Dataset

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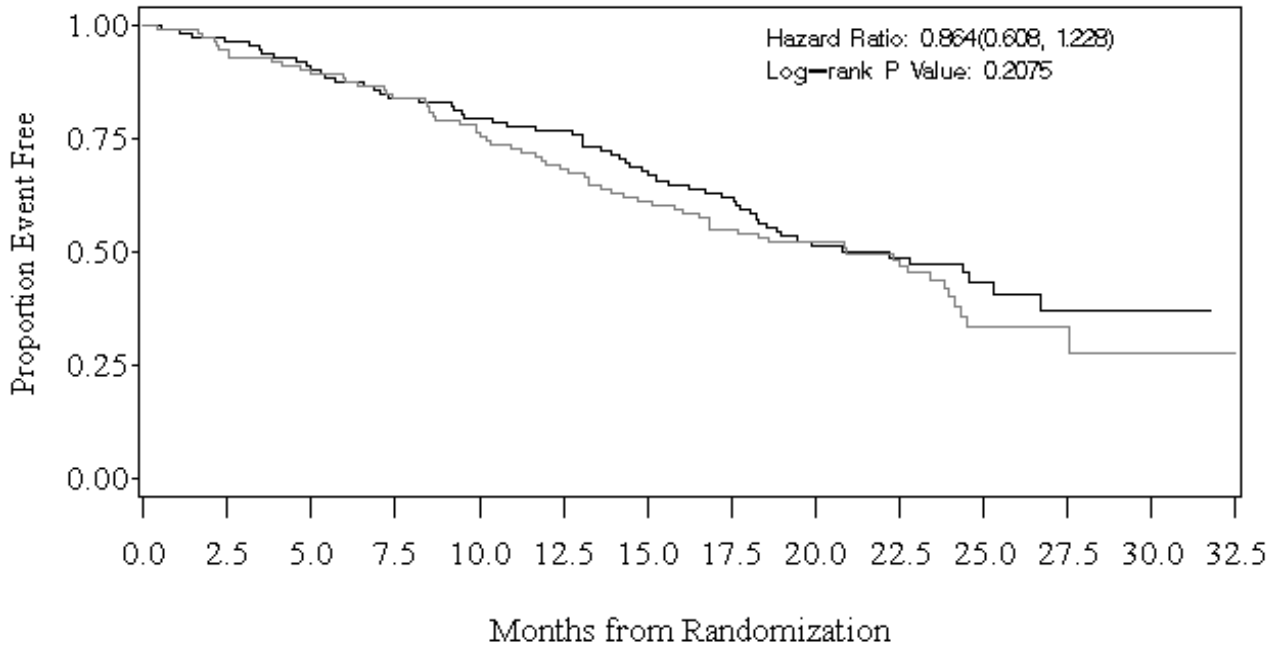
Figure 14.2.1: Overall Survival



Number at risk:

Placebo	114	106	99	93	85	76	68	61	47	34	12	6	2	0
Sorafenib	115	109	102	94	89	85	73	65	46	37	19	10	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_os.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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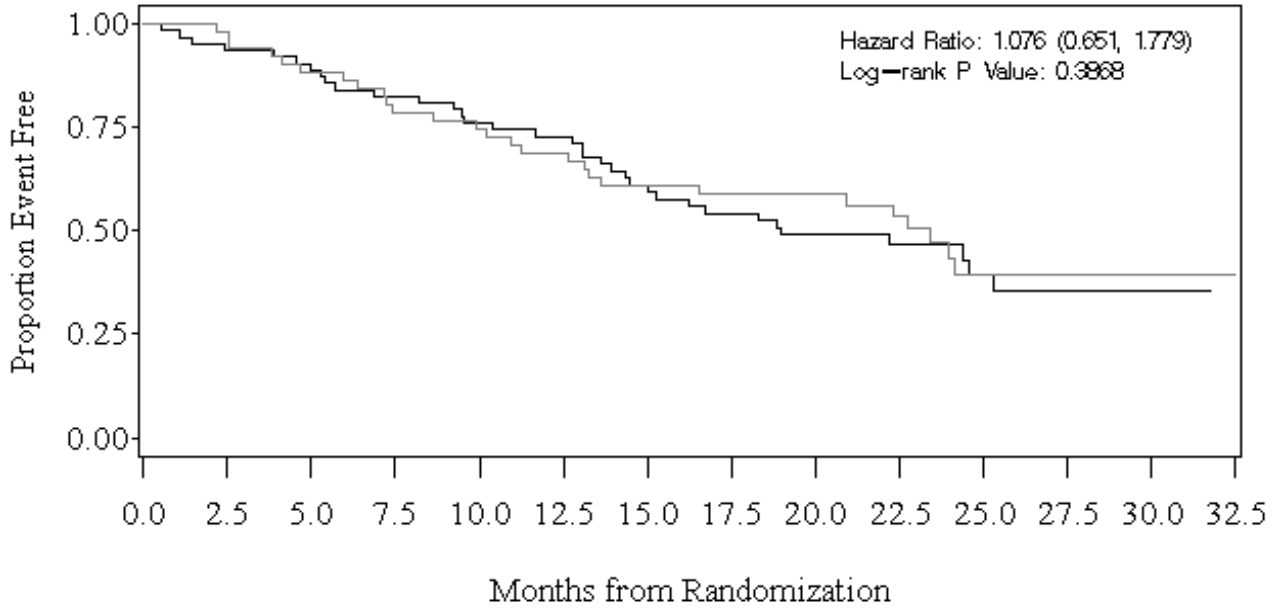
Figure 14.2.2.1.1: Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Chemotherapy for Metastatic Breast Cancer



Number at risk:

Placebo	51	50	45	40	38	35	31	30	25	19	7	4	2	0
Sorafenib	65	59	56	51	47	44	36	32	22	20	11	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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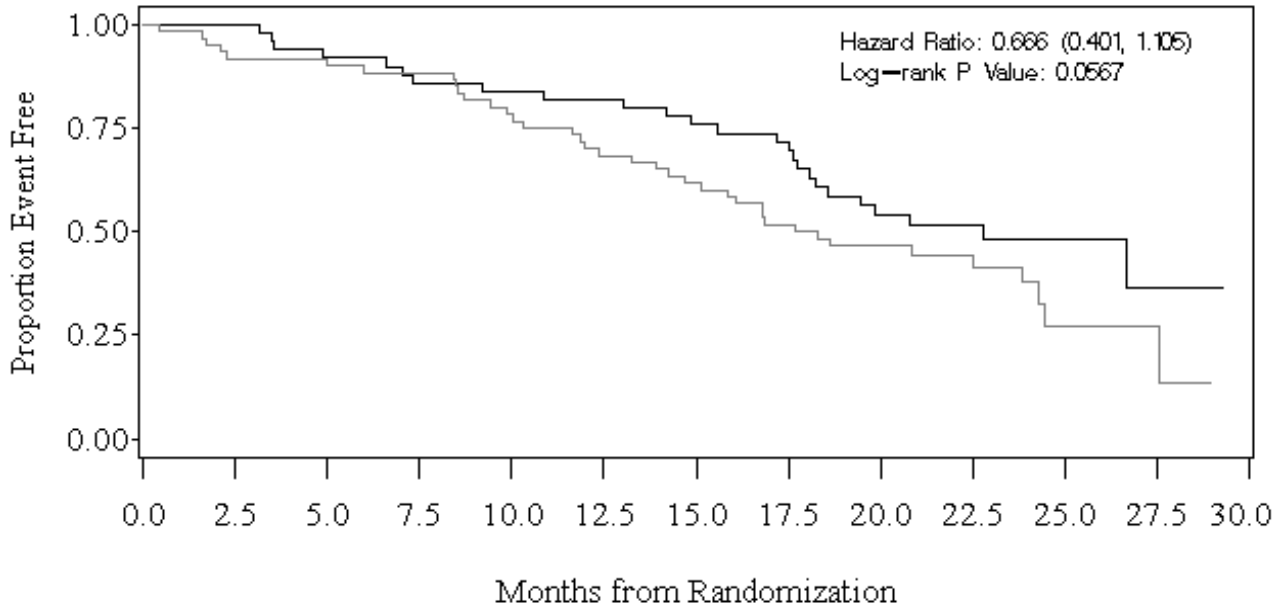
Figure 14.2.2.1.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Chemotherapy for Metastatic Breast Cancer



Number at risk:

Placebo	62	56	54	53	47	41	37	31	22	15	5	2	0
Sorafenib	50	50	46	43	42	41	37	33	24	17	8	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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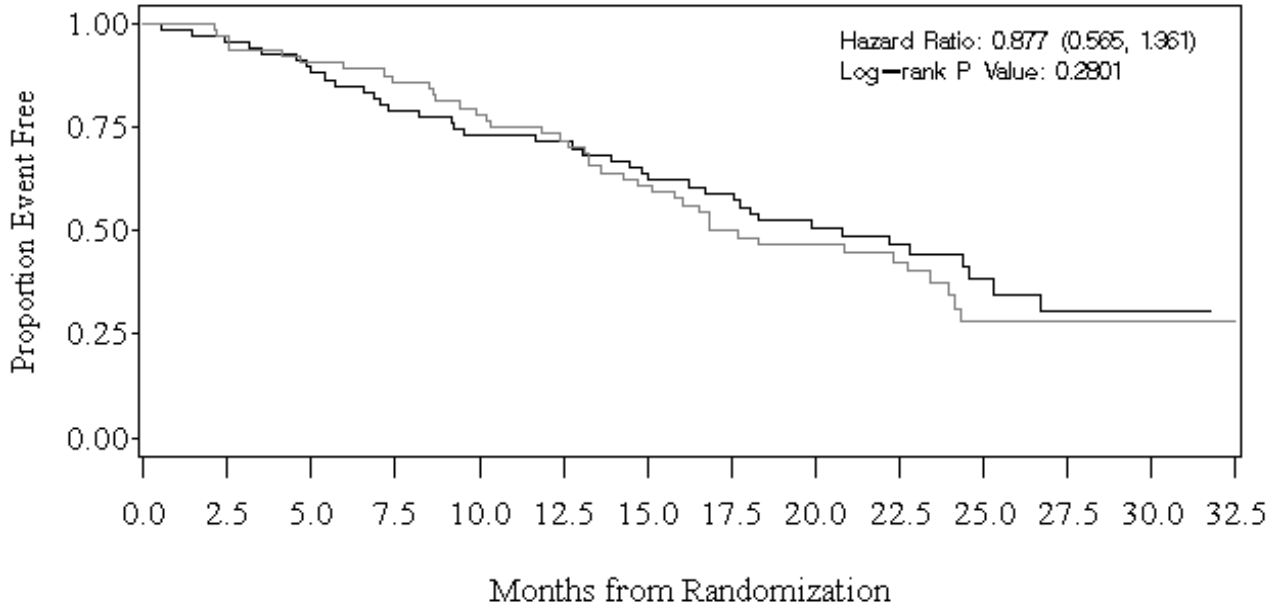
Figure 14.2.2.2.1: Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Anthracycline and Taxane



Number at risk:

Placebo	64	62	58	55	50	46	39	32	25	19	7	3	2	0
Sorafenib	69	64	59	52	48	46	41	36	29	23	12	7	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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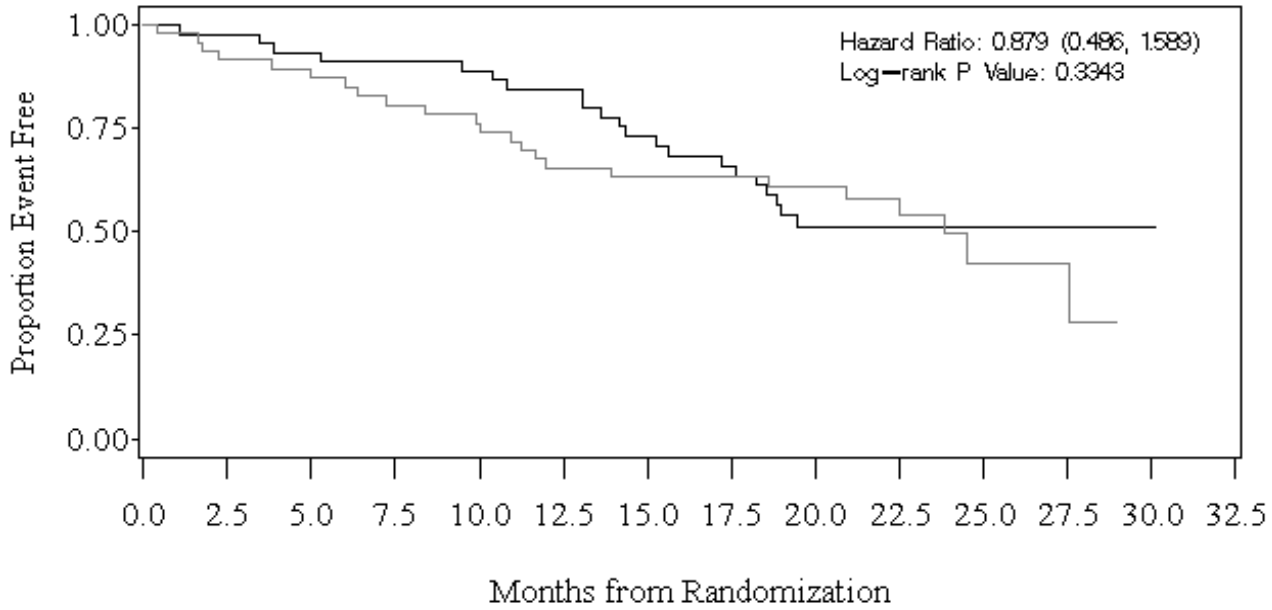
Figure 14.2.2.2.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Anthracycline and Taxane



Number at risk:

Placebo	48	43	40	37	35	30	29	29	22	15	5	3	0	0
Sorafenib	45	44	42	41	40	38	31	28	16	13	7	3	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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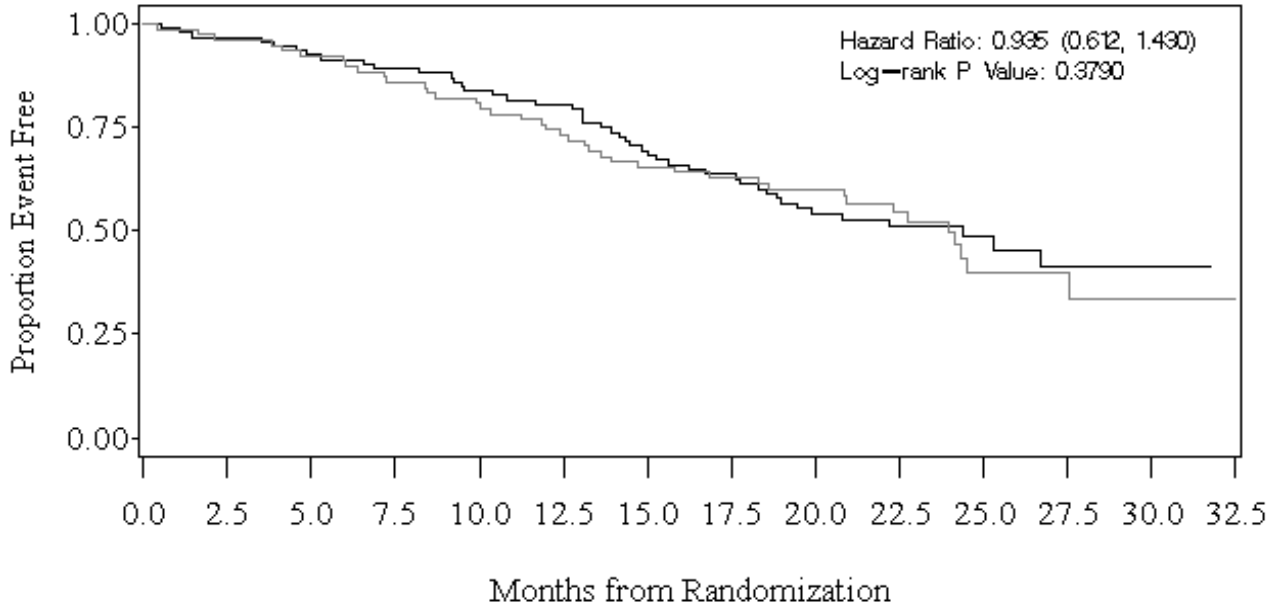
Figure 14.2.2.3.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Estrogen Receptor or Progesterone Receptor Positive



Number at risk:

Placebo	79	75	72	67	63	57	51	49	37	26	10	6	2	0
Sorafenib	94	90	86	82	77	73	61	55	40	33	18	10	3	0

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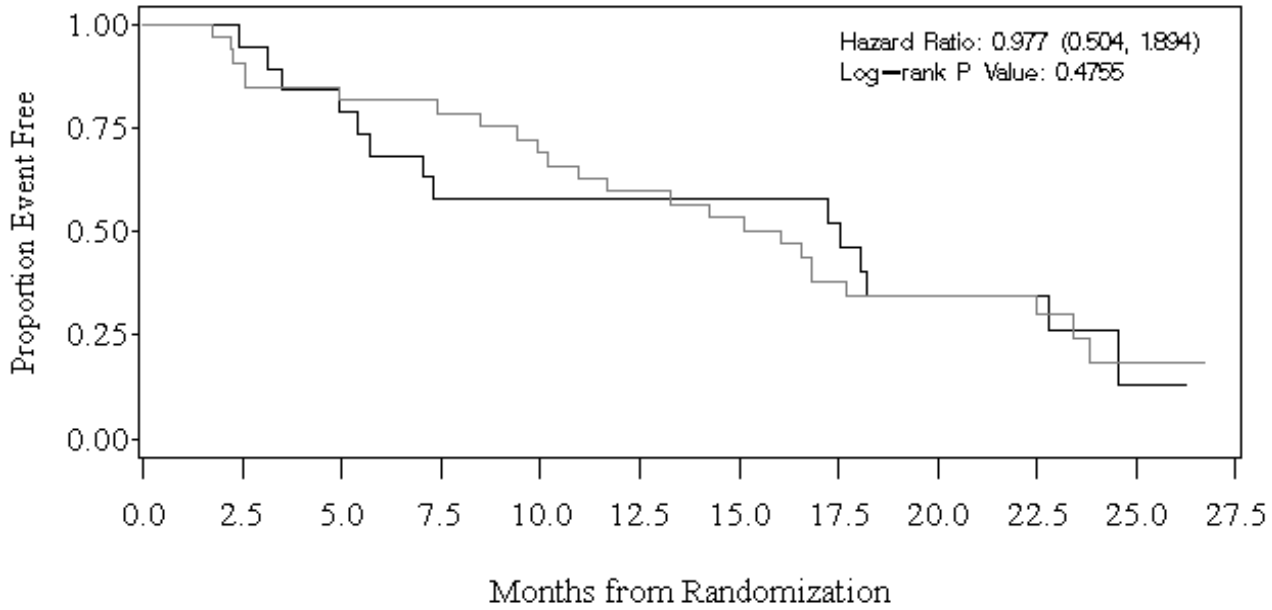
Figure 14.2.2.3.2 Subgroup Analysis of Overall Survival
Randomized Subjects with Estrogen Receptor and Progesterone Receptor Negative



Number at risk:

Placebo	33	30	26	25	22	19	17	12	10	8	2	0
Sorafenib	20	18	15	11	11	11	11	9	6	4	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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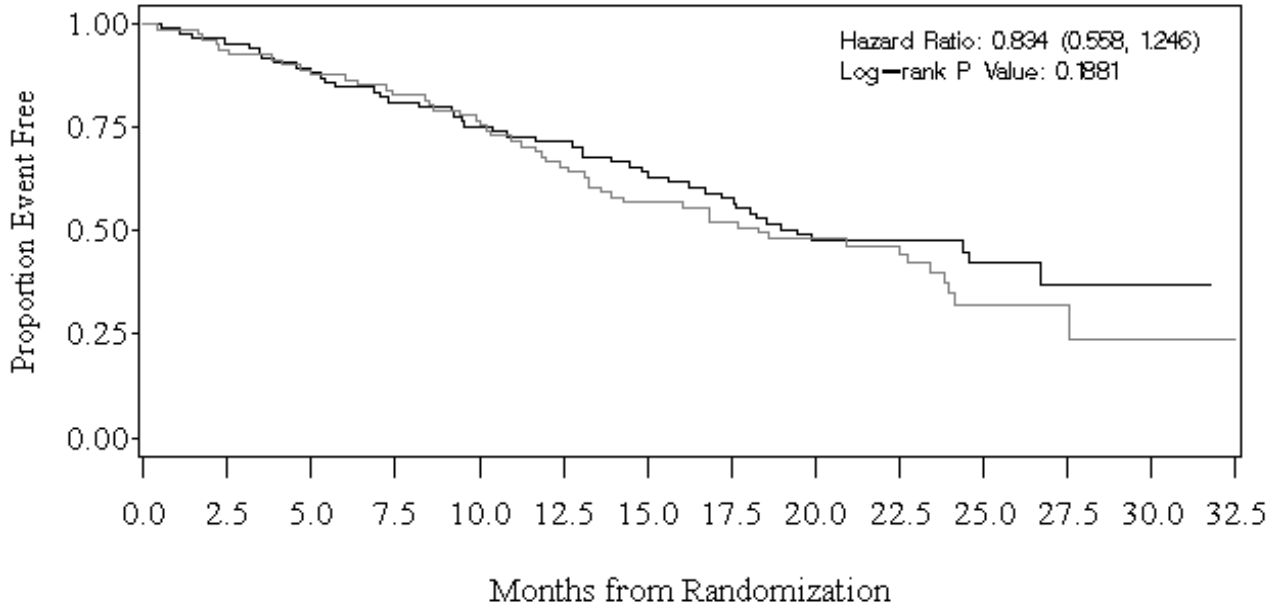
Figure 14.2.2.4.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Visceral Disease



Number at risk:

Placebo	84	77	71	67	62	53	46	42	31	22	8	4	1	0
Sorafenib	87	81	75	68	63	59	51	46	33	27	14	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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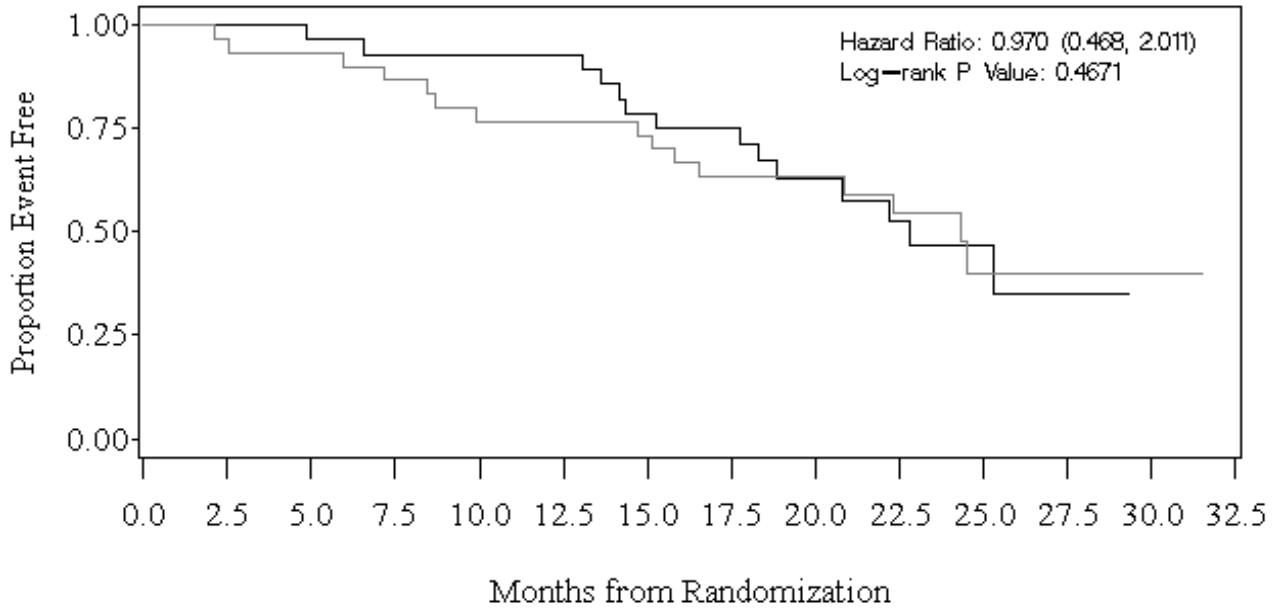
Figure 14.2.2.4.2 Subgroup Analysis of Overall Survival
Randomized Subjects without Visceral Disease



Number at risk:

Placebo	30	29	28	26	23	23	22	19	16	12	4	2	1	0
Sorafenib	28	28	27	26	26	26	22	19	13	10	5	3	0	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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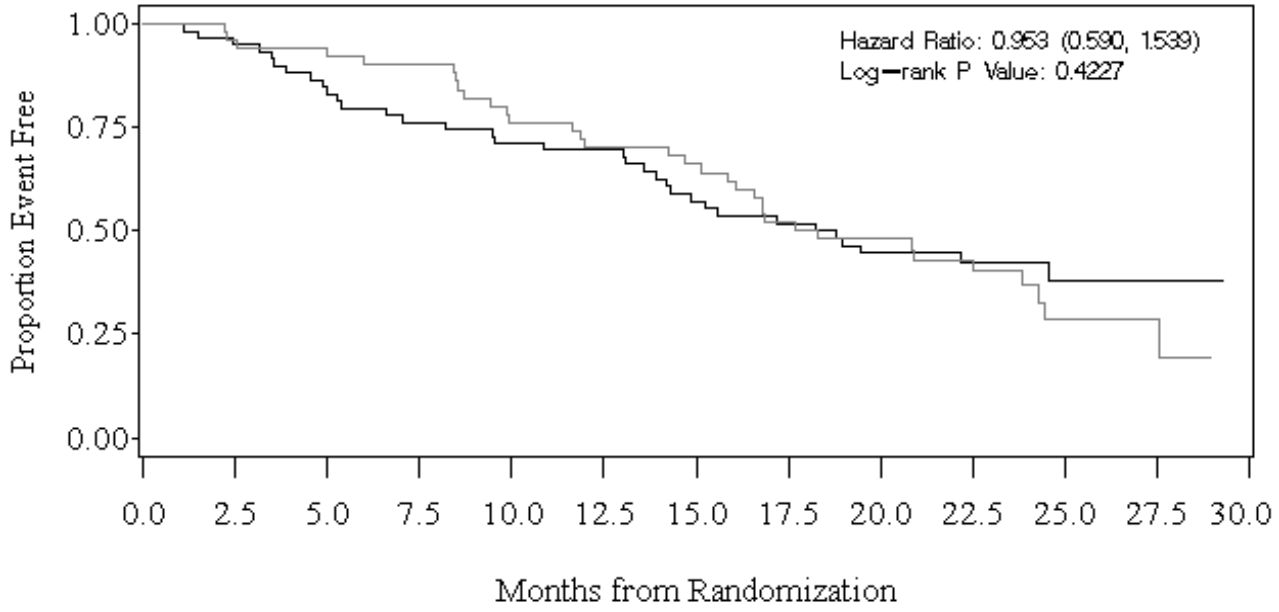
Figure 14.2.2.5.1 Subgroup Analysis of Overall Survival
Randomized Brazil Subjects



Number at risk:

Placebo	53	49	46	45	38	35	33	26	20	16	6	3	0
Sorafenib	59	56	49	45	42	41	32	29	22	17	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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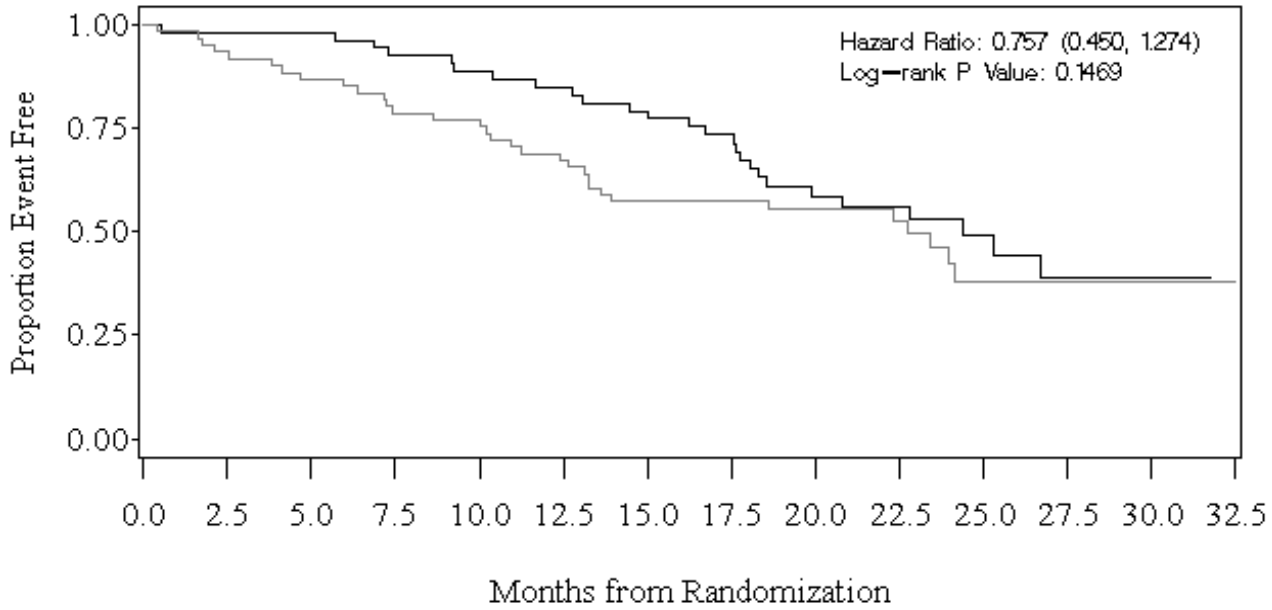
Figure 14.2.2.5.2 Subgroup Analysis of Overall Survival
Randomized France or Spain Subjects



Number at risk:

Placebo	61	57	53	48	47	41	35	35	27	18	6	3	2	0
Sorafenib	56	53	53	49	47	44	41	36	24	20	12	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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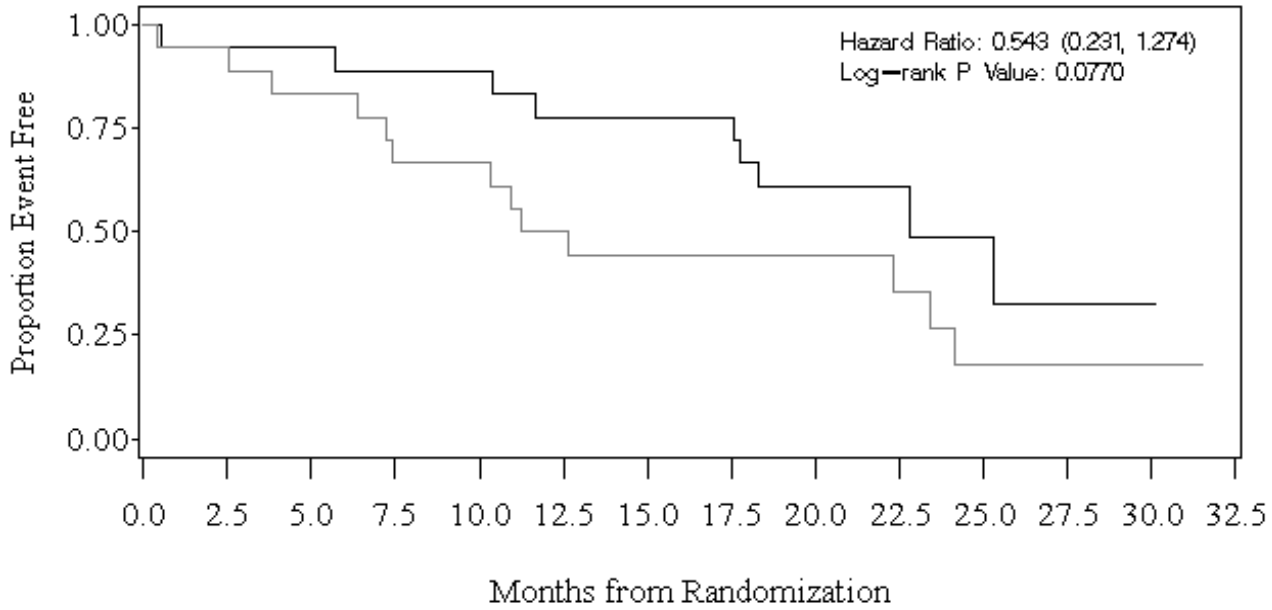
Figure 14.2.2.5.3 Subgroup Analysis of Overall Survival
Randomized France Subjects



Number at risk:

Placebo	18	17	15	12	12	9	8	8	8	4	2	1	1	0
Sorafenib	19	17	17	16	16	14	14	14	7	6	3	2	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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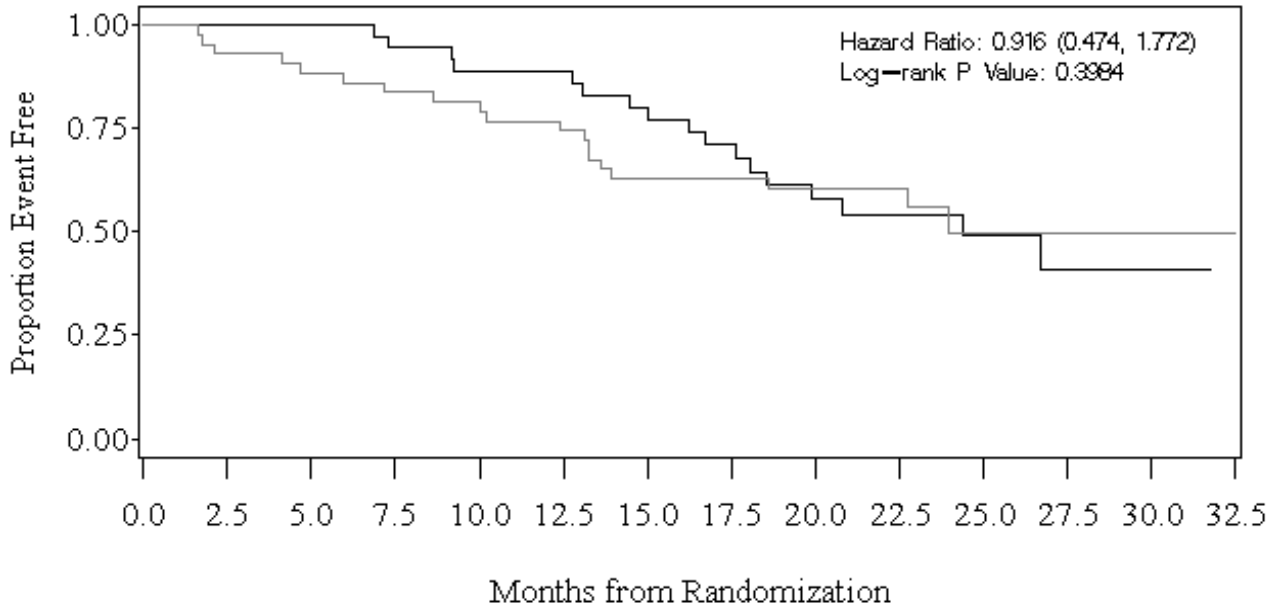
Figure 14.2.2.5.4 Subgroup Analysis of Overall Survival
Randomized Spain Subjects



Number at risk:

Placebo	43	40	38	36	35	32	27	27	19	14	4	2	1	0
Sorafenib	37	36	36	33	31	30	27	22	17	14	9	5	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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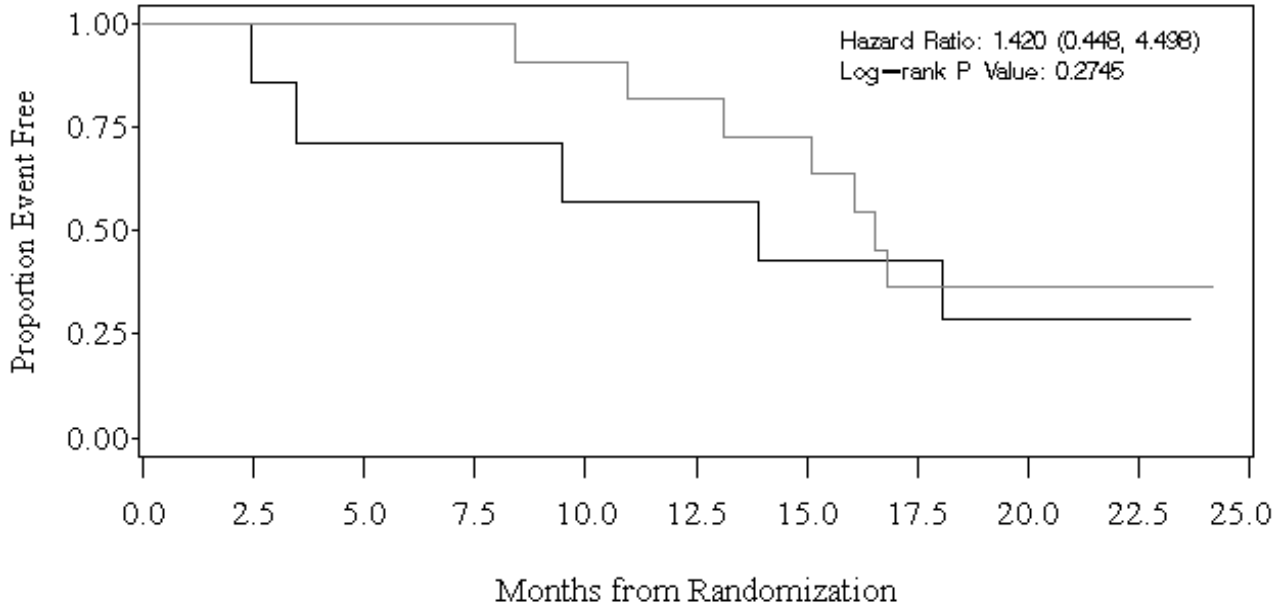
Figure 14.2.2.6.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Age < 40



Number at risk:

Placebo	11	11	11	11	10	9	8	4	2	1	0
Sorafenib	7	6	5	5	4	4	3	3	1	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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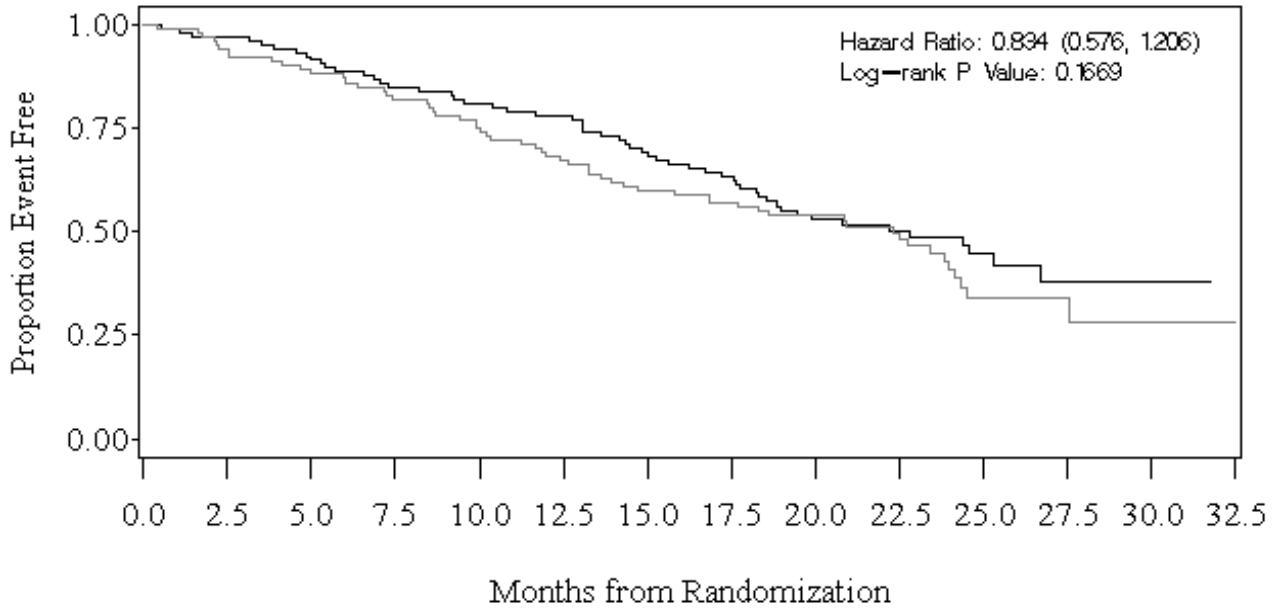
Figure 14.2.2.6.2 Subgroup Analysis of Overall Survival
Randomized Subjects with Age >= 40



Number at risk:

Placebo	103	95	88	82	75	67	60	57	45	33	12	6	2	0
Sorafenib	108	103	97	89	85	81	70	62	45	36	19	10	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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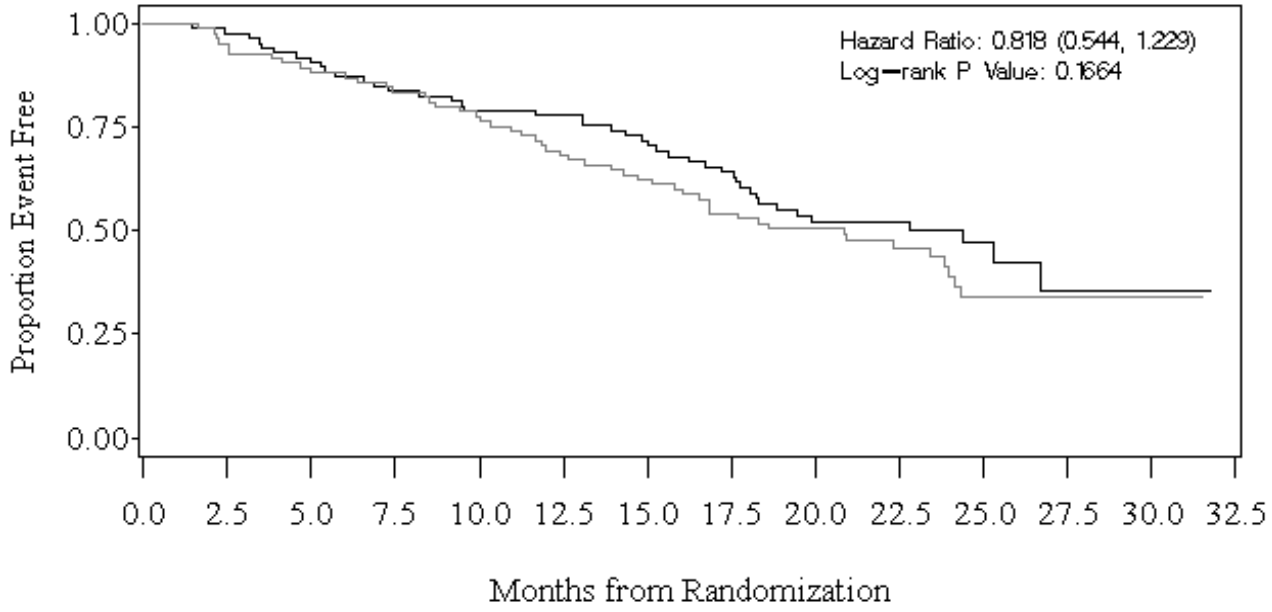
Figure 14.2.2.7.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Age < 65



Number at risk:

Placebo	87	81	75	71	66	58	53	46	37	26	9	4	1	0
Sorafenib	88	84	78	71	67	65	58	50	34	28	12	5	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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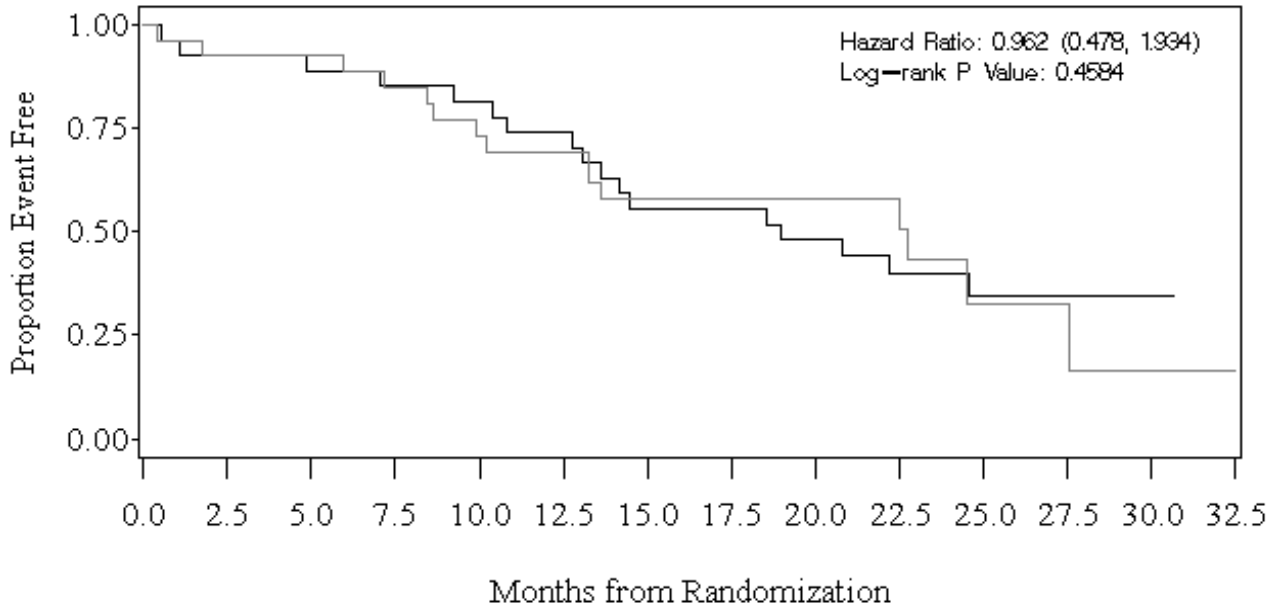
Figure 14.2.2.7.2 Subgroup Analysis of Overall Survival
Randomized Subjects with Age >= 65



Number at risk:

Placebo	27	25	24	22	19	18	15	15	10	8	3	2	1	0
Sorafenib	27	25	24	23	22	20	15	15	12	9	7	5	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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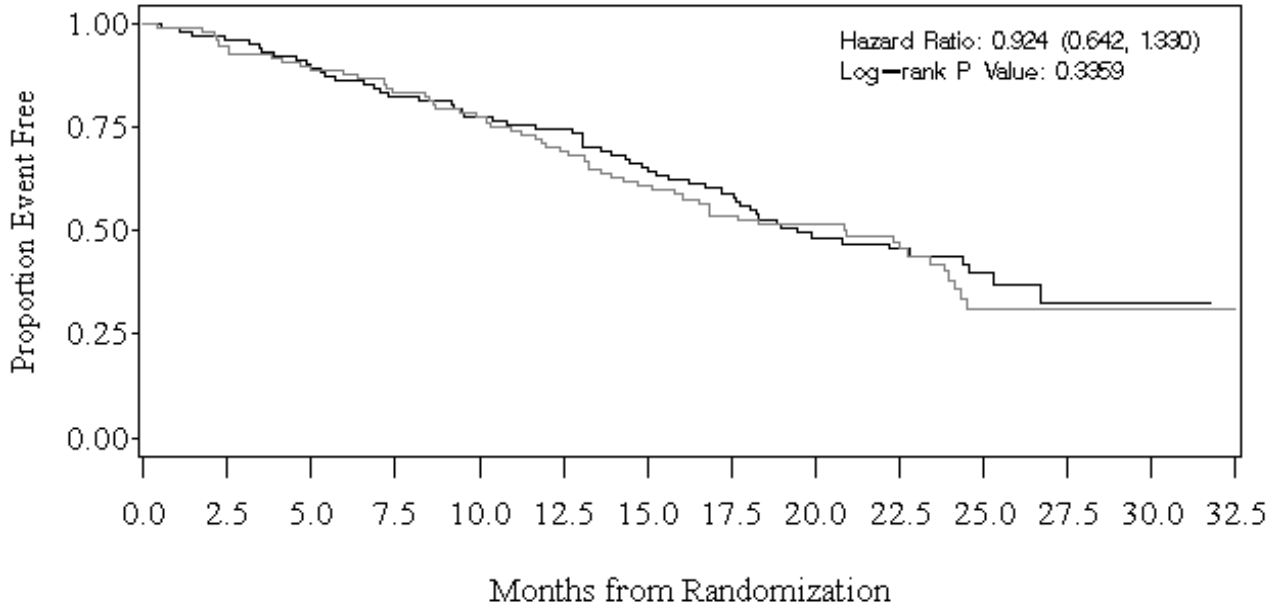
Figure 14.2.2.8.1 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Use of Anthracycline



Number at risk:

Placebo	98	92	86	81	75	67	59	52	41	30	11	5	2	0
Sorafenib	104	98	91	83	78	74	64	56	40	33	16	8	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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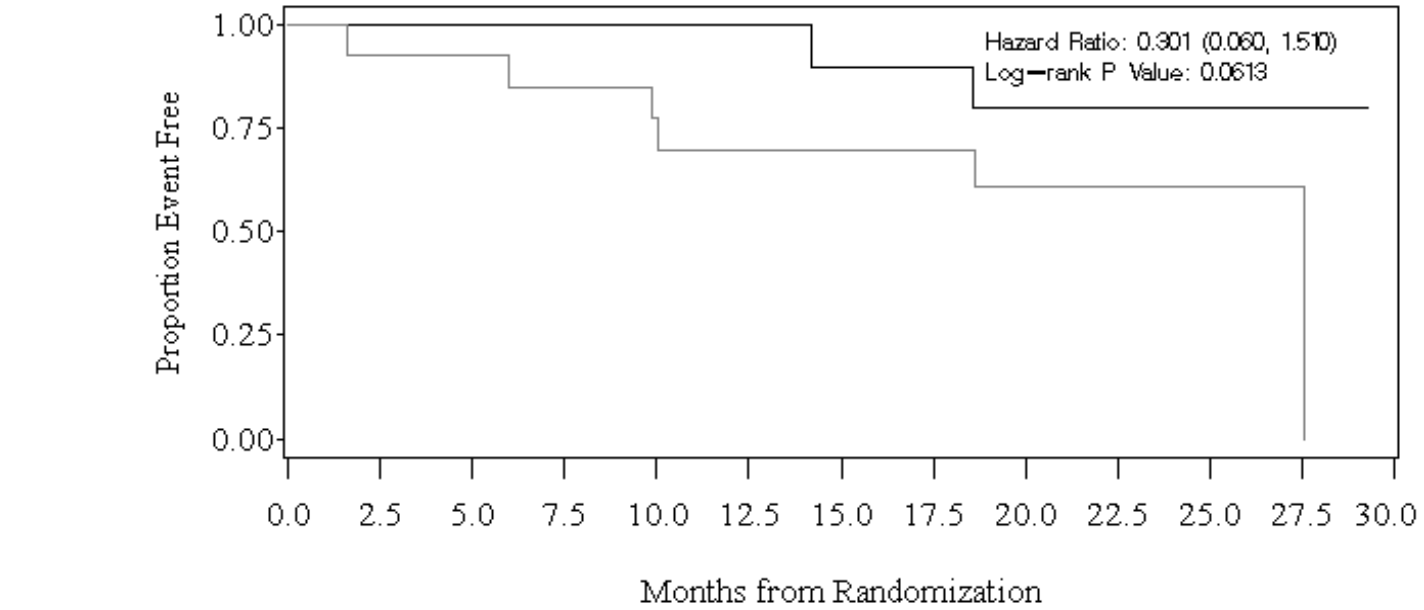
Figure 14.2.2.8.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Use of Anthracycline



Number at risk:

Placebo	14	13	12	11	10	9	9	9	6	4	1	1	0
Sorafenib	11	11	11	11	11	11	9	9	6	4	3	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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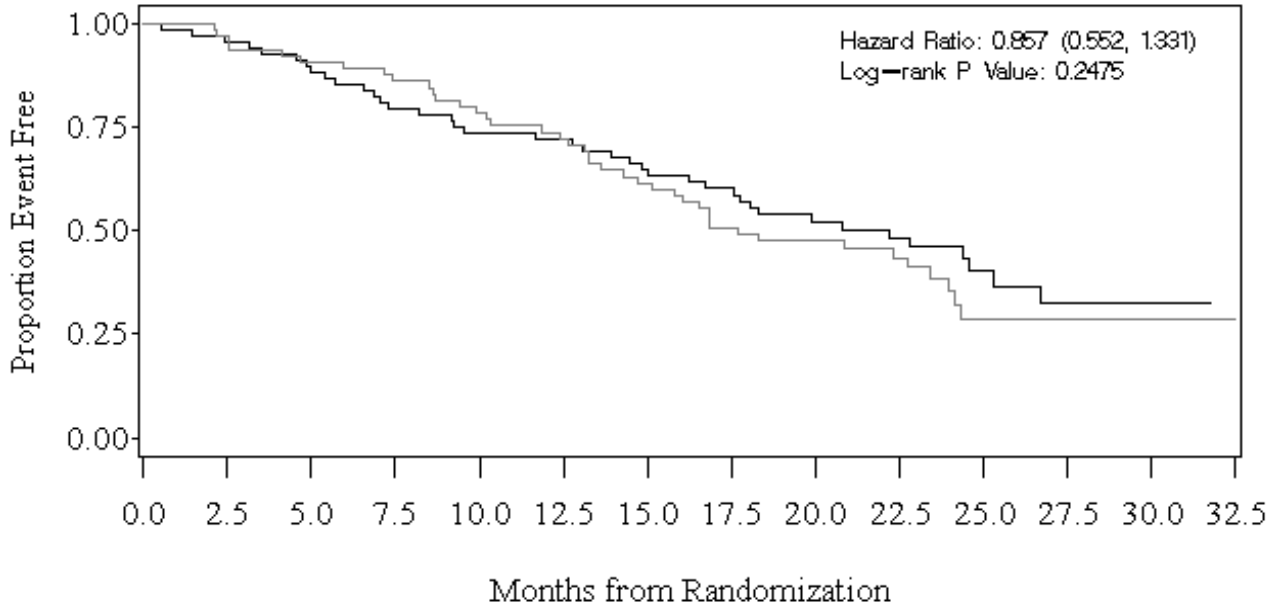
Figure 14.2.2.9.1 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Use of Taxane



Number at risk:

Placebo	65	63	59	56	51	47	40	33	26	20	7	3	2	0
Sorafenib	71	66	61	54	50	48	43	38	30	24	13	8	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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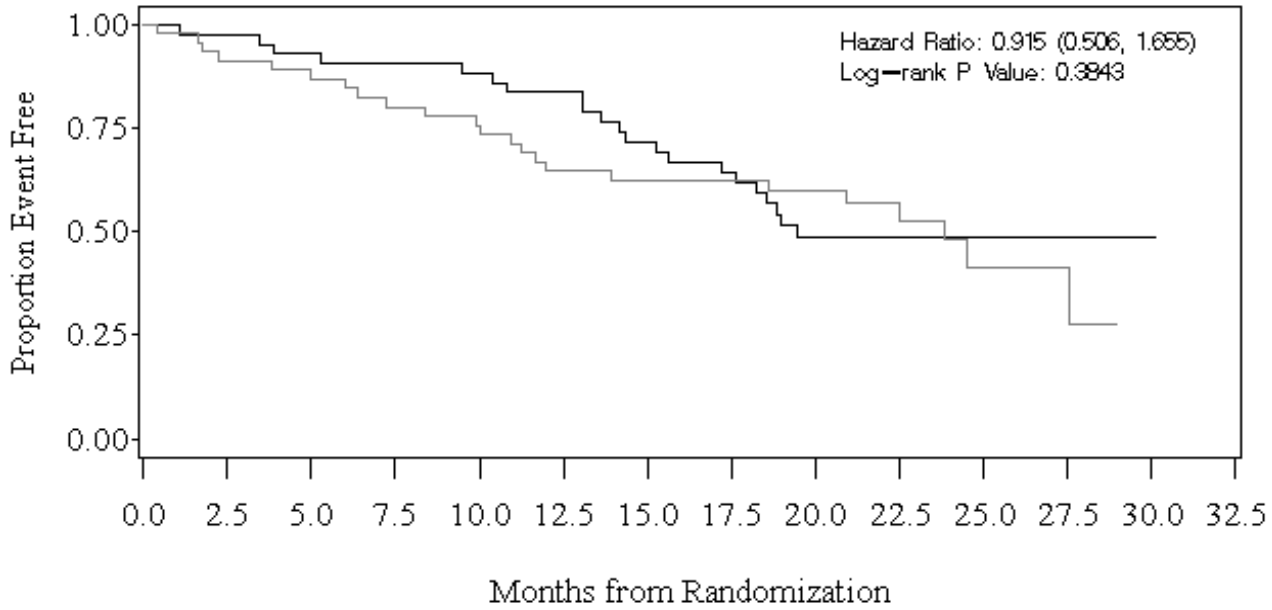
Figure 14.2.2.9.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Use of Taxane



Number at risk:

Placebo	47	42	39	36	34	29	28	28	21	14	5	3	0	0
Sorafenib	43	42	40	39	38	36	29	26	15	12	6	2	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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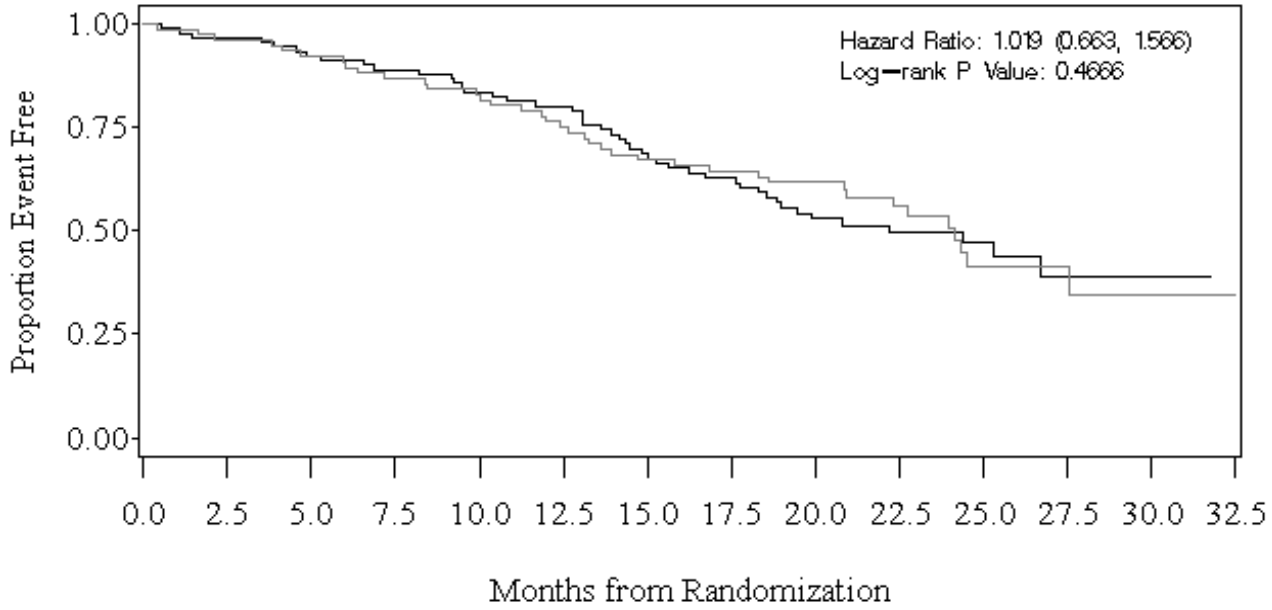
Figure 14.2.2.10.1 Subgroup Analysis of Overall Survival
Randomized Subjects With Estrogen Receptor Positive



Number at risk:

Placebo	77	73	70	66	63	57	51	49	37	26	10	6	2	0
Sorafenib	91	88	84	80	75	71	59	53	38	31	16	8	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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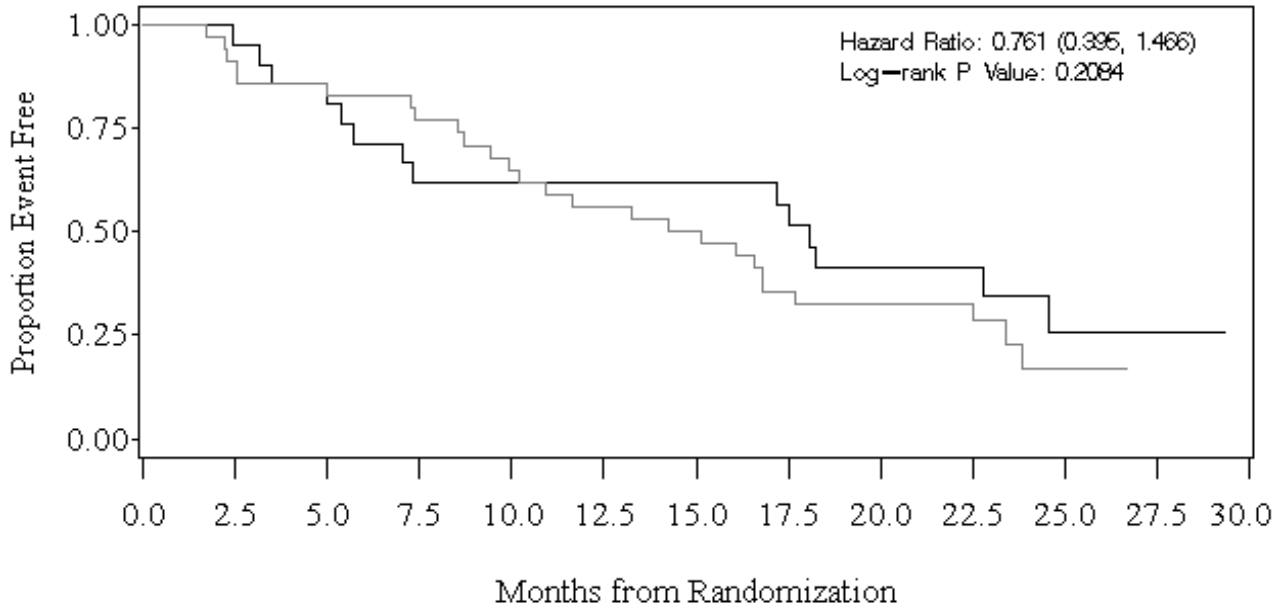
Figure 14.2.2.10.2 Subgroup Analysis of Overall Survival
Randomized Subjects With Estrogen Receptor Negative



Number at risk:

Placebo	35	32	28	26	22	19	17	12	10	8	2	0	0
Sorafenib	23	20	17	13	13	13	13	11	8	6	3	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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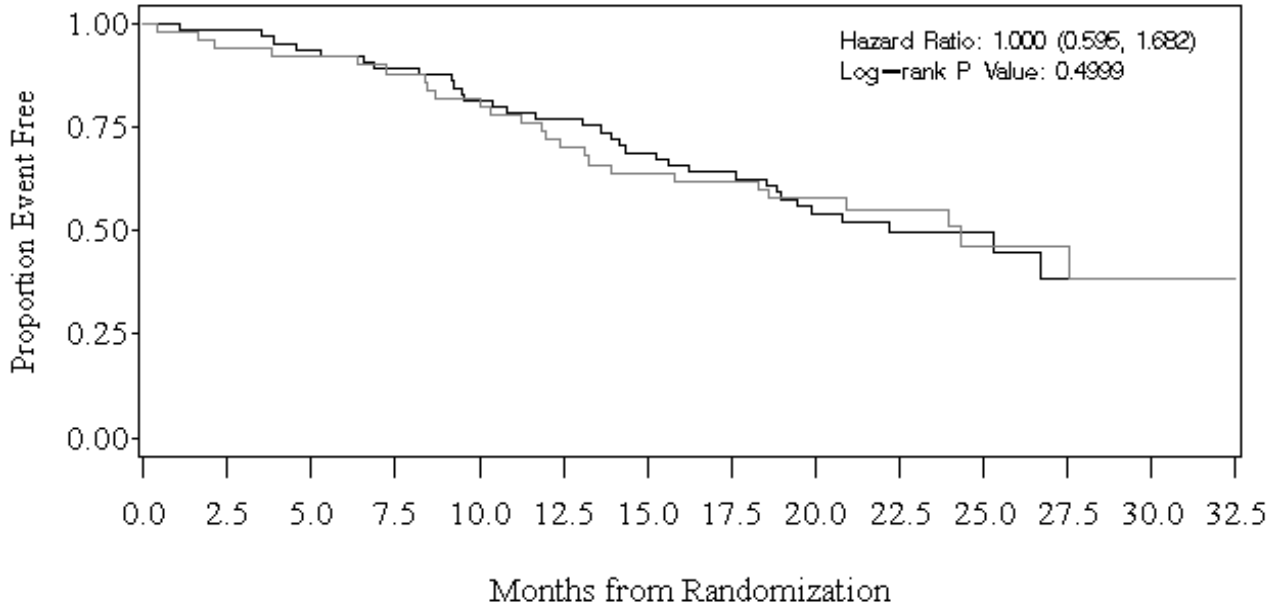
Figure 14.2.2.11.1 Subgroup Analysis of Overall Survival
Randomized Subjects With Progesterone Receptor Positive



Number at risk:

Placebo	51	47	46	44	41	35	32	31	24	15	9	6	2	0
Sorafenib	66	64	61	58	53	49	43	39	29	23	12	6	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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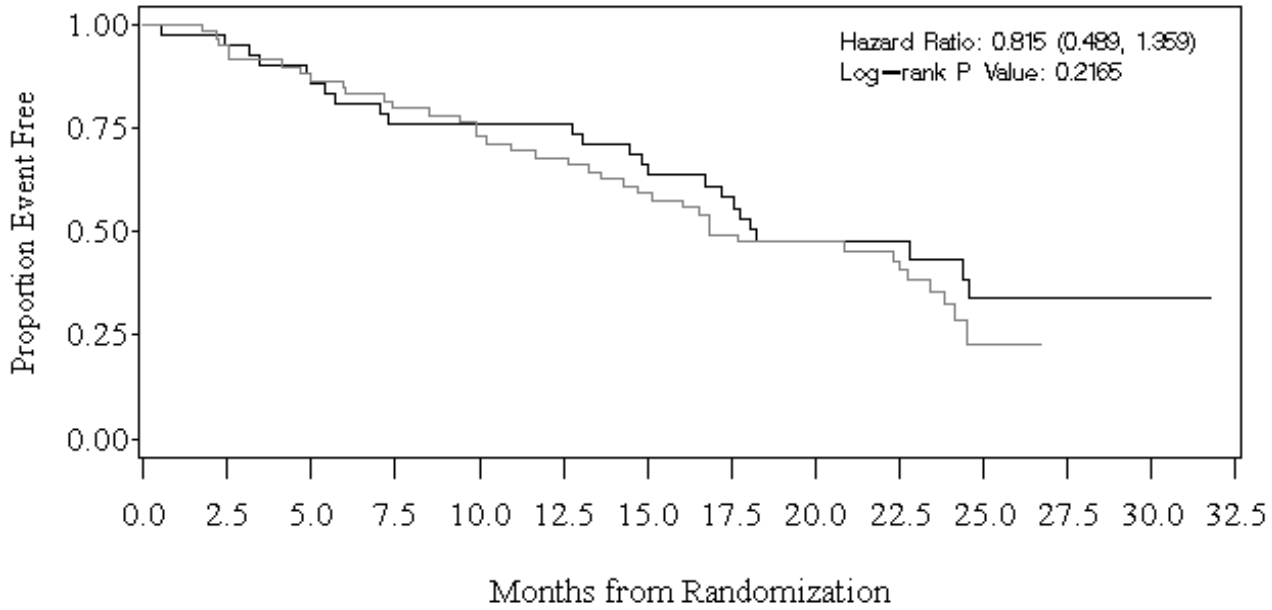
Figure 14.2.2.11.2 Subgroup Analysis of Overall Survival
Randomized Subjects With Progesterone Receptor Negative



Number at risk:

Placebo	60	57	51	47	43	40	35	29	23	19	3	0	0	0
Sorafenib	43	40	36	31	31	31	26	22	15	12	6	4	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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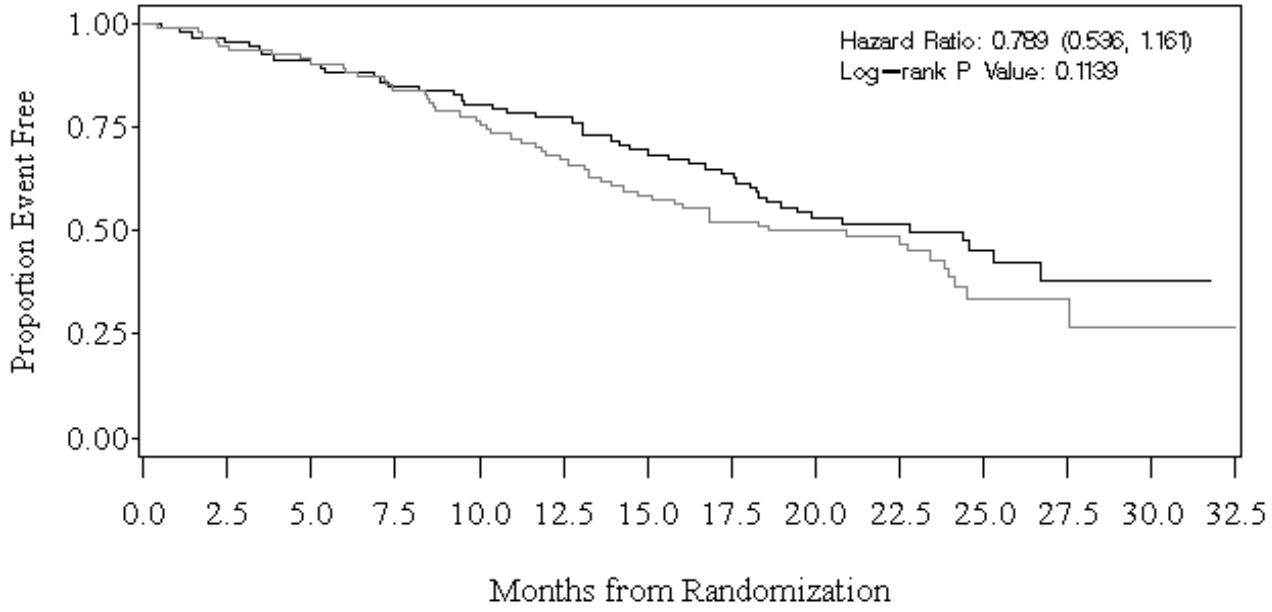
Figure 14.2.2.12.1 Subgroup Analysis of Overall Survival
Randomized Subjects With Measurable Disease



Number at risk:

Placebo	96	90	86	79	72	63	55	49	39	29	10	5	1	0
Sorafenib	95	89	84	78	74	70	62	55	39	32	18	9	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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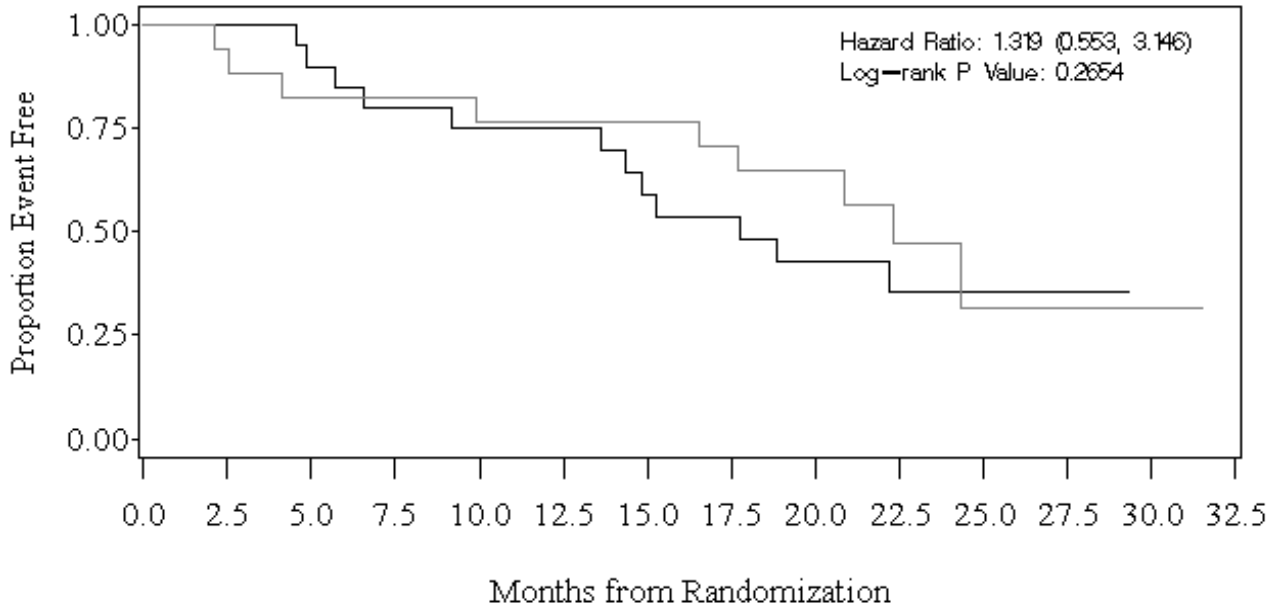
Figure 14.2.2.12.2 Subgroup Analysis of Overall Survival
Randomized Subjects Without Measurable Disease



Number at risk:

Placebo	17	16	14	14	13	13	13	12	8	5	2	1	1	0
Sorafenib	20	20	18	16	15	15	11	10	7	5	1	1	0	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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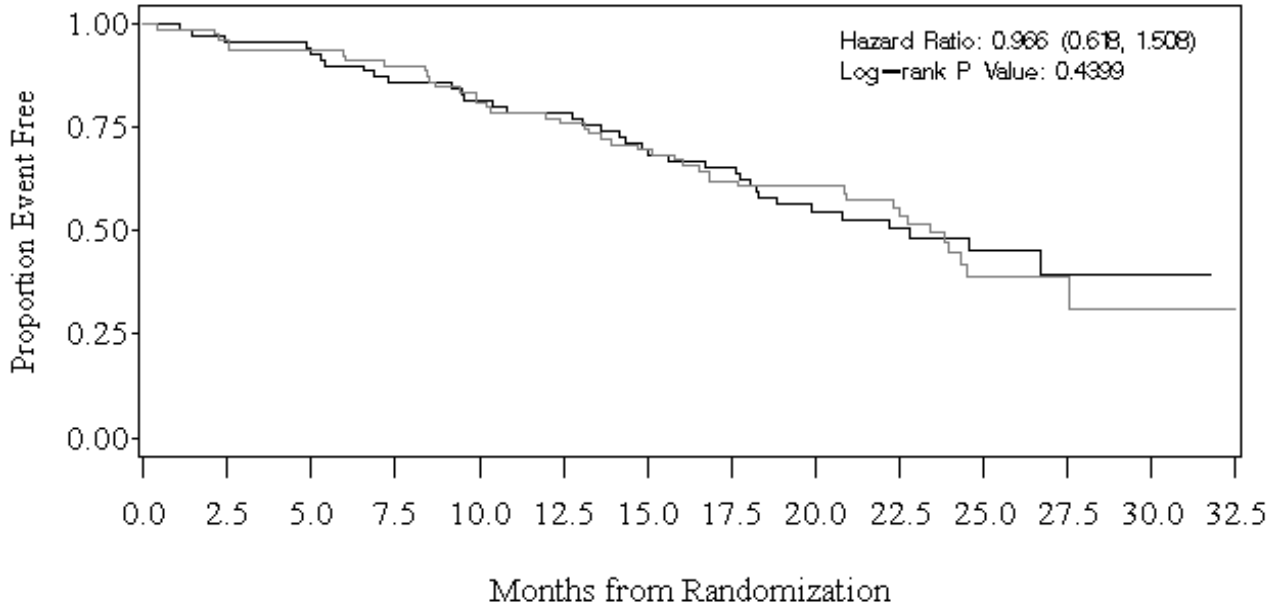
Figure 14.2.2.13.1 Subgroup Analysis of Overall Survival
Randomized Subjects With <3 Metastatic Sites



Number at risk:

Placebo	79	76	74	71	64	60	55	49	40	30	11	5	2	0
Sorafenib	71	67	65	60	57	55	48	43	30	24	13	7	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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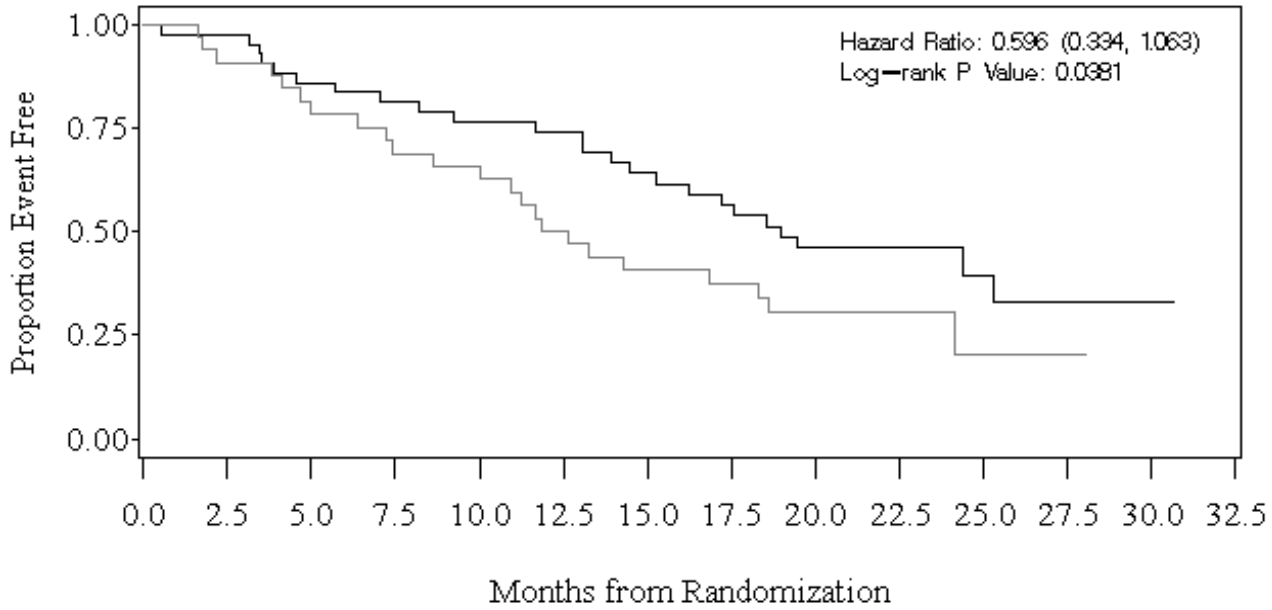
Figure 14.2.2.13.2 Subgroup Analysis of Overall Survival
Randomized Subjects with 3+ Metastatic Sites



Number at risk:

Placebo	34	30	25	22	21	16	13	12	7	4	1	1	0	0
Sorafenib	44	42	37	34	32	30	25	22	16	13	6	3	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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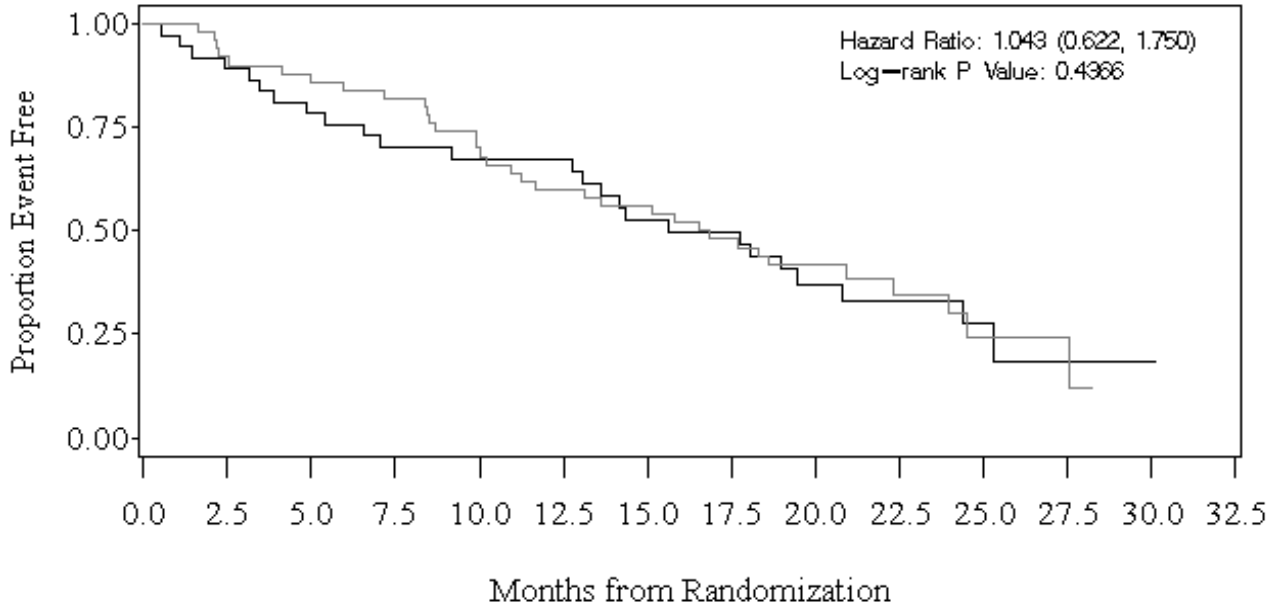
Figure 14.2.2.14.1 Subgroup Analysis of Overall Survival
Randomized Subjects With <12 Months from adjuvant treatment to metastatic disease



Number at risk:

Placebo	50	46	43	41	35	30	28	24	15	9	4	2	0	0
Sorafenib	37	33	29	25	24	23	18	17	10	7	4	1	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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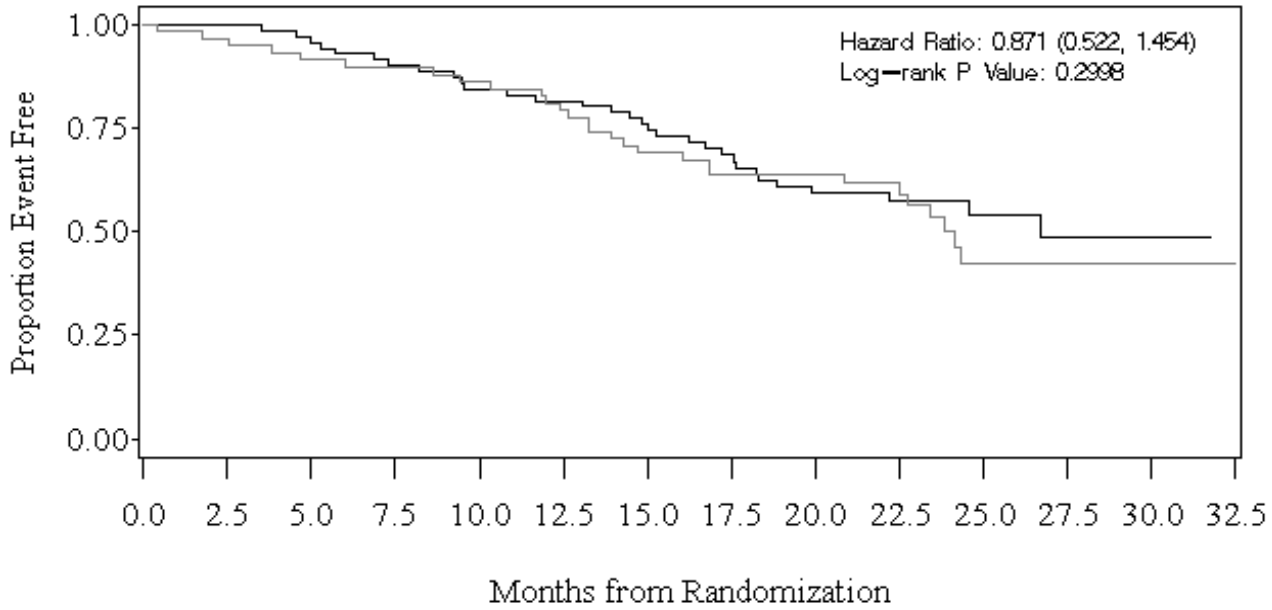
Figure 14.2.2.14.2 Subgroup Analysis of Overall Survival
Randomized Subjects with 12+ Months from adjuvant treatment to metastatic disease



Number at risk:

Placebo	60	57	53	52	50	46	40	37	32	25	8	4	2	0
Sorafenib	73	71	68	64	60	58	52	45	35	29	15	9	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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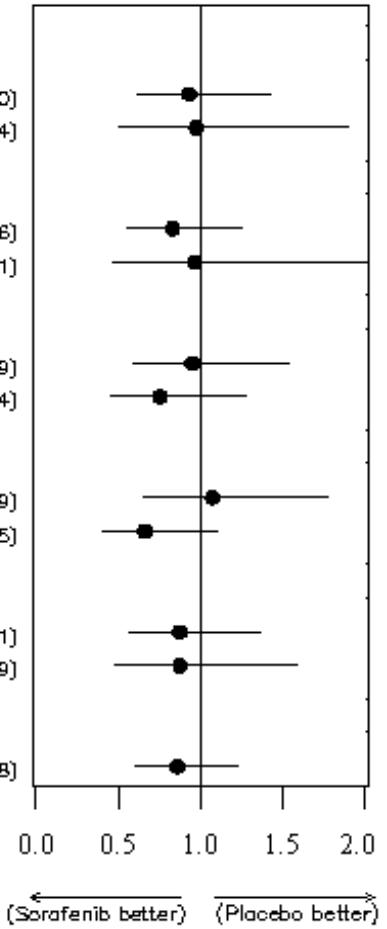
Progression-free Data Summary Tables

Figure 14.2.3.1: Subgroup Analysis of Overall Survival

Subgroup	Number of Patients	Overall Survival (Months) Placebo	Sorafenib	Hazard Ratio (95% CI)
Hormone receptor status				
ER+ or PgR+	173	24	24.4	0.935 (0.612,1.430)
ER– and PgR–	53	16.1	17.5	0.977 (0.504,1.894)
Visceral disease				
Yes	171	18.3	19.5	0.834 (0.558,1.246)
No	58	24.3	22.8	0.970 (0.468,2.011)
Region				
Brazil	112	18.3	18.8	0.953 (0.590,1.539)
France or Spain	117	22.7	24.4	0.757 (0.450,1.274)
Prior chemotherapy for metastatic breast cancer				
Yes	116	23.4	19	1.076 (0.651,1.779)
No	112	18.3	22.8	0.666 (0.401,1.105)
Prior anthracycline and taxane				
Yes	133	17.3	20.8	0.877 (0.565,1.361)
No	93	23.8	NR	0.879 (0.486,1.589)
Total	229	20.9	22.2	0.864 (0.608,1.228)



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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\figpgm\f_ossubf1.sas
Data Cutoff: 30JUN10, Download: 18AUG10, Run Date: 24SEP2010 9:56

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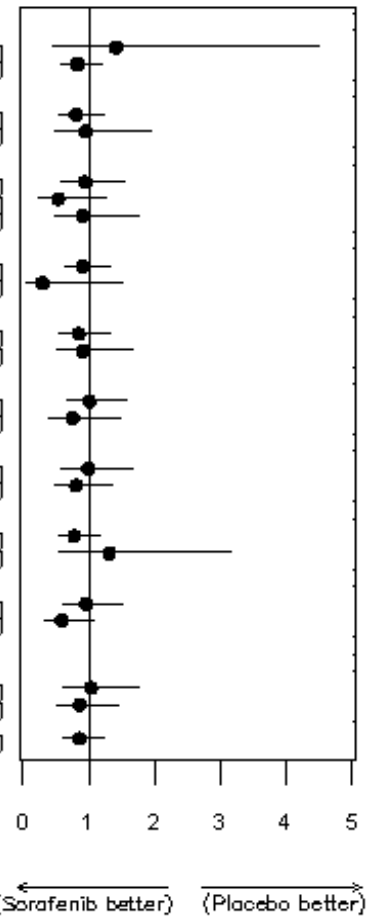
Progression-free Data Summary Tables

Figure 14.2.3.2: Subgroup Analysis of Overall Survival

Subgroup	Number of Patients	Overall Survival (Months) Placebo	Overall Survival (Months) Sorafenib	Hazard Ratio (95% CI)
Age				
< 40	18	16.6	13.9	1.420 (0.448,4.498)
>=40	211	22.3	22.8	0.834 (0.578,1.208)
Age				
< 65	175	20.9	24.4	0.818 (0.544,1.229)
>=65	54	22.7	19	0.962 (0.478,1.934)
Country				
Brazil	112	18.3	18.8	0.953 (0.590,1.539)
France	37	11.9	22.8	0.543 (0.231,1.274)
Spain	80	24	24.4	0.918 (0.474,1.772)
Prior use of anthracycline				
Yes	202	20.9	19.5	0.924 (0.642,1.330)
No	25	27.6	NR	0.301 (0.080,1.510)
Prior use of taxane				
Yes	136	17.7	22.2	0.857 (0.552,1.331)
No	90	23.8	19.5	0.915 (0.506,1.655)
Estrogen receptor				
Positive	168	24.1	22.2	1.019 (0.663,1.566)
Negative	58	15.1	18.1	0.761 (0.395,1.466)
Progesterone receptor				
Positive	117	24.3	22.2	1.000 (0.595,1.682)
Negative	103	16.9	18.2	0.815 (0.489,1.359)
Measurable disease				
Yes	191	18.6	22.8	0.789 (0.536,1.161)
No	37	22.3	17.7	1.319 (0.553,3.148)
Number of metastatic sites				
< 3	150	23.4	22.8	0.966 (0.618,1.508)
>=3	78	12.6	19	0.598 (0.334,1.083)
Months from adjuvant treatment to recurrence or metastatic diagnosis				
<= 12 months	87	16.7	15.6	1.043 (0.622,1.750)
> 12 months	133	24.1	26.7	0.871 (0.522,1.454)
Total	229	20.9	22.2	0.864 (0.608,1.228)



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Data Cutoff: 30JUN10, Download: 18AUG10, Run Date: 24SEP2010 11:33

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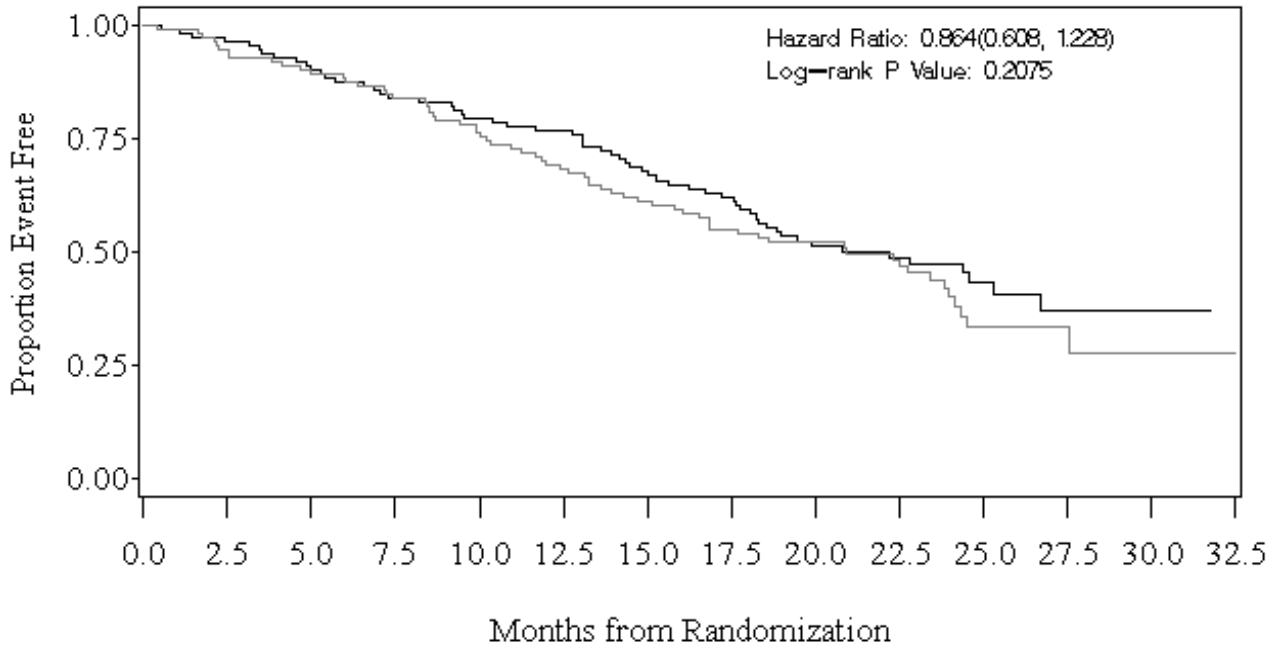
Figure 14.2.1: Overall Survival



Number at risk:

Placebo	114	106	99	93	85	76	68	61	47	34	12	6	2	0
Sorafenib	115	109	102	94	89	85	73	65	46	37	19	10	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_os.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_os.sas (Run Date: 24SEP2010 11:30)

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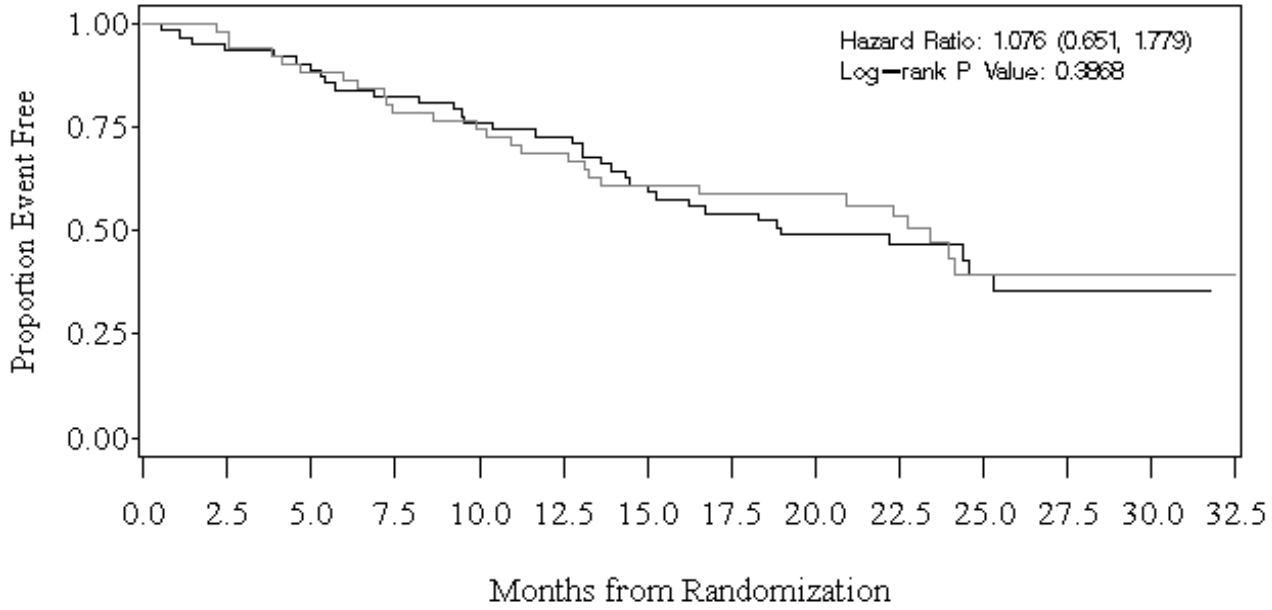
Figure 14.2.2.1.1: Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Chemotherapy for Metastatic Breast Cancer



Number at risk:

Placebo	51	50	45	40	38	35	31	30	25	19	7	4	2	0
Sorafenib	65	59	56	51	47	44	36	32	22	20	11	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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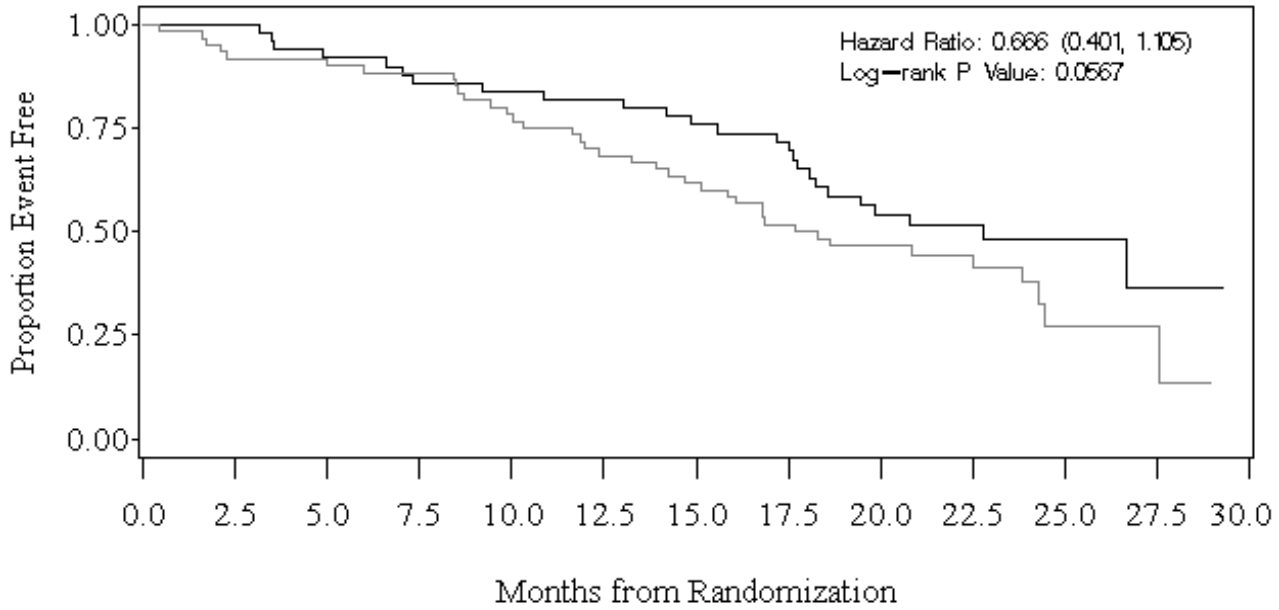
Figure 14.2.2.1.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Chemotherapy for Metastatic Breast Cancer



Number at risk:

Placebo	62	56	54	53	47	41	37	31	22	15	5	2	0
Sorafenib	50	50	46	43	42	41	37	33	24	17	8	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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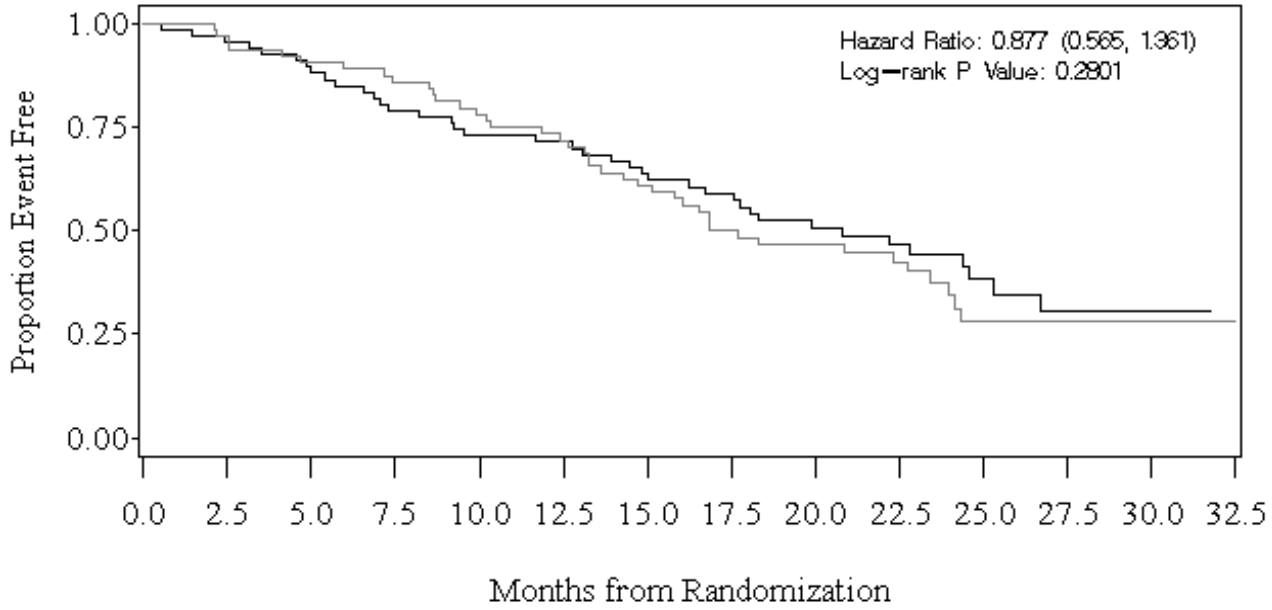
Figure 14.2.2.2.1: Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Anthracycline and Taxane



Number at risk:

Placebo	64	62	58	55	50	46	39	32	25	19	7	3	2	0
Sorafenib	69	64	59	52	48	46	41	36	29	23	12	7	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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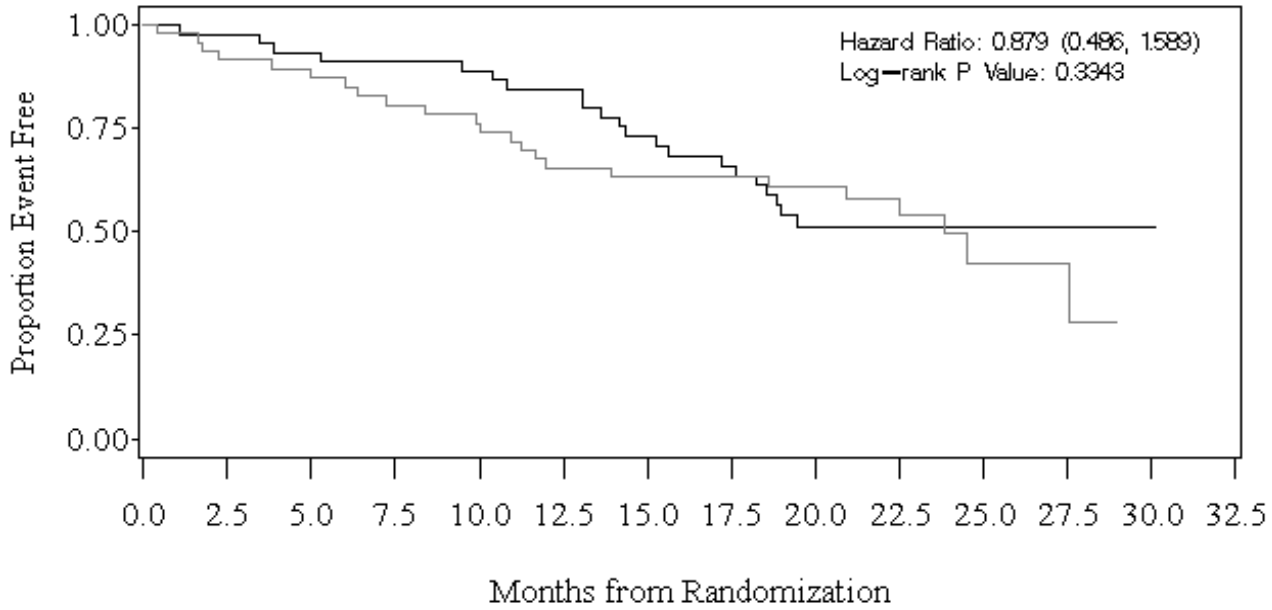
Figure 14.2.2.2.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Anthracycline and Taxane



Number at risk:

Placebo	48	43	40	37	35	30	29	29	22	15	5	3	0	0
Sorafenib	45	44	42	41	40	38	31	28	16	13	7	3	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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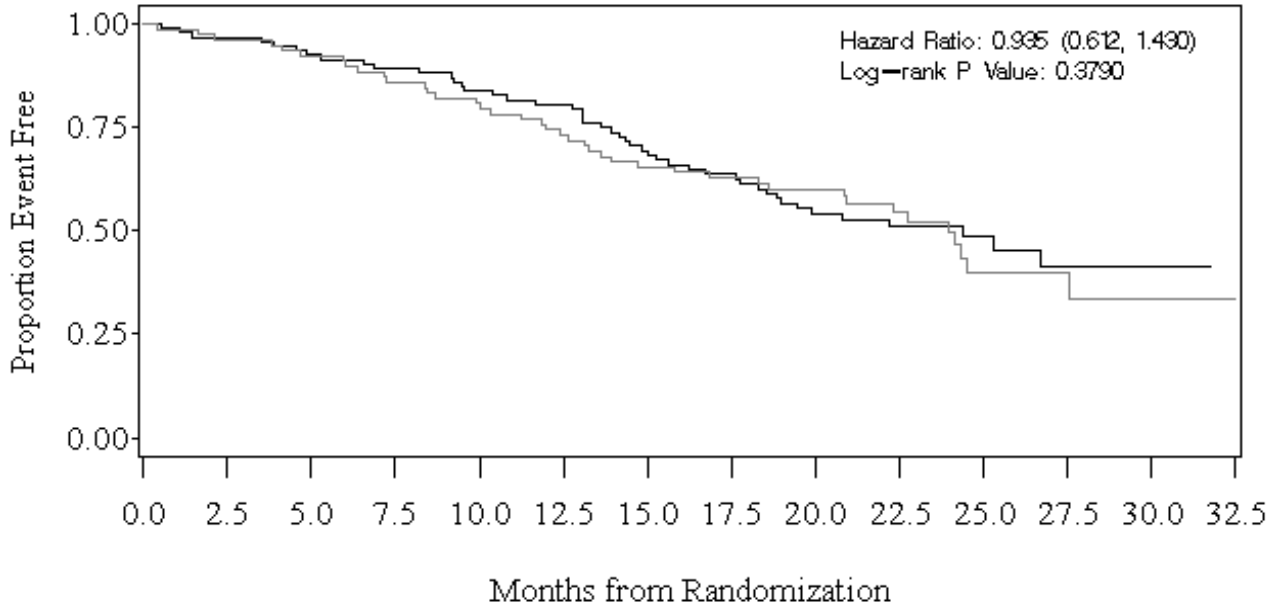
Figure 14.2.2.3.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Estrogen Receptor or Progesterone Receptor Positive



Number at risk:

Placebo	79	75	72	67	63	57	51	49	37	26	10	6	2	0
Sorafenib	94	90	86	82	77	73	61	55	40	33	18	10	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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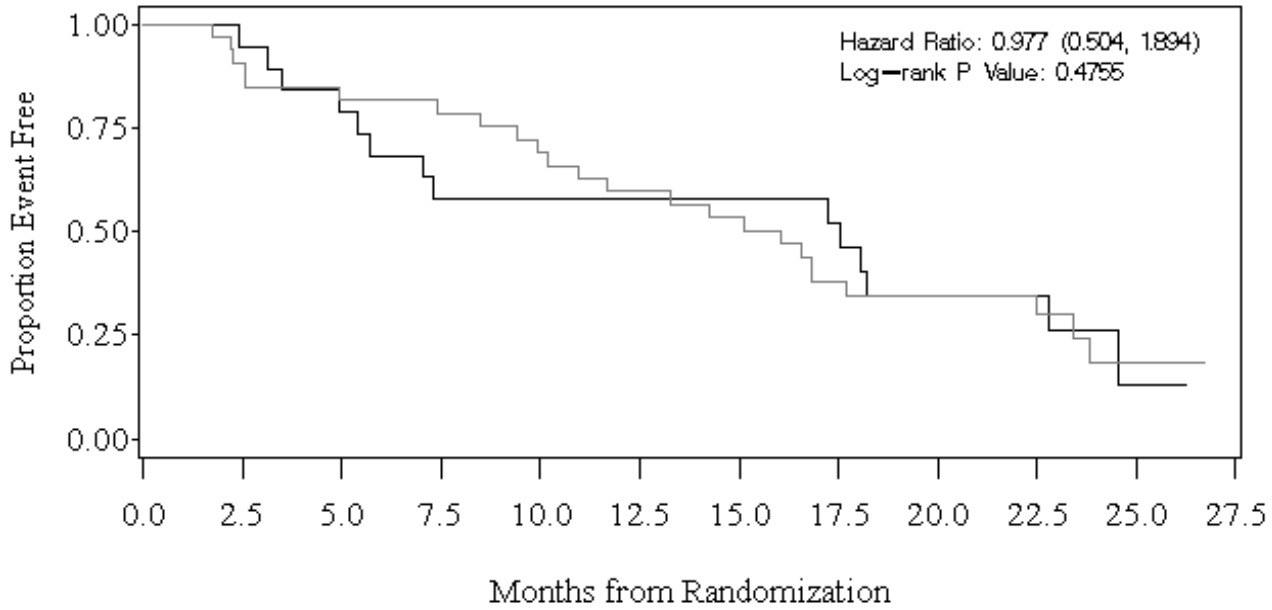
Figure 14.2.2.3.2 Subgroup Analysis of Overall Survival
Randomized Subjects with Estrogen Receptor and Progesterone Receptor Negative



Number at risk:

Placebo	33	30	26	25	22	19	17	12	10	8	2	0
Sorafenib	20	18	15	11	11	11	11	9	6	4	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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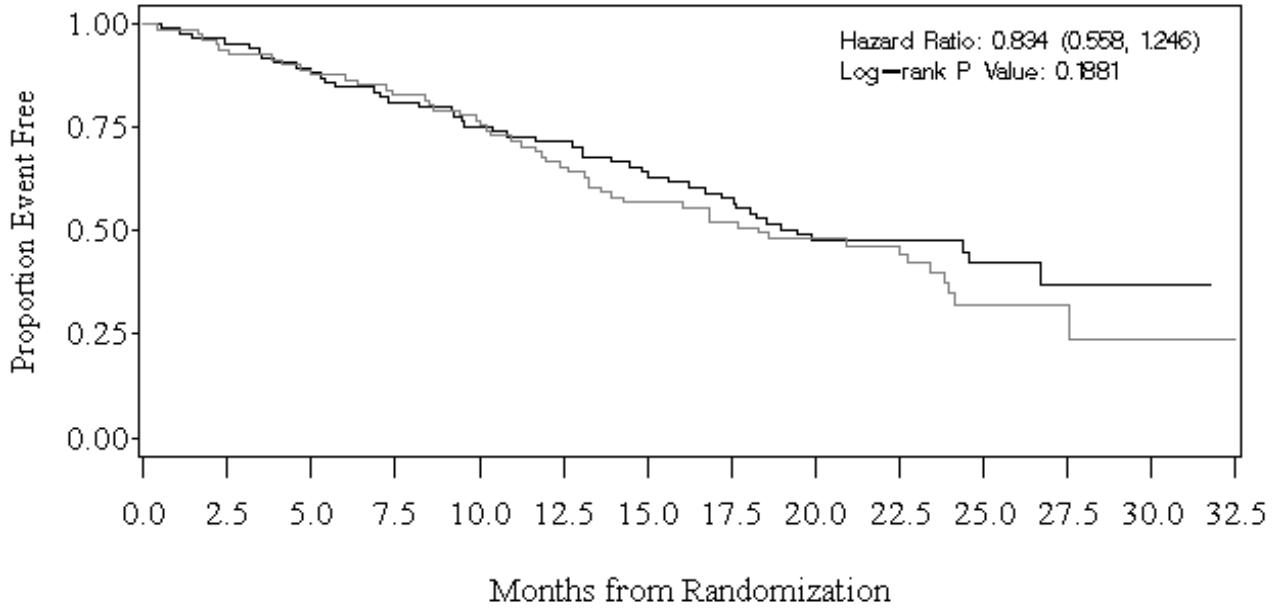
Figure 14.2.2.4.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Visceral Disease



Number at risk:

Placebo	84	77	71	67	62	53	46	42	31	22	8	4	1	0
Sorafenib	87	81	75	68	63	59	51	46	33	27	14	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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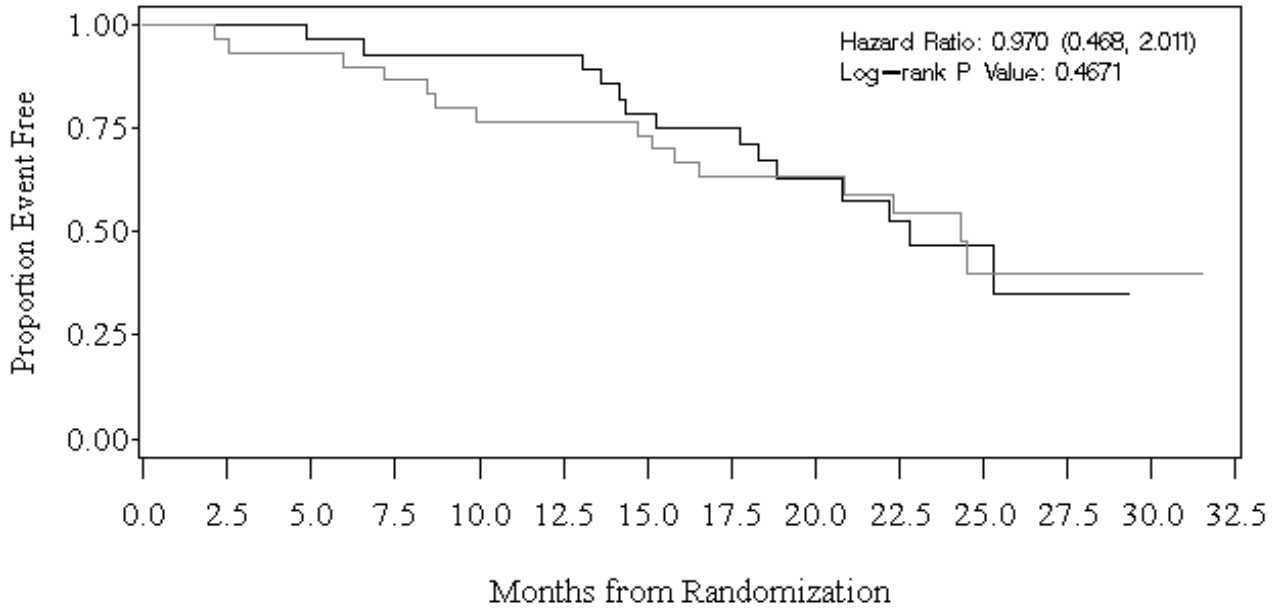
Figure 14.2.2.4.2 Subgroup Analysis of Overall Survival
Randomized Subjects without Visceral Disease



Number at risk:

Placebo	30	29	28	26	23	23	22	19	16	12	4	2	1	0
Sorafenib	28	28	27	26	26	26	22	19	13	10	5	3	0	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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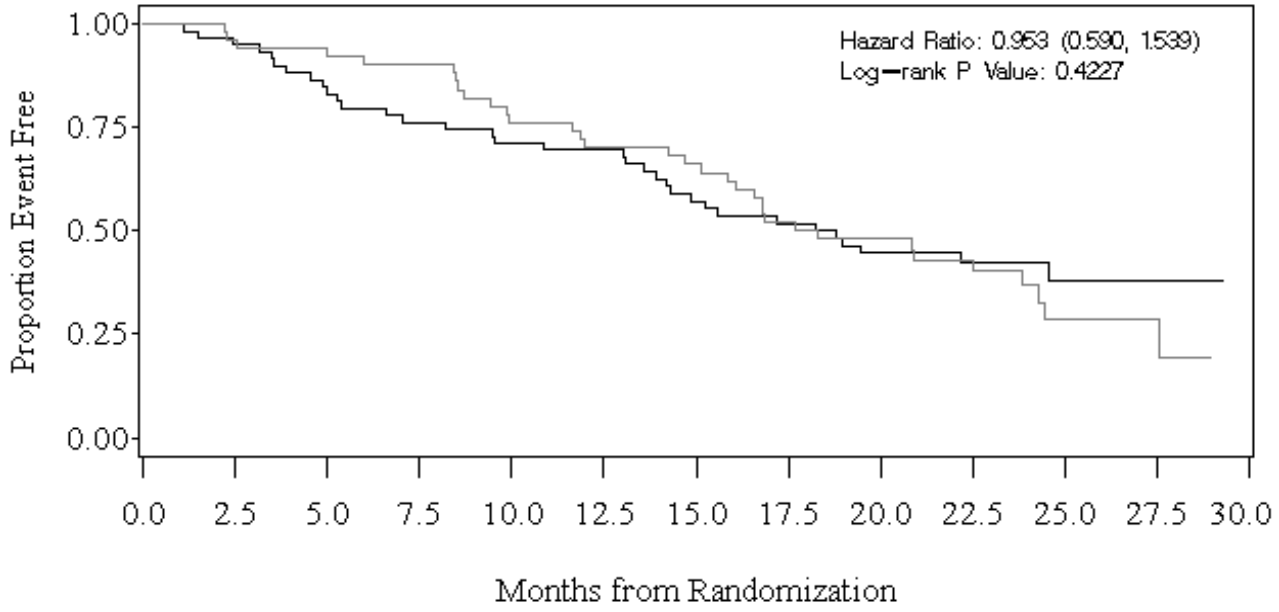
Figure 14.2.2.5.1 Subgroup Analysis of Overall Survival
Randomized Brazil Subjects



Number at risk:

Placebo	53	49	46	45	38	35	33	26	20	16	6	3	0
Sorafenib	59	56	49	45	42	41	32	29	22	17	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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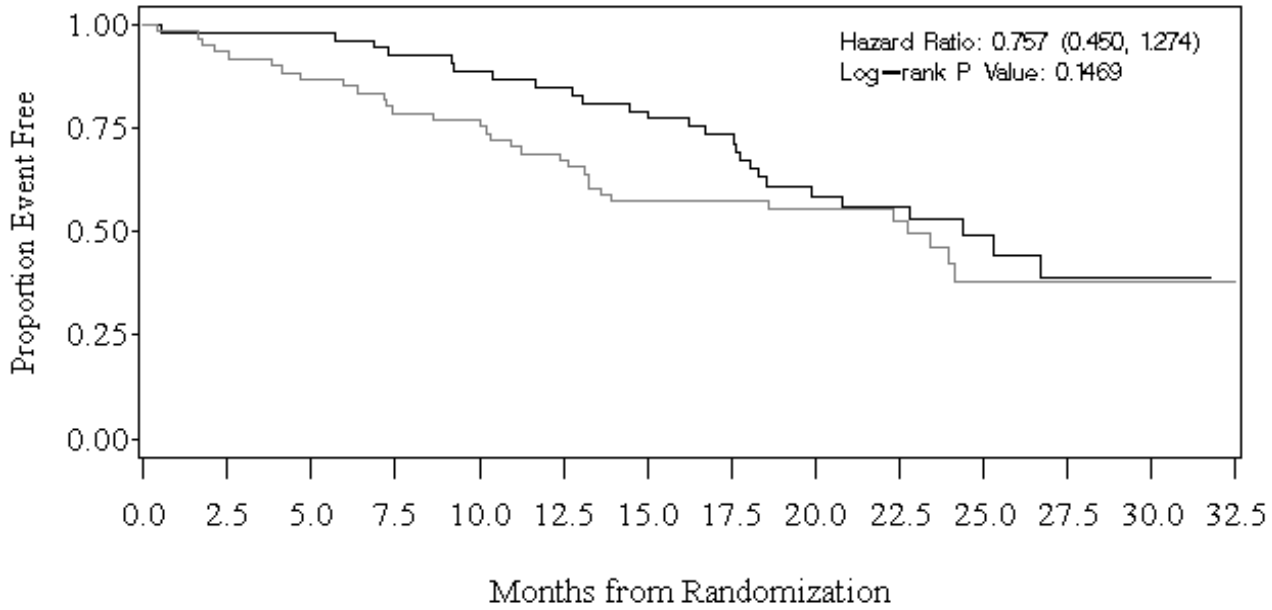
Figure 14.2.2.5.2 Subgroup Analysis of Overall Survival
Randomized France or Spain Subjects



Number at risk:

Placebo	61	57	53	48	47	41	35	35	27	18	6	3	2	0
Sorafenib	56	53	53	49	47	44	41	36	24	20	12	7	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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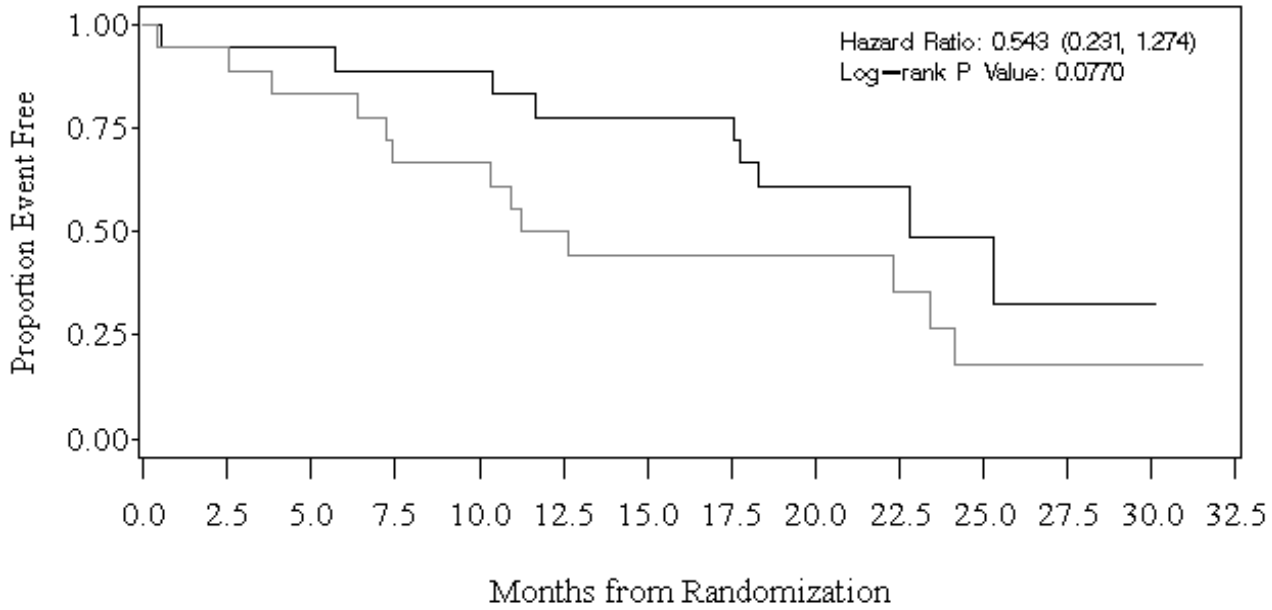
Figure 14.2.2.5.3 Subgroup Analysis of Overall Survival
Randomized France Subjects



Number at risk:

Placebo	18	17	15	12	12	9	8	8	8	4	2	1	1	0
Sorafenib	19	17	17	16	16	14	14	14	7	6	3	2	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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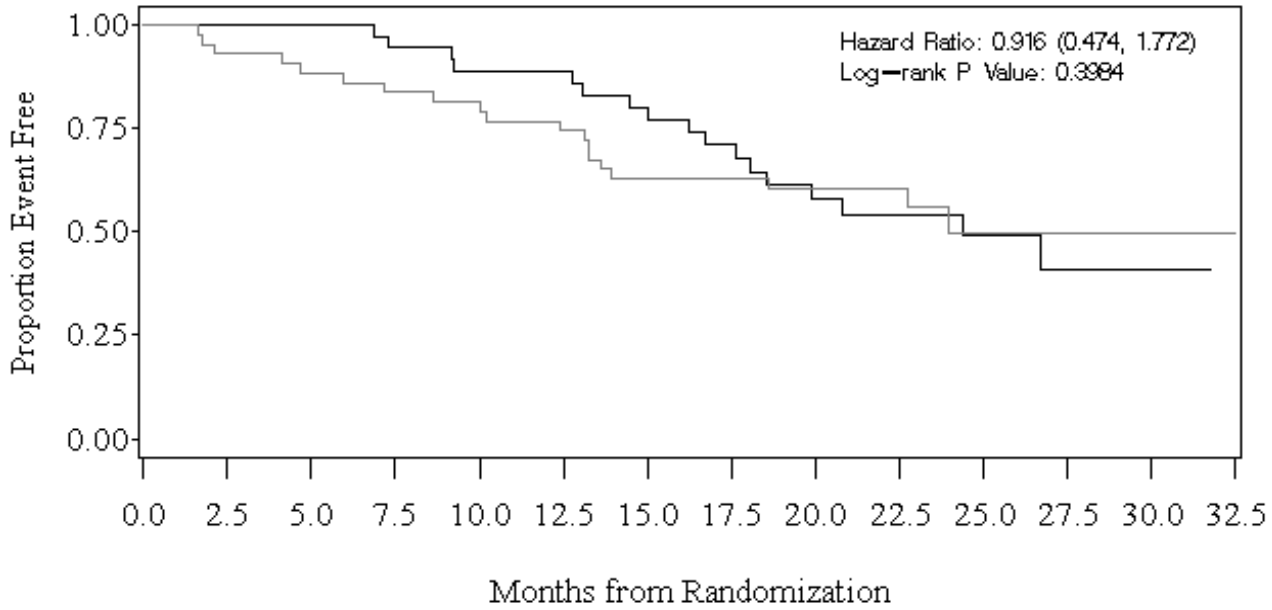
Figure 14.2.2.5.4 Subgroup Analysis of Overall Survival
Randomized Spain Subjects



Number at risk:

Placebo	43	40	38	36	35	32	27	27	19	14	4	2	1	0
Sorafenib	37	36	36	33	31	30	27	22	17	14	9	5	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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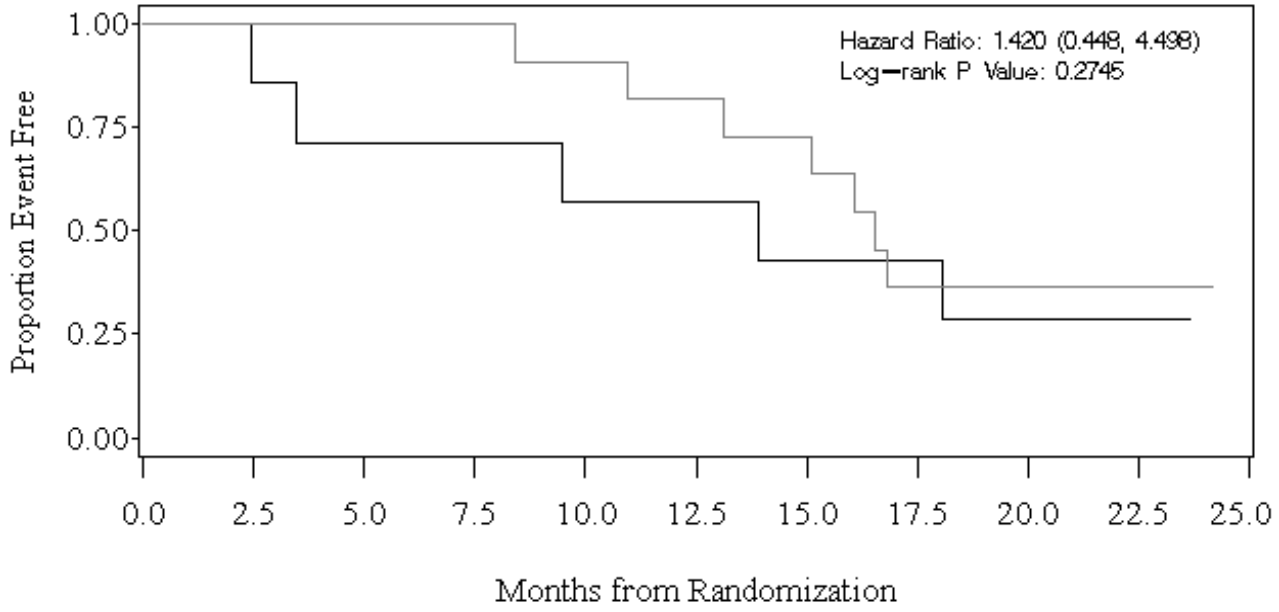
Figure 14.2.2.6.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Age < 40



Number at risk:

Placebo	11	11	11	11	10	9	8	4	2	1	0
Sorafenib	7	6	5	5	4	4	3	3	1	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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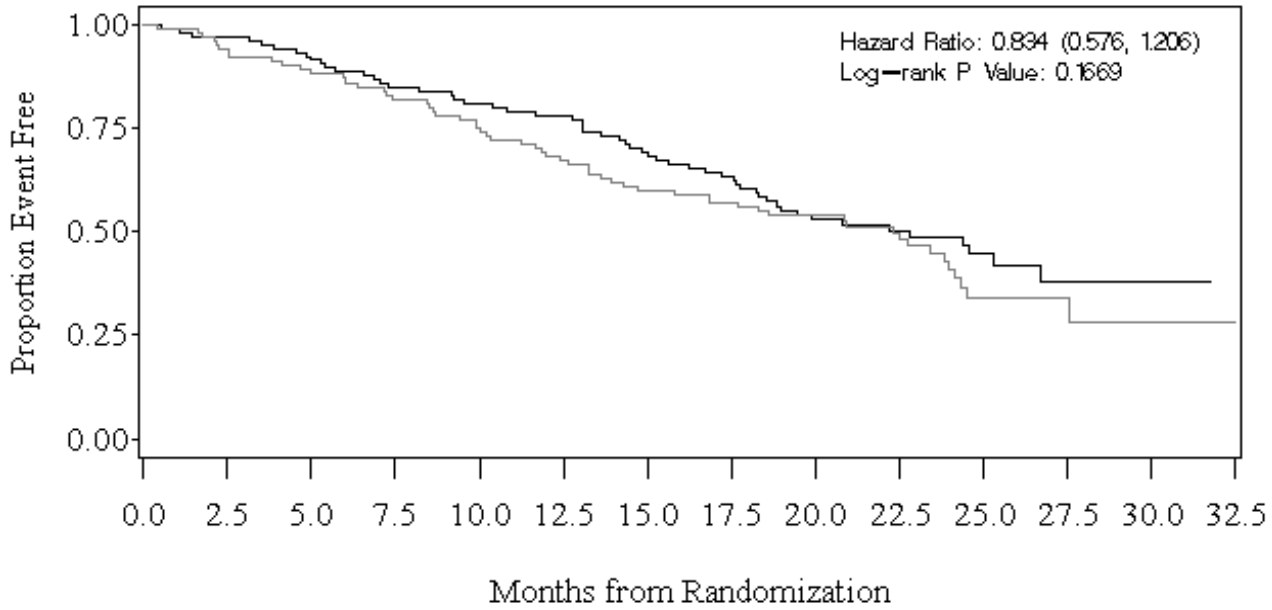
Figure 14.2.2.6.2 Subgroup Analysis of Overall Survival
Randomized Subjects with Age >= 40



Number at risk:

Placebo	103	95	88	82	75	67	60	57	45	33	12	6	2	0
Sorafenib	108	103	97	89	85	81	70	62	45	36	19	10	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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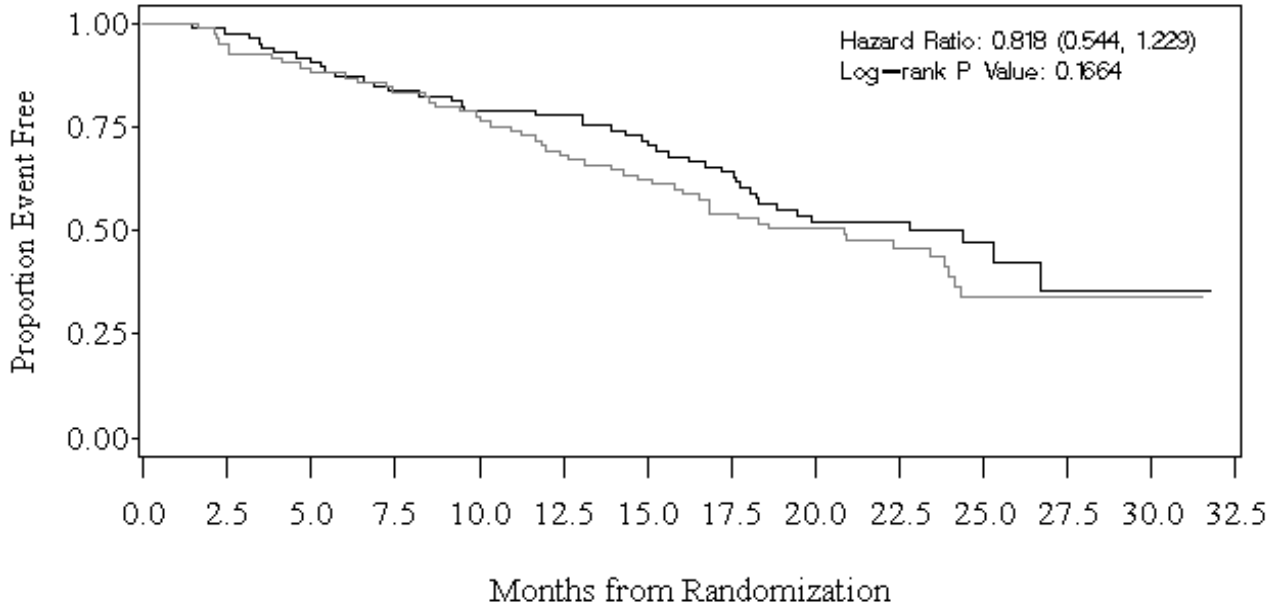
Figure 14.2.2.7.1 Subgroup Analysis of Overall Survival
Randomized Subjects with Age < 65



Number at risk:

Placebo	87	81	75	71	66	58	53	46	37	26	9	4	1	0
Sorafenib	88	84	78	71	67	65	58	50	34	28	12	5	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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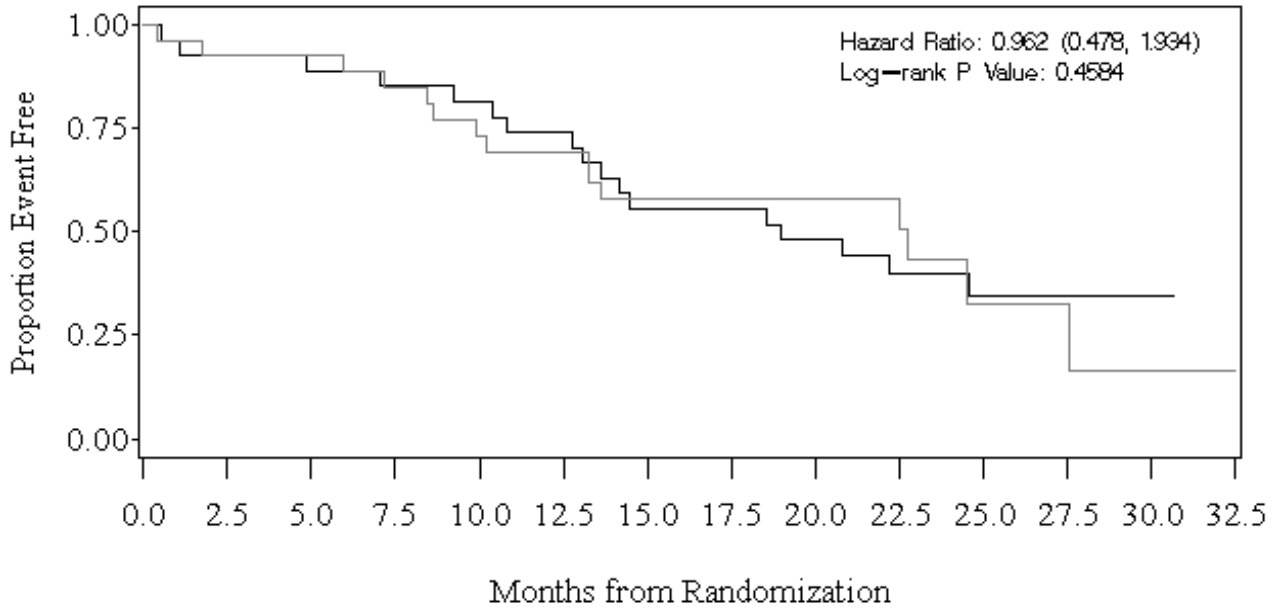
Figure 14.2.2.7.2 Subgroup Analysis of Overall Survival
Randomized Subjects with Age >= 65



Number at risk:

Placebo	27	25	24	22	19	18	15	15	10	8	3	2	1	0
Sorafenib	27	25	24	23	22	20	15	15	12	9	7	5	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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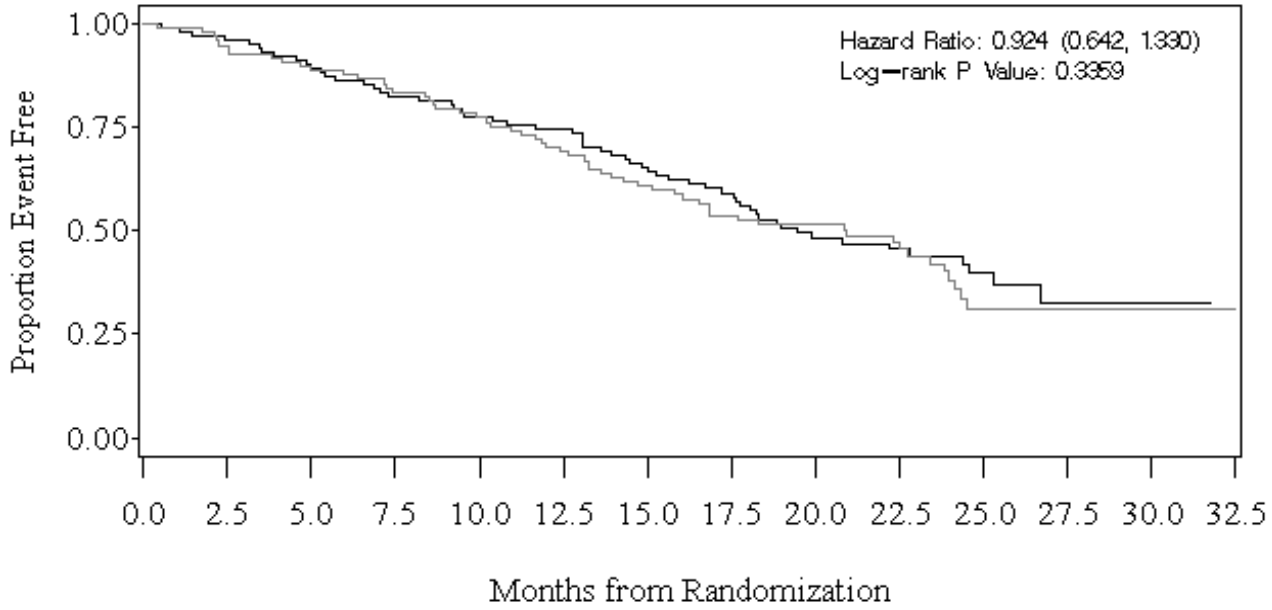
Figure 14.2.2.8.1 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Use of Anthracycline



Number at risk:

Placebo	98	92	86	81	75	67	59	52	41	30	11	5	2	0
Sorafenib	104	98	91	83	78	74	64	56	40	33	16	8	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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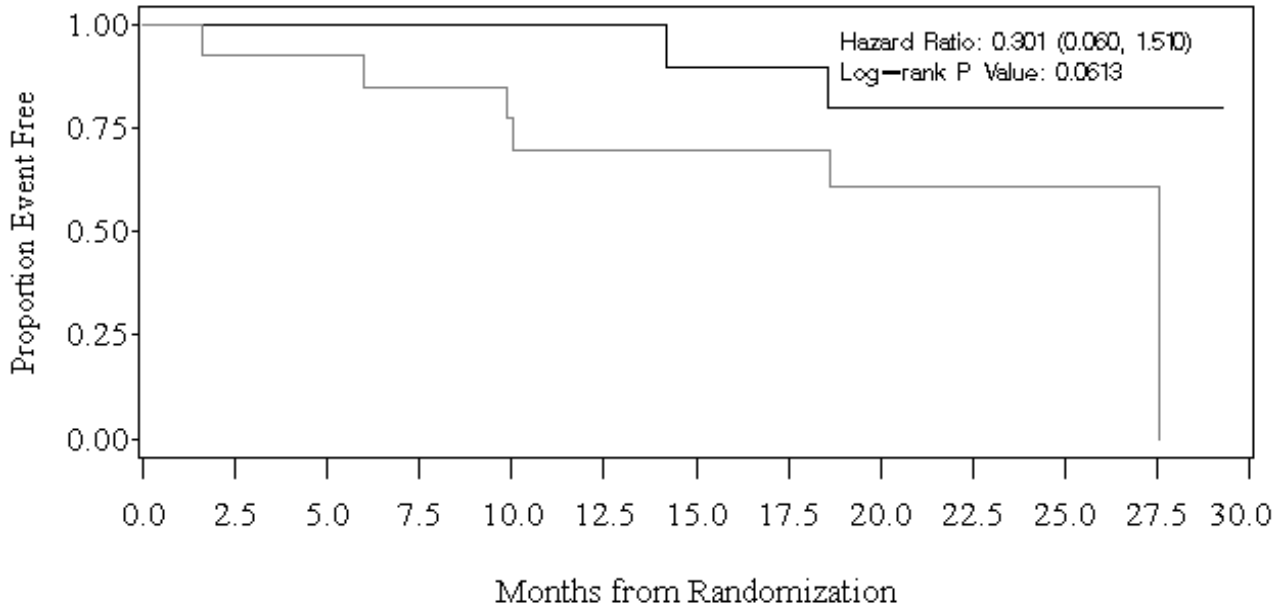
Figure 14.2.2.8.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Use of Anthracycline



Number at risk:

Placebo	14	13	12	11	10	9	9	9	6	4	1	1	0
Sorafenib	11	11	11	11	11	11	9	9	6	4	3	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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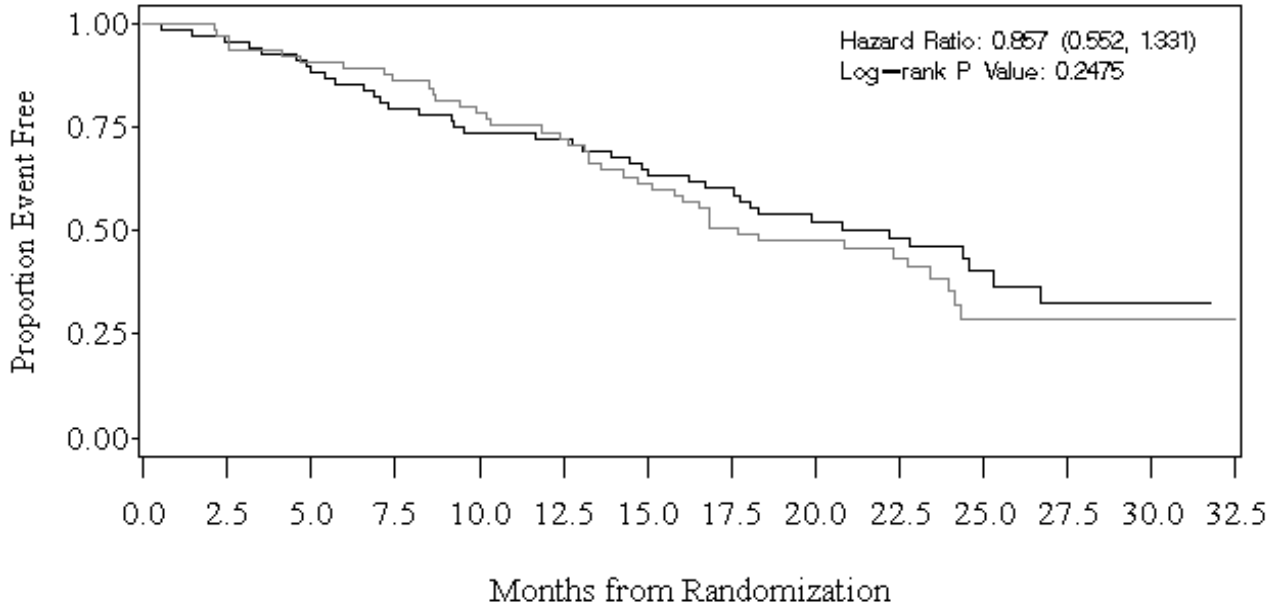
Figure 14.2.2.9.1 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had Prior Use of Taxane



Number at risk:

Placebo	65	63	59	56	51	47	40	33	26	20	7	3	2	0
Sorafenib	71	66	61	54	50	48	43	38	30	24	13	8	2	0

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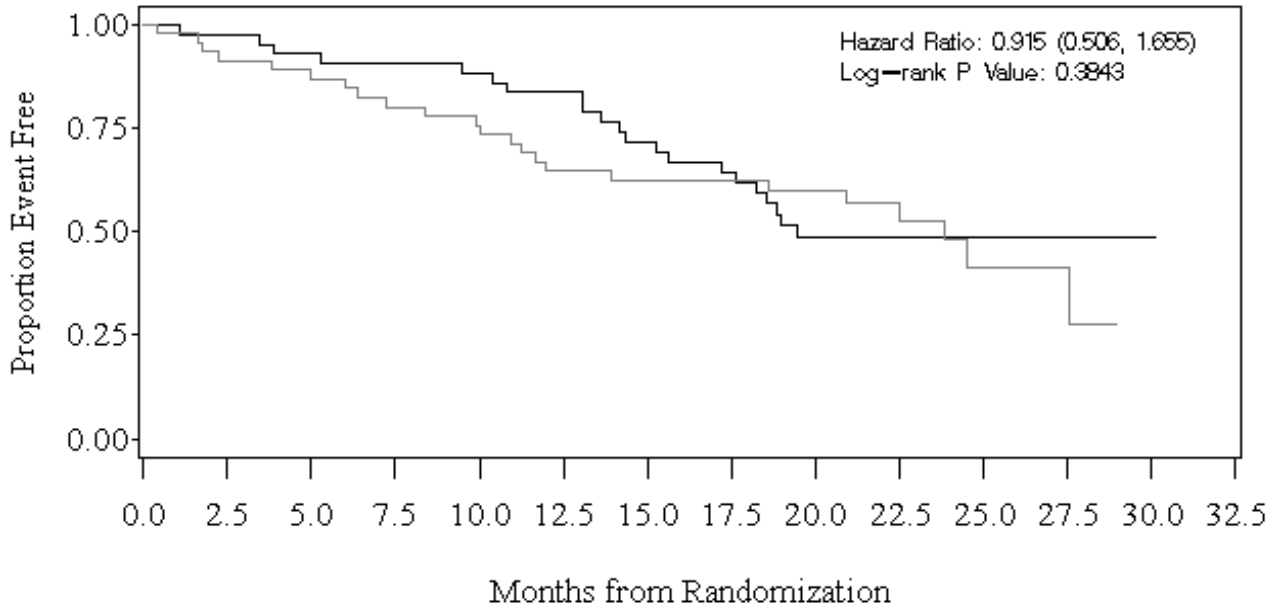
Figure 14.2.2.9.2 Subgroup Analysis of Overall Survival
Randomized Subjects Who Had No Prior Use of Taxane



Number at risk:

Placebo	47	42	39	36	34	29	28	28	21	14	5	3	0	0
Sorafenib	43	42	40	39	38	36	29	26	15	12	6	2	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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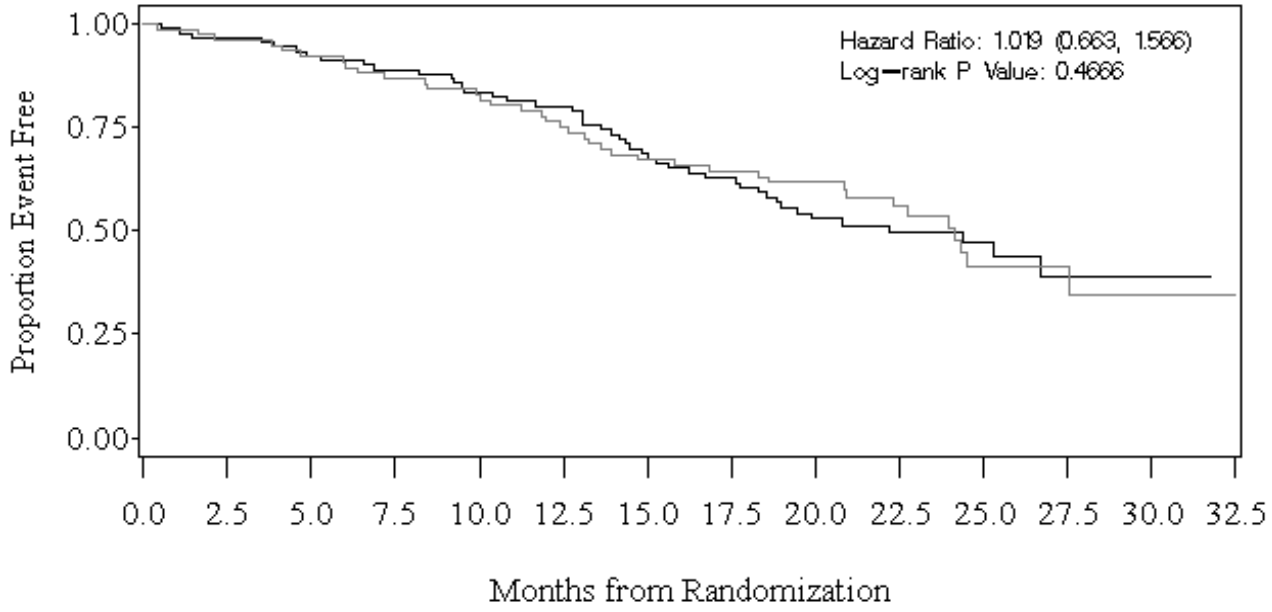
Figure 14.2.2.10.1 Subgroup Analysis of Overall Survival
Randomized Subjects With Estrogen Receptor Positive



Number at risk:

Placebo	77	73	70	66	63	57	51	49	37	26	10	6	2	0
Sorafenib	91	88	84	80	75	71	59	53	38	31	16	8	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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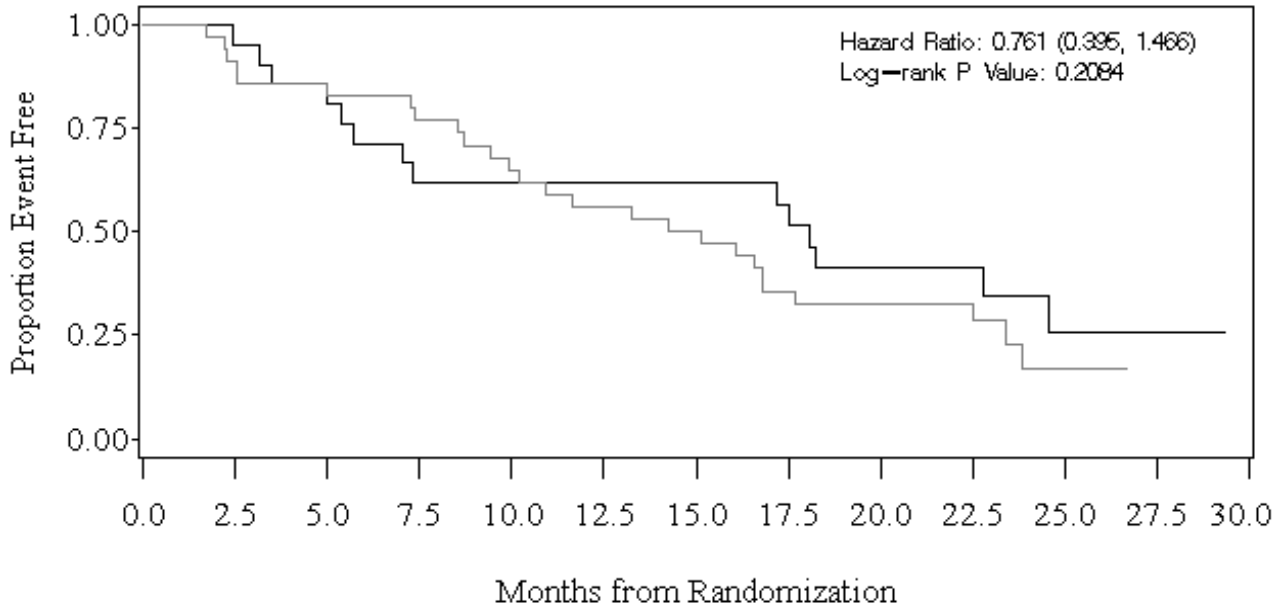
Figure 14.2.2.10.2 Subgroup Analysis of Overall Survival
Randomized Subjects With Estrogen Receptor Negative



Number at risk:

Placebo	35	32	28	26	22	19	17	12	10	8	2	0	0
Sorafenib	23	20	17	13	13	13	13	11	8	6	3	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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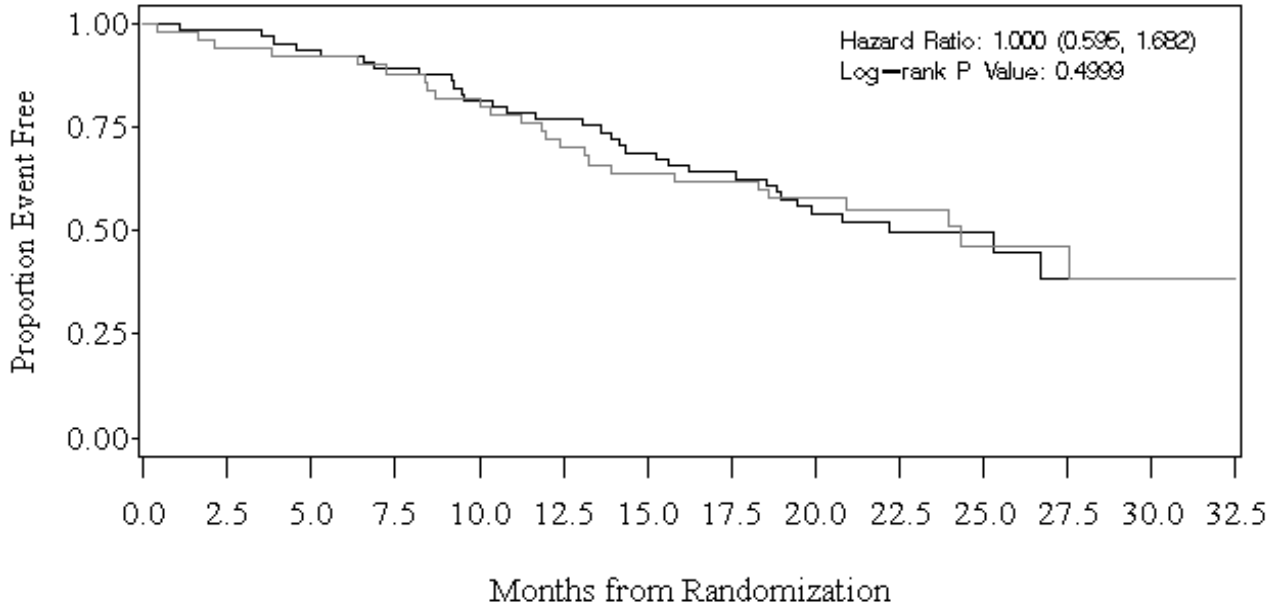
Figure 14.2.2.11.1 Subgroup Analysis of Overall Survival
Randomized Subjects With Progesterone Receptor Positive



Number at risk:

Placebo	51	47	46	44	41	35	32	31	24	15	9	6	2	0
Sorafenib	66	64	61	58	53	49	43	39	29	23	12	6	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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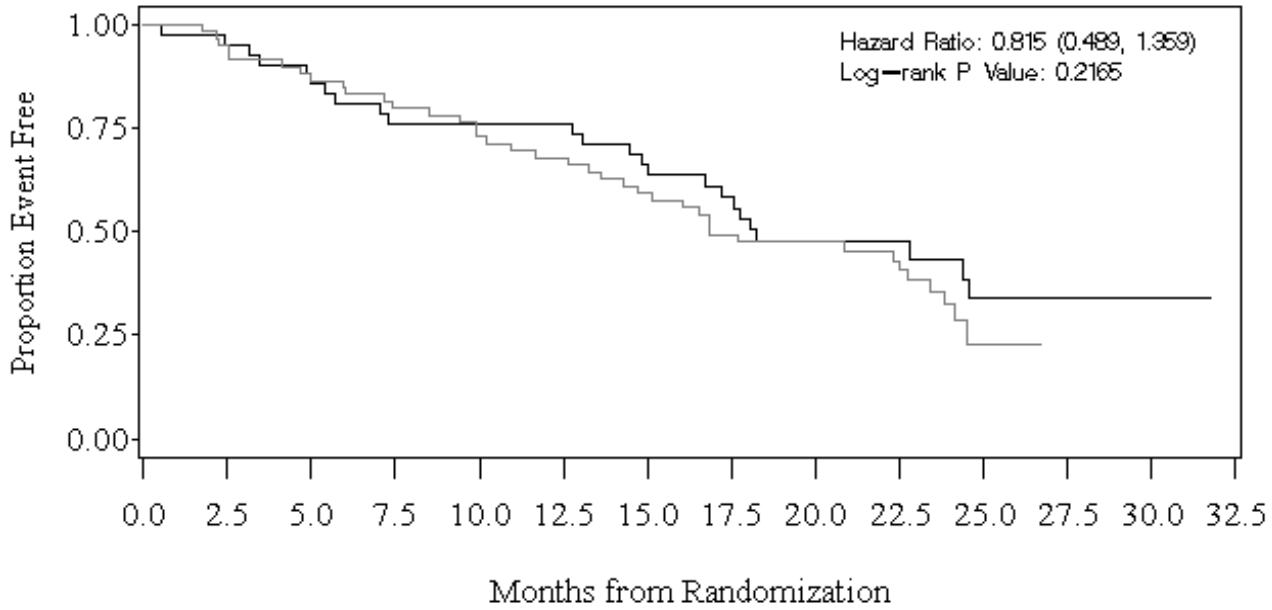
Figure 14.2.2.11.2 Subgroup Analysis of Overall Survival
Randomized Subjects With Progesterone Receptor Negative



Number at risk:

Placebo	60	57	51	47	43	40	35	29	23	19	3	0	0	0
Sorafenib	43	40	36	31	31	31	26	22	15	12	6	4	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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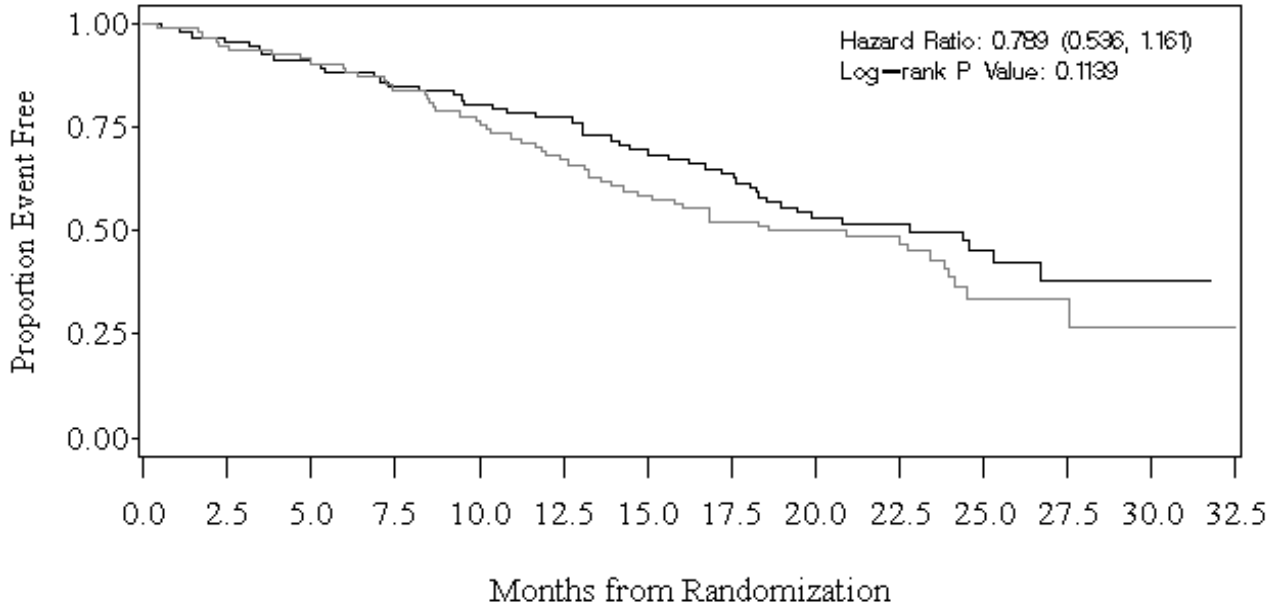
Figure 14.2.2.12.1 Subgroup Analysis of Overall Survival
Randomized Subjects With Measurable Disease



Number at risk:

Placebo	96	90	86	79	72	63	55	49	39	29	10	5	1	0
Sorafenib	95	89	84	78	74	70	62	55	39	32	18	9	3	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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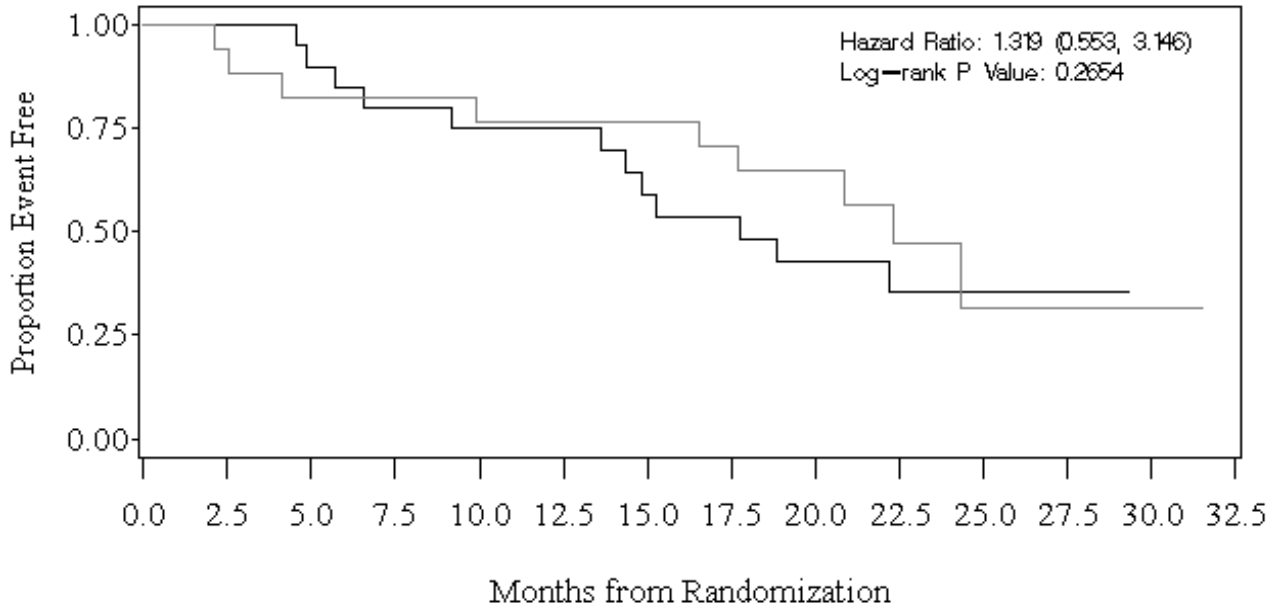
Figure 14.2.2.12.2 Subgroup Analysis of Overall Survival
Randomized Subjects Without Measurable Disease



Number at risk:

Placebo	17	16	14	14	13	13	13	12	8	5	2	1	1	0
Sorafenib	20	20	18	16	15	15	11	10	7	5	1	1	0	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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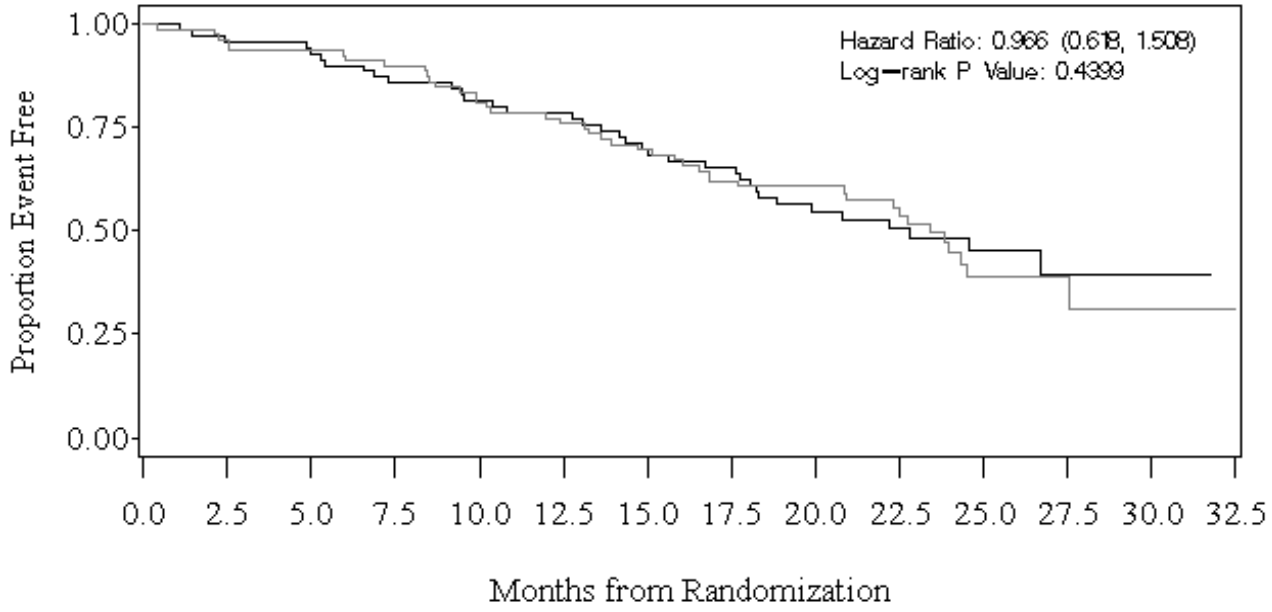
Figure 14.2.2.13.1 Subgroup Analysis of Overall Survival
Randomized Subjects With <3 Metastatic Sites



Number at risk:

Placebo	79	76	74	71	64	60	55	49	40	30	11	5	2	0
Sorafenib	71	67	65	60	57	55	48	43	30	24	13	7	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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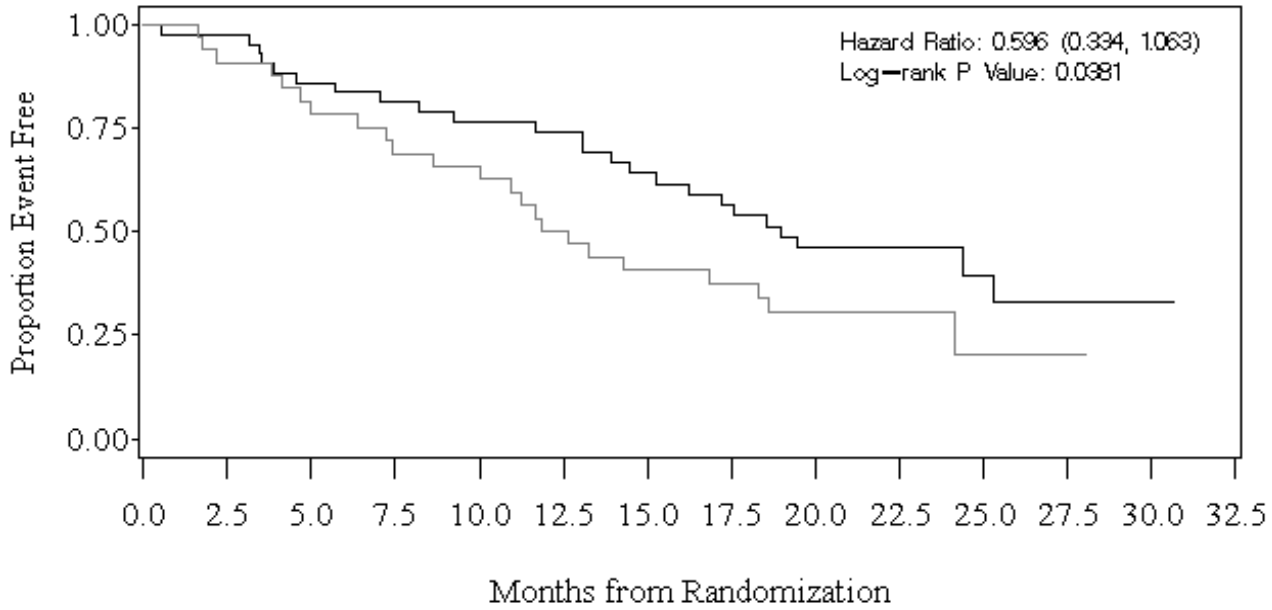
Figure 14.2.2.13.2 Subgroup Analysis of Overall Survival
Randomized Subjects with 3+ Metastatic Sites



Number at risk:

Placebo	34	30	25	22	21	16	13	12	7	4	1	1	0	0
Sorafenib	44	42	37	34	32	30	25	22	16	13	6	3	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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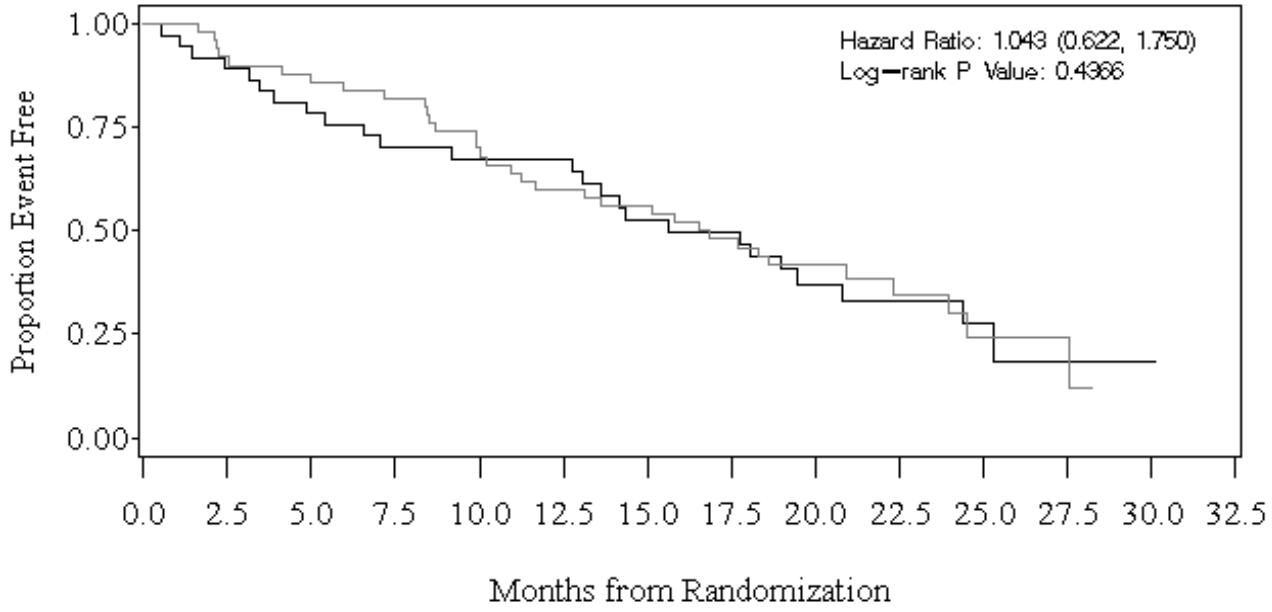
Figure 14.2.2.14.1 Subgroup Analysis of Overall Survival
Randomized Subjects With <12 Months from adjuvant treatment to metastatic disease



Number at risk:

Placebo	50	46	43	41	35	30	28	24	15	9	4	2	0	0
Sorafenib	37	33	29	25	24	23	18	17	10	7	4	1	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXI2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

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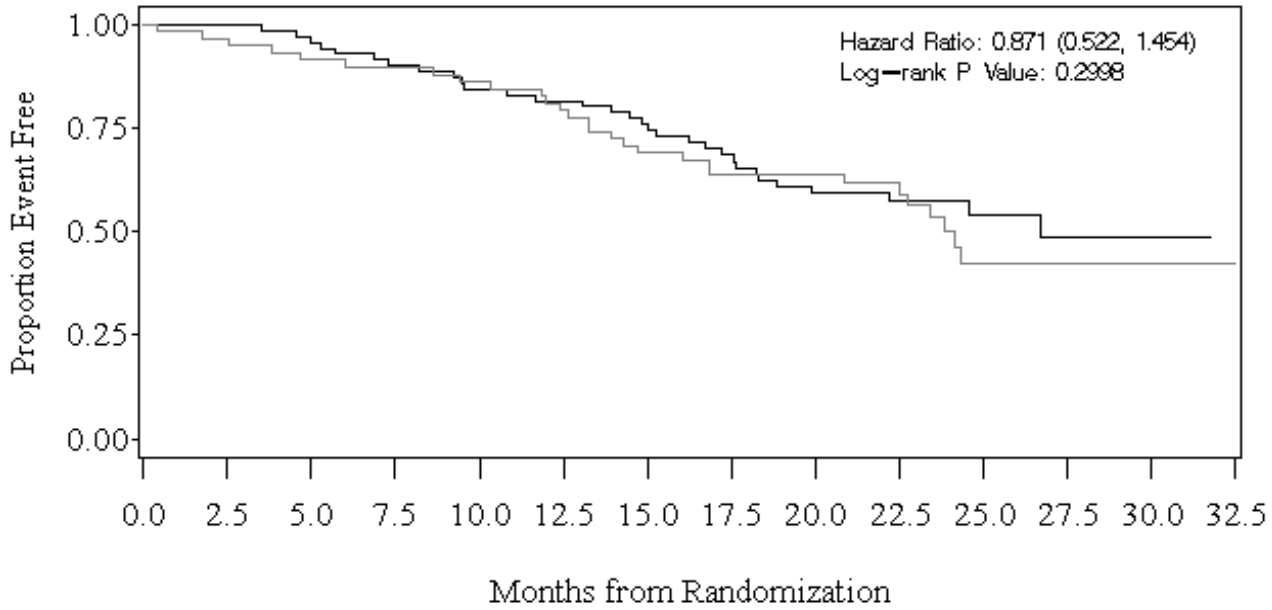
Figure 14.2.2.14.2 Subgroup Analysis of Overall Survival
Randomized Subjects with 12+ Months from adjuvant treatment to metastatic disease



Number at risk:

Placebo	60	57	53	52	50	46	40	37	32	25	8	4	2	0
Sorafenib	73	71	68	64	60	58	52	45	35	29	15	9	2	0

Source: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\Output\Figures\f_ossub.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OXL2740\OS\figpgm\f_ossub.sas (Run Date: 24SEP2010 9:56)

Overall Survival Dataset

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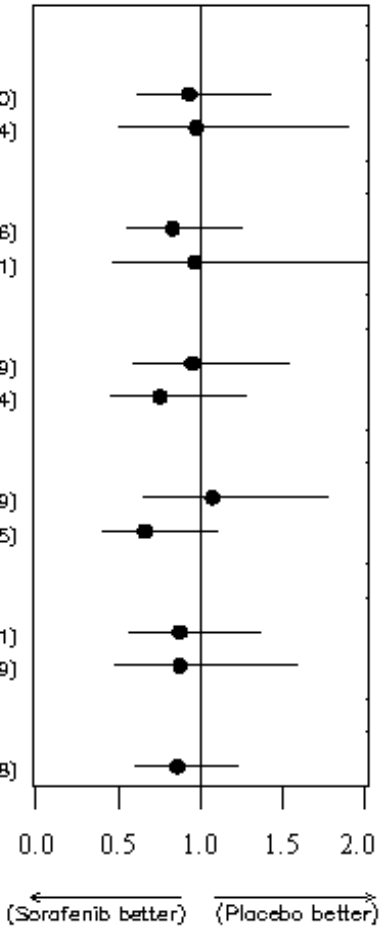
Figure 14.2.3.1: Subgroup Analysis of Overall Survival

Subgroup	Number of Patients	Overall Survival (Months) Placebo	Sorafenib	Hazard Ratio (95% CI)
Hormone receptor status				
ER+ or PgR+	173	24	24.4	0.935 (0.612,1.430)
ER– and PgR–	53	16.1	17.5	0.977 (0.504,1.894)
Visceral disease				
Yes	171	18.3	19.5	0.834 (0.558,1.246)
No	58	24.3	22.8	0.970 (0.468,2.011)
Region				
Brazil	112	18.3	18.8	0.953 (0.590,1.539)
France or Spain	117	22.7	24.4	0.757 (0.450,1.274)
Prior chemotherapy for metastatic breast cancer				
Yes	116	23.4	19	1.076 (0.651,1.779)
No	112	18.3	22.8	0.666 (0.401,1.105)
Prior anthracycline and taxane				
Yes	133	17.3	20.8	0.877 (0.565,1.361)
No	93	23.8	NR	0.879 (0.486,1.589)
Total	229	20.9	22.2	0.864 (0.608,1.228)



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Data Cutoff: 30JUN10, Download: 18AUG10, Run Date: 24SEP2010 9:56

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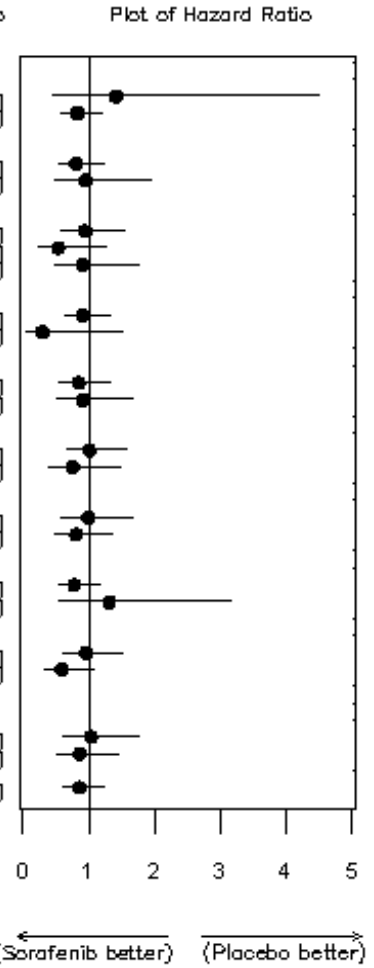
Overall Survival Dataset

Figure 14.2.3.2: Subgroup Analysis of Overall Survival

Subgroup	Number of Patients	Overall Survival (Months) Placebo	Sorafenib	Hazard Ratio (95% CI)
Age				
< 40	18	16.6	13.9	1.420 (0.448,4.498)
>=40	211	22.3	22.8	0.834 (0.578,1.208)
Age				
< 65	175	20.9	24.4	0.818 (0.544,1.229)
>=65	54	22.7	19	0.962 (0.478,1.934)
Country				
Brazil	112	18.3	18.8	0.953 (0.590,1.539)
France	37	11.9	22.8	0.543 (0.231,1.274)
Spain	80	24	24.4	0.918 (0.474,1.772)
Prior use of anthracycline				
Yes	202	20.9	19.5	0.924 (0.642,1.330)
No	25	27.6	NR	0.301 (0.080,1.510)
Prior use of taxane				
Yes	136	17.7	22.2	0.857 (0.552,1.331)
No	90	23.8	19.5	0.915 (0.506,1.655)
Estrogen receptor				
Positive	168	24.1	22.2	1.019 (0.663,1.566)
Negative	58	15.1	18.1	0.761 (0.395,1.466)
Progesterone receptor				
Positive	117	24.3	22.2	1.000 (0.595,1.682)
Negative	103	16.9	18.2	0.815 (0.489,1.359)
Measurable disease				
Yes	191	18.6	22.8	0.789 (0.536,1.161)
No	37	22.3	17.7	1.319 (0.553,3.148)
Number of metastatic sites				
< 3	150	23.4	22.8	0.966 (0.618,1.508)
>=3	78	12.6	19	0.598 (0.334,1.083)
Months from adjuvant treatment to recurrence or metastatic diagnosis				
<= 12 months	87	16.7	15.6	1.043 (0.622,1.750)
> 12 months	133	24.1	26.7	0.871 (0.522,1.454)
Total	229	20.9	22.2	0.864 (0.608,1.228)



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14.3 Safety Data Summary Tables

Progression-free Survival Dataset

Overall Survival Dataset

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	106 (94.6%)	111 (99.1%)
Skin and subcutaneous tissue disorders/Any Term	79 (70.5%)	100 (89.3%)
Palmar-plantar erythrodysaesthesia syndrome	70 (62.5%)	100 (89.3%)
Alopecia	5 (4.5%)	32 (28.6%)
Rash	9 (8.0%)	25 (22.3%)
Dry skin	8 (7.1%)	10 (8.9%)
Pruritus	5 (4.5%)	7 (6.3%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Dermatitis	5 (4.5%)	4 (3.6%)
Nail disorder	3 (2.7%)	3 (2.7%)
Erythema	5 (4.5%)	0 (0.0%)
Rash erythematous	2 (1.8%)	1 (0.9%)
Dermal cyst	0 (0.0%)	2 (1.8%)
Dermatitis acneiform	1 (0.9%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Nail bed bleeding	0 (0.0%)	2 (1.8%)
Nail toxicity	1 (0.9%)	1 (0.9%)
Onycholysis	1 (0.9%)	1 (0.9%)
Pruritus generalised	1 (0.9%)	1 (0.9%)
Rash generalised	0 (0.0%)	2 (1.8%)
Skin lesion	1 (0.9%)	1 (0.9%)
Skin toxicity	0 (0.0%)	2 (1.8%)
Skin ulcer	1 (0.9%)	1 (0.9%)
Acne	0 (0.0%)	1 (0.9%)
Blister	1 (0.9%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)
Eczema	1 (0.9%)	0 (0.0%)
Exfoliative rash	0 (0.0%)	1 (0.9%)
Hair colour changes	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Ingrowing nail	0 (0.0%)	1 (0.9%)
Nail discolouration	1 (0.9%)	0 (0.0%)
Onychalgia	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	1 (0.9%)
Rash papular	1 (0.9%)	0 (0.0%)
Scar pain	0 (0.0%)	1 (0.9%)
Skin chapped	1 (0.9%)	0 (0.0%)
Skin fissures	1 (0.9%)	0 (0.0%)
Skin nodule	0 (0.0%)	1 (0.9%)
Skin reaction	0 (0.0%)	1 (0.9%)
Subcutaneous nodule	0 (0.0%)	1 (0.9%)
Urticaria	1 (0.9%)	0 (0.0%)
Xeroderma	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Gastrointestinal disorders/Any Term	63 (56.3%)	84 (75.0%)
Diarrhoea	33 (29.5%)	59 (52.7%)
Nausea	35 (31.3%)	30 (26.8%)
Vomiting	18 (16.1%)	23 (20.5%)
Constipation	11 (9.8%)	25 (22.3%)
Abdominal pain upper	12 (10.7%)	17 (15.2%)
Abdominal pain	11 (9.8%)	11 (9.8%)
Stomatitis	7 (6.3%)	7 (6.3%)
Dyspepsia	5 (4.5%)	5 (4.5%)
Dry mouth	2 (1.8%)	3 (2.7%)
Flatulence	1 (0.9%)	3 (2.7%)
Abdominal distension	3 (2.7%)	0 (0.0%)
Gastritis	1 (0.9%)	2 (1.8%)
Haemorrhoids	2 (1.8%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Odynophagia	1 (0.9%)	2 (1.8%)
Abdominal discomfort	1 (0.9%)	1 (0.9%)
Dysphagia	0 (0.0%)	2 (1.8%)
Gastrointestinal haemorrhage	1 (0.9%)	1 (0.9%)
Intestinal obstruction	2 (1.8%)	0 (0.0%)
Mouth ulceration	1 (0.9%)	1 (0.9%)
Aerophagia	0 (0.0%)	1 (0.9%)
Anal haemorrhage	0 (0.0%)	1 (0.9%)
Aphthous stomatitis	1 (0.9%)	0 (0.0%)
Ascites	1 (0.9%)	0 (0.0%)
Cheilitis	0 (0.0%)	1 (0.9%)
Enteritis	0 (0.0%)	1 (0.9%)
Gastrointestinal pain	1 (0.9%)	0 (0.0%)
Gastrointestinal toxicity	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Gastrooesophageal reflux disease	1 (0.9%)	0 (0.0%)
Gingival bleeding	0 (0.0%)	1 (0.9%)
Gingivitis	0 (0.0%)	1 (0.9%)
Glossodynia	0 (0.0%)	1 (0.9%)
Lip oedema	0 (0.0%)	1 (0.9%)
Oesophagitis	1 (0.9%)	0 (0.0%)
Oral pain	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Pancreatitis chronic	1 (0.9%)	0 (0.0%)
Proctalgia	0 (0.0%)	1 (0.9%)
Tongue discolouration	1 (0.9%)	0 (0.0%)
Toothache	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	66 (58.9%)	71 (63.4%)
Asthenia	30 (26.8%)	27 (24.1%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Mucosal inflammation	21 (18.8%)	36 (32.1%)
Fatigue	14 (12.5%)	16 (14.3%)
Oedema peripheral	8 (7.1%)	11 (9.8%)
Pyrexia	7 (6.3%)	11 (9.8%)
Chest pain	9 (8.0%)	5 (4.5%)
Pain	5 (4.5%)	5 (4.5%)
Axillary pain	1 (0.9%)	2 (1.8%)
General physical health deterioration	2 (1.8%)	1 (0.9%)
Facial pain	1 (0.9%)	1 (0.9%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Oedema	1 (0.9%)	1 (0.9%)
Chest discomfort	0 (0.0%)	1 (0.9%)
Chills	0 (0.0%)	1 (0.9%)
Disease progression	1 (0.9%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Heparin-induced thrombocytopenia	1 (0.9%)	0 (0.0%)
Localised oedema	1 (0.9%)	0 (0.0%)
Malaise	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal ulceration	1 (0.9%)	0 (0.0%)
Secretion discharge	0 (0.0%)	1 (0.9%)
Nervous system disorders/Any Term	38 (33.9%)	39 (34.8%)
Headache	17 (15.2%)	18 (16.1%)
Paraesthesia	10 (8.9%)	14 (12.5%)
Dizziness	3 (2.7%)	7 (6.3%)
Dysgeusia	5 (4.5%)	5 (4.5%)
Neuropathy	3 (2.7%)	1 (0.9%)
Hyperaesthesia	1 (0.9%)	2 (1.8%)
Monoparesis	2 (1.8%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neuropathy peripheral	3 (2.7%)	0 (0.0%)
Peripheral sensory neuropathy	2 (1.8%)	0 (0.0%)
Somnolence	1 (0.9%)	1 (0.9%)
Amnesia	1 (0.9%)	0 (0.0%)
Cognitive disorder	0 (0.0%)	1 (0.9%)
Convulsion	0 (0.0%)	1 (0.9%)
Dysaesthesia	1 (0.9%)	0 (0.0%)
Facial palsy	1 (0.9%)	0 (0.0%)
Intracranial pressure increased	0 (0.0%)	1 (0.9%)
Migraine	1 (0.9%)	0 (0.0%)
Sciatica	1 (0.9%)	0 (0.0%)
Syncope vasovagal	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	35 (31.3%)	37 (33.0%)
Back pain	12 (10.7%)	10 (8.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Musculoskeletal pain	7 (6.3%)	13 (11.6%)
Pain in extremity	6 (5.4%)	7 (6.3%)
Arthralgia	6 (5.4%)	5 (4.5%)
Myalgia	6 (5.4%)	5 (4.5%)
Neck pain	5 (4.5%)	3 (2.7%)
Bone pain	5 (4.5%)	2 (1.8%)
Musculoskeletal chest pain	4 (3.6%)	3 (2.7%)
Muscle spasms	4 (3.6%)	2 (1.8%)
Flank pain	1 (0.9%)	1 (0.9%)
Chondropathy	0 (0.0%)	1 (0.9%)
Groin pain	1 (0.9%)	0 (0.0%)
Joint stiffness	1 (0.9%)	0 (0.0%)
Muscle contracture	0 (0.0%)	1 (0.9%)
Nodule on extremity	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Osteoporosis	0 (0.0%)	1 (0.9%)
Sensation of heaviness	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	20 (17.9%)	32 (28.6%)
Dyspnoea	13 (11.6%)	13 (11.6%)
Cough	7 (6.3%)	13 (11.6%)
Pleural effusion	2 (1.8%)	6 (5.4%)
Dysphonia	1 (0.9%)	6 (5.4%)
Productive cough	0 (0.0%)	5 (4.5%)
Respiratory failure	1 (0.9%)	3 (2.7%)
Epistaxis	1 (0.9%)	2 (1.8%)
Asthma	2 (1.8%)	0 (0.0%)
Pharyngolaryngeal pain	0 (0.0%)	2 (1.8%)
Bronchospasm	0 (0.0%)	1 (0.9%)
Dyspnoea exertional	1 (0.9%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Haemoptysis	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	1 (0.9%)
Pneumothorax	1 (0.9%)	0 (0.0%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	26 (23.2%)	25 (22.3%)
Upper respiratory tract infection	5 (4.5%)	4 (3.6%)
Influenza	4 (3.6%)	4 (3.6%)
Nasopharyngitis	2 (1.8%)	4 (3.6%)
Pneumonia	1 (0.9%)	3 (2.7%)
Urinary tract infection	2 (1.8%)	2 (1.8%)
Fungal infection	2 (1.8%)	1 (0.9%)
Sinusitis	3 (2.7%)	0 (0.0%)
Herpes zoster	2 (1.8%)	0 (0.0%)
Localised infection	1 (0.9%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Paronychia	1 (0.9%)	1 (0.9%)
Rhinitis	1 (0.9%)	1 (0.9%)
Tonsillitis	1 (0.9%)	1 (0.9%)
Folliculitis	0 (0.0%)	1 (0.9%)
Foot and mouth disease	0 (0.0%)	1 (0.9%)
Furuncle	0 (0.0%)	1 (0.9%)
Genital herpes	0 (0.0%)	1 (0.9%)
Herpes virus infection	1 (0.9%)	0 (0.0%)
Mastitis	0 (0.0%)	1 (0.9%)
Oral herpes	1 (0.9%)	0 (0.0%)
Otitis media acute	0 (0.0%)	1 (0.9%)
Pharyngitis	1 (0.9%)	0 (0.0%)
Purulent discharge	0 (0.0%)	1 (0.9%)
Pyothorax	1 (0.9%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Respiratory tract infection	1 (0.9%)	0 (0.0%)
Sepsis	0 (0.0%)	1 (0.9%)
Septic shock	1 (0.9%)	0 (0.0%)
Tooth abscess	0 (0.0%)	1 (0.9%)
Vascular disorders/Any Term	21 (18.8%)	28 (25.0%)
Hypertension	13 (11.6%)	19 (17.0%)
Hypotension	2 (1.8%)	3 (2.7%)
Haematoma	2 (1.8%)	1 (0.9%)
Deep vein thrombosis	1 (0.9%)	1 (0.9%)
Hot flush	0 (0.0%)	2 (1.8%)
Lymphoedema	2 (1.8%)	0 (0.0%)
Phlebitis	1 (0.9%)	1 (0.9%)
Flushing	0 (0.0%)	1 (0.9%)
Varicophlebitis	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Varicose ulceration	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	18 (16.1%)	25 (22.3%)
Anorexia	13 (11.6%)	22 (19.6%)
Cell death	2 (1.8%)	0 (0.0%)
Dehydration	0 (0.0%)	2 (1.8%)
Hypokalaemia	2 (1.8%)	0 (0.0%)
Decreased appetite	0 (0.0%)	1 (0.9%)
Hypercalcaemia	1 (0.9%)	0 (0.0%)
Hyperglycaemia	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Hypertriglyceridaemia	0 (0.0%)	1 (0.9%)
Hypoglycaemia	1 (0.9%)	0 (0.0%)
Hyponatraemia	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	17 (15.2%)	21 (18.8%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neutropenia	4 (3.6%)	12 (10.7%)
Anaemia	6 (5.4%)	9 (8.0%)
Thrombocytopenia	6 (5.4%)	2 (1.8%)
Leukopenia	1 (0.9%)	4 (3.6%)
Febrile neutropenia	1 (0.9%)	0 (0.0%)
Lymphadenopathy	1 (0.9%)	0 (0.0%)
Lymphopenia	0 (0.0%)	1 (0.9%)
White blood cell disorder	0 (0.0%)	1 (0.9%)
Psychiatric disorders/Any Term	13 (11.6%)	15 (13.4%)
Insomnia	6 (5.4%)	9 (8.0%)
Anxiety	5 (4.5%)	2 (1.8%)
Depression	5 (4.5%)	2 (1.8%)
Confusional state	0 (0.0%)	3 (2.7%)
Depressed mood	1 (0.9%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Investigations/Any Term	6 (5.4%)	21 (18.8%)
Weight decreased	0 (0.0%)	9 (8.0%)
Alanine aminotransferase increased	0 (0.0%)	5 (4.5%)
Aspartate aminotransferase increased	2 (1.8%)	3 (2.7%)
Blood bilirubin increased	2 (1.8%)	3 (2.7%)
Aspartate aminotransferase	0 (0.0%)	2 (1.8%)
Platelet count decreased	0 (0.0%)	2 (1.8%)
Alanine aminotransferase	0 (0.0%)	1 (0.9%)
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)
Blood amylase	0 (0.0%)	1 (0.9%)
Blood amylase increased	1 (0.9%)	0 (0.0%)
Blood creatinine increased	1 (0.9%)	0 (0.0%)
Blood triglycerides increased	0 (0.0%)	1 (0.9%)
Blood uric acid increased	1 (0.9%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Gamma-glutamyltransferase increased	1 (0.9%)	0 (0.0%)
Haemoglobin decreased	0 (0.0%)	1 (0.9%)
International normalised ratio increased	0 (0.0%)	1 (0.9%)
Lumbar puncture	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Eye disorders/Any Term	19 (17.0%)	7 (6.3%)
Conjunctivitis	8 (7.1%)	1 (0.9%)
Lacrimation increased	6 (5.4%)	0 (0.0%)
Eye irritation	3 (2.7%)	0 (0.0%)
Vision blurred	1 (0.9%)	2 (1.8%)
Dry eye	1 (0.9%)	1 (0.9%)
Eye pruritus	1 (0.9%)	0 (0.0%)
Eyelid oedema	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)
Pupils unequal	0 (0.0%)	1 (0.9%)
Scleral discolouration	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	1 (0.9%)
Visual disturbance	1 (0.9%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	8 (7.1%)	11 (9.8%)
Breast pain	1 (0.9%)	3 (2.7%)
Vaginal haemorrhage	2 (1.8%)	1 (0.9%)
Breast haemorrhage	1 (0.9%)	1 (0.9%)
Dysmenorrhoea	0 (0.0%)	2 (1.8%)
Pelvic pain	2 (1.8%)	0 (0.0%)
Vaginal discharge	1 (0.9%)	1 (0.9%)
Cervix oedema	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pruritus genital	1 (0.9%)	0 (0.0%)
Uterine polyp	0 (0.0%)	1 (0.9%)
Vaginal inflammation	0 (0.0%)	1 (0.9%)
Ear and labyrinth disorders/Any Term	8 (7.1%)	5 (4.5%)
Ear pain	3 (2.7%)	2 (1.8%)
Vertigo	3 (2.7%)	2 (1.8%)
Tinnitus	3 (2.7%)	1 (0.9%)
Cardiac disorders/Any Term	4 (3.6%)	6 (5.4%)
Palpitations	1 (0.9%)	1 (0.9%)
Tachycardia	1 (0.9%)	1 (0.9%)
Bradycardia	1 (0.9%)	0 (0.0%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pericardial effusion	0 (0.0%)	1 (0.9%)
Sinus tachycardia	0 (0.0%)	1 (0.9%)
Supraventricular tachycardia	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders/Any Term	3 (2.7%)	6 (5.4%)
Hyperbilirubinaemia	2 (1.8%)	4 (3.6%)
Cholestasis	1 (0.9%)	1 (0.9%)
Jaundice	1 (0.9%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	1 (0.9%)
Hepatic vein occlusion	0 (0.0%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	5 (4.5%)	2 (1.8%)
Metastases to central nervous system	2 (1.8%)	1 (0.9%)
Colon cancer metastatic	1 (0.9%)	0 (0.0%)
Metastases to liver	0 (0.0%)	1 (0.9%)
Metastases to meninges	1 (0.9%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Metastases to ovary	1 (0.9%)	0 (0.0%)
Injury, poisoning and procedural complications/Any Term	4 (3.6%)	2 (1.8%)
Traumatic haematoma	1 (0.9%)	1 (0.9%)
Contusion	1 (0.9%)	0 (0.0%)
Femur fracture	1 (0.9%)	0 (0.0%)
Upper limb fracture	1 (0.9%)	0 (0.0%)
Wound secretion	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	3 (2.7%)	2 (1.8%)
Haematuria	0 (0.0%)	1 (0.9%)
Renal failure	1 (0.9%)	0 (0.0%)
Ureteral disorder	1 (0.9%)	0 (0.0%)
Urinary hesitation	0 (0.0%)	1 (0.9%)
Urinary retention	1 (0.9%)	0 (0.0%)
Immune system disorders/Any Term	1 (0.9%)	2 (1.8%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hypersensitivity	0 (0.0%)	2 (1.8%)
Food allergy	1 (0.9%)	0 (0.0%)
Endocrine disorders/Any Term	0 (0.0%)	1 (0.9%)
Hypothyroidism	0 (0.0%)	1 (0.9%)
Social circumstances/Any Term	0 (0.0%)	1 (0.9%)
Drug abuser	0 (0.0%)	1 (0.9%)
Surgical and medical procedures/Any Term	1 (0.9%)	0 (0.0%)
Bone operation	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_01_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	15 (13.4%)	44 (39.3%)	38 (33.9%)	2 (1.8%)	7 (6.3%)	106 (94.6%)	2 (1.8%)	42 (37.5%)	59 (52.7%)	1 (0.9%)	7 (6.3%)	111 (99.1%)
Skin and subcutaneous tissue disorders/Any Term	35 (31.3%)	29 (25.9%)	15 (13.4%)	0 (0.0%)	0 (0.0%)	79 (70.5%)	5 (4.5%)	43 (38.4%)	52 (46.4%)	0 (0.0%)	0 (0.0%)	100 (89.3%)
Palmar-plantar erythrodysaesthesia syndrome	30 (26.8%)	25 (22.3%)	15 (13.4%)	0 (0.0%)	0 (0.0%)	70 (62.5%)	6 (5.4%)	44 (39.3%)	50 (44.6%)	0 (0.0%)	0 (0.0%)	100 (89.3%)
Alopecia	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	29 (25.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (28.6%)
Rash	6 (5.4%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	13 (11.6%)	9 (8.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	25 (22.3%)
Dry skin	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	10 (8.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Pruritus	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	6 (5.4%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Dermatitis	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Nail disorder	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dermal cyst	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Nail bed bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Rash generalised	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Skin hyperpigmentation	8 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Acne	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Dermatitis acneiform	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Exfoliative rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hair colour changes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Ingrowing nail	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Nail toxicity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Onychalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Onycholysis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pruritus generalised	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash erythematous	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Scar pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin lesion	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin nodule	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin ulcer	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Subcutaneous nodule	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Xeroderma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blister	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eczema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nail discolouration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash papular	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Skin chapped	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin fissures	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urticaria	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	34 (30.4%)	22 (19.6%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	63 (56.3%)	42 (37.5%)	32 (28.6%)	10 (8.9%)	0 (0.0%)	0 (0.0%)	84 (75.0%)
Diarrhoea	20 (17.9%)	8 (7.1%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	33 (29.5%)	37 (33.0%)	16 (14.3%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	59 (52.7%)
Nausea	30 (26.8%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (31.3%)	26 (23.2%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	30 (26.8%)
Constipation	9 (8.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (9.8%)	19 (17.0%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	25 (22.3%)
Vomiting	8 (7.1%)	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	18 (16.1%)	17 (15.2%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	23 (20.5%)
Abdominal pain upper	8 (7.1%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	11 (9.8%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	17 (15.2%)
Abdominal pain	5 (4.5%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	11 (9.8%)	7 (6.3%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	11 (9.8%)
Stomatitis	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	3 (2.7%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Dyspepsia	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Dry mouth	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Flatulence	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dysphagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Gastritis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Odynophagia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Abdominal discomfort	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Aerophagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Anal haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cheilitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Enteritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal haemorrhage	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gingival bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gingivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Glossodynia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haemorrhoids	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lip oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Mouth ulceration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oral pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Proctalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal distension	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Aphthous stomatitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ascites	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrooesophageal reflux disease	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Oesophagitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pancreatitis chronic	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue discolouration	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Toothache	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	35 (31.3%)	19 (17.0%)	10 (8.9%)	1 (0.9%)	1 (0.9%)	66 (58.9%)	31 (27.7%)	32 (28.6%)	5 (4.5%)	0 (0.0%)	3 (2.7%)	71 (63.4%)
Mucosal inflammation	15 (13.4%)	2 (1.8%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	21 (18.8%)	22 (19.6%)	13 (11.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	36 (32.1%)
Asthenia	21 (18.8%)	7 (6.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	30 (26.8%)	16 (14.3%)	11 (9.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (24.1%)
Fatigue	10 (8.9%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)	6 (5.4%)	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	16 (14.3%)
Oedema peripheral	6 (5.4%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	6 (5.4%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	11 (9.8%)
Pyrexia	5 (4.5%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	8 (7.1%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (9.8%)
Chest pain	3 (2.7%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	2 (1.8%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Pain	3 (2.7%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Axillary pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Multi-organ failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)
Chest discomfort	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Facial pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
General physical health deterioration	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oedema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Secretion discharge	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Disease progression	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Heparin-induced thrombocytopenia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Localised oedema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Malaise	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal ulceration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Nervous system disorders/Any Term	29 (25.9%)	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	38 (33.9%)	25 (22.3%)	11 (9.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	39 (34.8%)
Headache	13 (11.6%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (15.2%)	12 (10.7%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (16.1%)
Paraesthesia	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	10 (8.9%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Dizziness	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Dysgeusia	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Hyperaesthesia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Cognitive disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Convulsion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Intracranial pressure increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Monoparesis	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neuropathy	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Somnolence	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Amnesia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Dysaesthesia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Facial palsy	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Migraine	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy peripheral	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral sensory neuropathy	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sciatica	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Syncope vasovagal	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	16 (14.3%)	17 (15.2%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	35 (31.3%)	19 (17.0%)	13 (11.6%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	37 (33.0%)
Musculoskeletal pain	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	6 (5.4%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	13 (11.6%)
Back pain	7 (6.3%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	5 (4.5%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Pain in extremity	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	4 (3.6%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Arthralgia	2 (1.8%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Myalgia	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Musculoskeletal chest pain	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Neck pain	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Bone pain	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Muscle spasms	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Chondropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Flank pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Muscle contracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Nodule on extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Osteoporosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Groin pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Joint stiffness	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensation of heaviness	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	10 (8.9%)	5 (4.5%)	1 (0.9%)	1 (0.9%)	3 (2.7%)	20 (17.9%)	17 (15.2%)	7 (6.3%)	6 (5.4%)	0 (0.0%)	2 (1.8%)	32 (28.6%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Cough	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	11 (9.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.6%)
Dyspnoea	6 (5.4%)	3 (2.7%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	13 (11.6%)	4 (3.6%)	4 (3.6%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	13 (11.6%)
Dysphonia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Pleural effusion	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Productive cough	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Respiratory failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	3 (2.7%)
Epistaxis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pharyngolaryngeal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Bronchospasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haemoptysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthma	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnoea exertional	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pneumothorax	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders/Any Term	11 (9.8%)	6 (5.4%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	21 (18.8%)	11 (9.8%)	15 (13.4%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	28 (25.0%)
Hypertension	6 (5.4%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	13 (11.6%)	7 (6.3%)	11 (9.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	19 (17.0%)
Hypotension	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Hot flush	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Deep vein thrombosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Flushing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haematoma	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Phlebitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Varicophlebitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lymphoedema	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Varicose ulceration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Infections and infestations/Any Term	13 (11.6%)	10 (8.9%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	26 (23.2%)	10 (8.9%)	12 (10.7%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	25 (22.3%)
Influenza	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Nasopharyngitis	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Upper respiratory tract infection	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Pneumonia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	3 (2.7%)
Urinary tract infection	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Folliculitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Foot and mouth disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Fungal infection	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Furuncle	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Genital herpes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Localised infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Mastitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Otitis media acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Paronychia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Purulent discharge	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rhinitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Sepsis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Tonsillitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Tooth abscess	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Herpes virus infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Herpes zoster	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oral herpes	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pharyngitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyothorax	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory tract infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sinusitis	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	11 (9.8%)	3 (2.7%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	18 (16.1%)	12 (10.7%)	12 (10.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	25 (22.3%)
Anorexia	11 (9.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.6%)	12 (10.7%)	10 (8.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	22 (19.6%)
Dehydration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Decreased appetite	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperglycaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypertriglyceridaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cell death	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypercalcaemia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoglycaemia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypokalaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hyponatraemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	5 (4.5%)	4 (3.6%)	7 (6.3%)	1 (0.9%)	0 (0.0%)	17 (15.2%)	4 (3.6%)	9 (8.0%)	7 (6.3%)	1 (0.9%)	0 (0.0%)	21 (18.8%)
Neutropenia	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	6 (5.4%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	12 (10.7%)
Anaemia	3 (2.7%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	4 (3.6%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Leukopenia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	6 (5.4%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Lymphopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
White blood cell disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Febrile neutropenia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphadenopathy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations/Any Term	2 (1.8%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	9 (8.0%)	11 (9.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	21 (18.8%)
Weight decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Aspartate aminotransferase increased	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Blood bilirubin increased	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Aspartate aminotransferase	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Platelet count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Alanine aminotransferase	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood amylase	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood triglycerides increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haemoglobin decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
International normalised ratio increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lumbar puncture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blood amylase increased	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood creatinine increased	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood uric acid increased	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gamma-glutamyltransferase increased	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders/Any Term	8 (7.1%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.6%)	9 (8.0%)	4 (3.6%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	15 (13.4%)
Insomnia	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	9 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Confusional state	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	3 (2.7%)
Anxiety	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Depression	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Depressed mood	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	3 (2.7%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	5 (4.5%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	11 (9.8%)
Breast pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dysmenorrhoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Breast haemorrhage	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cervix oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Uterine polyp	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal discharge	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal haemorrhage	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pelvic pain	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pruritus genital	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye disorders/Any Term	17 (15.2%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (17.0%)	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Vision blurred	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Conjunctivitis	6 (5.4%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Dry eye	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Eyelid oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pupils unequal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Scleral discolouration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Eye irritation	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye pruritus	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lacrimation increased	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visual disturbance	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders/Any Term	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (3.6%)	1 (0.9%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Cardiac failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Palpitations	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pericardial effusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Sinus tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Supraventricular tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Tachycardia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Bradycardia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatobiliary disorders/Any Term	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	2 (1.8%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	6 (5.4%)
Hyperbilirubinaemia	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	4 (3.6%)
Cholestasis	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hepatic vein occlusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Jaundice	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Ear and labyrinth disorders/Any Term	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Ear pain	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Vertigo	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Tinnitus	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Immune system disorders/Any Term	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Food allergy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications/Any Term	2 (1.8%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Traumatic haematoma	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Wound secretion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Contusion	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Femur fracture	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Upper limb fracture	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	3 (2.7%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Metastases to central nervous system	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Metastases to liver	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Colon cancer metastatic	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metastases to meninges	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metastases to ovary	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Haematuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Urinary hesitation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Renal failure	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ureteral disorder	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urinary retention	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endocrine disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypothyroidism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Social circumstances/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Drug abuser	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Surgical and medical procedures/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bone operation	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_02_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	97 (86.6%)	108 (96.4%)
Skin and subcutaneous tissue disorders/Any Term	77 (68.8%)	100 (89.3%)
Palmar-plantar erythrodysaesthesia syndrome	70 (62.5%)	100 (89.3%)
Alopecia	4 (3.6%)	29 (25.9%)
Rash	9 (8.0%)	22 (19.6%)
Dry skin	7 (6.3%)	9 (8.0%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Pruritus	5 (4.5%)	4 (3.6%)
Nail disorder	3 (2.7%)	3 (2.7%)
Dermatitis	3 (2.7%)	2 (1.8%)
Erythema	4 (3.6%)	0 (0.0%)
Rash erythematous	2 (1.8%)	1 (0.9%)
Dermatitis acneiform	1 (0.9%)	1 (0.9%)
Nail bed bleeding	0 (0.0%)	2 (1.8%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Nail toxicity	1 (0.9%)	1 (0.9%)
Onycholysis	1 (0.9%)	1 (0.9%)
Rash generalised	0 (0.0%)	2 (1.8%)
Skin toxicity	0 (0.0%)	2 (1.8%)
Acne	0 (0.0%)	1 (0.9%)
Blister	1 (0.9%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)
Eczema	1 (0.9%)	0 (0.0%)
Exfoliative rash	0 (0.0%)	1 (0.9%)
Hair colour changes	0 (0.0%)	1 (0.9%)
Nail discolouration	1 (0.9%)	0 (0.0%)
Onychalgia	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Rash papular	1 (0.9%)	0 (0.0%)
Skin chapped	1 (0.9%)	0 (0.0%)
Skin fissures	1 (0.9%)	0 (0.0%)
Skin reaction	0 (0.0%)	1 (0.9%)
Subcutaneous nodule	0 (0.0%)	1 (0.9%)
Xeroderma	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	58 (51.8%)	75 (67.0%)
Diarrhoea	28 (25.0%)	57 (50.9%)
Nausea	32 (28.6%)	24 (21.4%)
Vomiting	14 (12.5%)	18 (16.1%)
Abdominal pain upper	10 (8.9%)	16 (14.3%)
Constipation	7 (6.3%)	14 (12.5%)
Abdominal pain	7 (6.3%)	8 (7.1%)
Stomatitis	7 (6.3%)	6 (5.4%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Dyspepsia	3 (2.7%)	4 (3.6%)
Dry mouth	2 (1.8%)	3 (2.7%)
Abdominal distension	3 (2.7%)	0 (0.0%)
Flatulence	0 (0.0%)	3 (2.7%)
Dysphagia	0 (0.0%)	2 (1.8%)
Odynophagia	0 (0.0%)	2 (1.8%)
Abdominal discomfort	1 (0.9%)	0 (0.0%)
Aerophagia	0 (0.0%)	1 (0.9%)
Aphthous stomatitis	1 (0.9%)	0 (0.0%)
Cheilitis	0 (0.0%)	1 (0.9%)
Gastritis	0 (0.0%)	1 (0.9%)
Gastrointestinal haemorrhage	1 (0.9%)	0 (0.0%)
Gastrointestinal pain	1 (0.9%)	0 (0.0%)
Gastrointestinal toxicity	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Gastrooesophageal reflux disease	1 (0.9%)	0 (0.0%)
Gingivitis	0 (0.0%)	1 (0.9%)
Glossodynia	0 (0.0%)	1 (0.9%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Lip oedema	0 (0.0%)	1 (0.9%)
Mouth ulceration	0 (0.0%)	1 (0.9%)
Oral pain	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Tongue discolouration	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	53 (47.3%)	60 (53.6%)
Mucosal inflammation	19 (17.0%)	36 (32.1%)
Asthenia	28 (25.0%)	23 (20.5%)
Fatigue	12 (10.7%)	16 (14.3%)
Oedema peripheral	3 (2.7%)	3 (2.7%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pyrexia	2 (1.8%)	3 (2.7%)
Chest pain	1 (0.9%)	1 (0.9%)
Chills	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal ulceration	1 (0.9%)	0 (0.0%)
Oedema	0 (0.0%)	1 (0.9%)
Nervous system disorders/Any Term	26 (23.2%)	26 (23.2%)
Paraesthesia	9 (8.0%)	13 (11.6%)
Headache	8 (7.1%)	9 (8.0%)
Dysgeusia	5 (4.5%)	5 (4.5%)
Neuropathy	3 (2.7%)	1 (0.9%)
Dizziness	2 (1.8%)	1 (0.9%)
Hyperaesthesia	1 (0.9%)	2 (1.8%)
Monoparesis	2 (1.8%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neuropathy peripheral	2 (1.8%)	0 (0.0%)
Dysaesthesia	1 (0.9%)	0 (0.0%)
Peripheral sensory neuropathy	1 (0.9%)	0 (0.0%)
Somnolence	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	11 (9.8%)	19 (17.0%)
Neutropenia	4 (3.6%)	11 (9.8%)
Anaemia	3 (2.7%)	8 (7.1%)
Thrombocytopenia	5 (4.5%)	2 (1.8%)
Leukopenia	0 (0.0%)	3 (2.7%)
Lymphadenopathy	1 (0.9%)	0 (0.0%)
Lymphopenia	0 (0.0%)	1 (0.9%)
White blood cell disorder	0 (0.0%)	1 (0.9%)
Vascular disorders/Any Term	12 (10.7%)	17 (15.2%)
Hypertension	10 (8.9%)	17 (15.2%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Deep vein thrombosis	1 (0.9%)	0 (0.0%)
Haematoma	1 (0.9%)	0 (0.0%)
Lymphoedema	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	10 (8.9%)	18 (16.1%)
Anorexia	9 (8.0%)	15 (13.4%)
Cell death	1 (0.9%)	0 (0.0%)
Decreased appetite	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Hypertriglyceridaemia	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	8 (7.1%)	12 (10.7%)
Myalgia	4 (3.6%)	4 (3.6%)
Musculoskeletal pain	2 (1.8%)	5 (4.5%)
Arthralgia	1 (0.9%)	2 (1.8%)
Pain in extremity	0 (0.0%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Bone pain	0 (0.0%)	1 (0.9%)
Muscle spasms	1 (0.9%)	0 (0.0%)
Neck pain	1 (0.9%)	0 (0.0%)
Eye disorders/Any Term	14 (12.5%)	5 (4.5%)
Lacrimation increased	6 (5.4%)	0 (0.0%)
Conjunctivitis	4 (3.6%)	0 (0.0%)
Vision blurred	1 (0.9%)	2 (1.8%)
Eye irritation	2 (1.8%)	0 (0.0%)
Dry eye	0 (0.0%)	1 (0.9%)
Eye pruritus	1 (0.9%)	0 (0.0%)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)
Scleral discolouration	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	1 (0.9%)
Investigations/Any Term	3 (2.7%)	14 (12.5%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Alanine aminotransferase increased	0 (0.0%)	5 (4.5%)
Weight decreased	0 (0.0%)	5 (4.5%)
Aspartate aminotransferase increased	0 (0.0%)	3 (2.7%)
Blood bilirubin increased	0 (0.0%)	3 (2.7%)
Platelet count decreased	0 (0.0%)	2 (1.8%)
Aspartate aminotransferase	0 (0.0%)	1 (0.9%)
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)
Blood amylase	0 (0.0%)	1 (0.9%)
Blood amylase increased	1 (0.9%)	0 (0.0%)
Blood creatinine increased	1 (0.9%)	0 (0.0%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	5 (4.5%)	8 (7.1%)
Dyspnoea	1 (0.9%)	4 (3.6%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Cough	2 (1.8%)	1 (0.9%)
Epistaxis	1 (0.9%)	2 (1.8%)
Bronchospasm	0 (0.0%)	1 (0.9%)
Dysphonia	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	1 (0.9%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	6 (5.4%)	4 (3.6%)
Fungal infection	2 (1.8%)	0 (0.0%)
Paronychia	1 (0.9%)	1 (0.9%)
Folliculitis	0 (0.0%)	1 (0.9%)
Foot and mouth disease	0 (0.0%)	1 (0.9%)
Herpes zoster	1 (0.9%)	0 (0.0%)
Pneumonia	0 (0.0%)	1 (0.9%)
Rhinitis	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Upper respiratory tract infection	1 (0.9%)	0 (0.0%)
Ear and labyrinth disorders/Any Term	4 (3.6%)	2 (1.8%)
Vertigo	2 (1.8%)	2 (1.8%)
Tinnitus	3 (2.7%)	0 (0.0%)
Hepatobiliary disorders/Any Term	2 (1.8%)	4 (3.6%)
Hyperbilirubinaemia	2 (1.8%)	3 (2.7%)
Cholestasis	0 (0.0%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	2 (1.8%)	4 (3.6%)
Vaginal haemorrhage	1 (0.9%)	1 (0.9%)
Breast haemorrhage	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	1 (0.9%)
Pelvic pain	1 (0.9%)	0 (0.0%)
Vaginal inflammation	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Cardiac disorders/Any Term	2 (1.8%)	1 (0.9%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Tachycardia	1 (0.9%)	0 (0.0%)
Psychiatric disorders/Any Term	1 (0.9%)	1 (0.9%)
Insomnia	1 (0.9%)	1 (0.9%)
Endocrine disorders/Any Term	0 (0.0%)	1 (0.9%)
Hypothyroidism	0 (0.0%)	1 (0.9%)
Immune system disorders/Any Term	0 (0.0%)	1 (0.9%)
Hypersensitivity	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	1 (0.9%)	0 (0.0%)
Traumatic haematoma	1 (0.9%)	0 (0.0%)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_03_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	30 (26.8%)	39 (34.8%)	25 (22.3%)	1 (0.9%)	2 (1.8%)	97 (86.6%)	1 (0.9%)	44 (39.3%)	62 (55.4%)	1 (0.9%)	0 (0.0%)	108 (96.4%)
Skin and subcutaneous tissue disorders/Any Term	34 (30.4%)	28 (25.0%)	15 (13.4%)	0 (0.0%)	0 (0.0%)	77 (68.8%)	5 (4.5%)	43 (38.4%)	52 (46.4%)	0 (0.0%)	0 (0.0%)	100 (89.3%)
Palmar-plantar erythrodysaesthesia syndrome	30 (26.8%)	25 (22.3%)	15 (13.4%)	0 (0.0%)	0 (0.0%)	70 (62.5%)	6 (5.4%)	44 (39.3%)	50 (44.6%)	0 (0.0%)	0 (0.0%)	100 (89.3%)
Alopecia	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	26 (23.2%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	29 (25.9%)
Rash	6 (5.4%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	11 (9.8%)	8 (7.1%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	22 (19.6%)
Dry skin	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	9 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Pruritus	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	3 (2.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Nail disorder	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dermatitis	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Nail bed bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Rash generalised	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Skin hyperpigmentation	8 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_aeSEV.sas (Run Date: 17JUL2009 14:24)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Acne	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Dermatitis acneiform	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Exfoliative rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hair colour changes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Nail toxicity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Onychalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Onycholysis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash erythematous	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Subcutaneous nodule	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Xeroderma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blister	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eczema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nail discolouration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash papular	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin chapped	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin fissures	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	39 (34.8%)	13 (11.6%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	58 (51.8%)	39 (34.8%)	26 (23.2%)	10 (8.9%)	0 (0.0%)	0 (0.0%)	75 (67.0%)
Diarrhoea	17 (15.2%)	6 (5.4%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	28 (25.0%)	36 (32.1%)	15 (13.4%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	57 (50.9%)
Nausea	27 (24.1%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (28.6%)	22 (19.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	24 (21.4%)
Vomiting	8 (7.1%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)	14 (12.5%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (16.1%)
Abdominal pain upper	7 (6.3%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	11 (9.8%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	16 (14.3%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Constipation	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	11 (9.8%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Abdominal pain	2 (1.8%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	8 (7.1%)
Stomatitis	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	2 (1.8%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Dyspepsia	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Dry mouth	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Flatulence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dysphagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Odynophagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Aerophagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cheilitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gingivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_aeSEV.sas (Run Date: 17JUL2009 14:24)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Glossodynia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lip oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Mouth ulceration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oral pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal discomfort	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal distension	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Aphthous stomatitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal haemorrhage	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrooesophageal reflux disease	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue discolouration	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_aeSEV.sas (Run Date: 17JUL2009 14:24)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
General disorders and administration site conditions/Any Term	37 (33.0%)	11 (9.8%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	53 (47.3%)	30 (26.8%)	27 (24.1%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	60 (53.6%)
Mucosal inflammation	14 (12.5%)	2 (1.8%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	19 (17.0%)	22 (19.6%)	13 (11.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	36 (32.1%)
Asthenia	21 (18.8%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (25.0%)	12 (10.7%)	11 (9.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	23 (20.5%)
Fatigue	9 (8.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	8 (7.1%)	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	16 (14.3%)
Oedema peripheral	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Pyrexia	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Chest pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Mucosal ulceration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders/Any Term	23 (20.5%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (23.2%)	18 (16.1%)	6 (5.4%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	26 (23.2%)
Paraesthesia	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	9 (8.0%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	13 (11.6%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Headache	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	7 (6.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Dysgeusia	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Hyperaesthesia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dizziness	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Monoparesis	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neuropathy	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Somnolence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Dysaesthesia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy peripheral	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral sensory neuropathy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	2 (1.8%)	3 (2.7%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	11 (9.8%)	4 (3.6%)	9 (8.0%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	19 (17.0%)
Neutropenia	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	5 (4.5%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	11 (9.8%)
Anaemia	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	8 (7.1%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Leukopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Lymphopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
White blood cell disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lymphadenopathy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	7 (6.3%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	9 (8.0%)	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	18 (16.1%)
Anorexia	7 (6.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	9 (8.0%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (13.4%)
Decreased appetite	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypertriglyceridaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cell death	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders/Any Term	5 (4.5%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	7 (6.3%)	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	17 (15.2%)
Hypertension	3 (2.7%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	7 (6.3%)	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	17 (15.2%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Deep vein thrombosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematoma	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphoedema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations/Any Term	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Weight decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Aspartate aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Blood bilirubin increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Platelet count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Aspartate aminotransferase	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood amylase	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood amylase increased	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood creatinine increased	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	8 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	8 (7.1%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	12 (10.7%)
Musculoskeletal pain	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Myalgia	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Arthralgia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pain in extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Bone pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Muscle spasms	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neck pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	5 (4.5%)	6 (5.4%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	8 (7.1%)
Dyspnoea	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Epistaxis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Bronchospasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cough	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Dysphonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye disorders/Any Term	13 (11.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (12.5%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Vision blurred	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dry eye	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Scleral discolouration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Conjunctivitis	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye irritation	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Eye pruritus	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lacrimation increased	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatobiliary disorders/Any Term	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Hyperbilirubinaemia	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Cholestasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Folliculitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Foot and mouth disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Paronychia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pneumonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Fungal infection	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Herpes zoster	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rhinitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Upper respiratory tract infection	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Breast haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal haemorrhage	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pelvic pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ear and labyrinth disorders/Any Term	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Vertigo	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Ear congestion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Tinnitus	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachycardia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endocrine disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypothyroidism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Immune system disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Psychiatric disorders/Any Term	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Insomnia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Traumatic haematoma	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Renal failure	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_04_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	47 (42.0%)	67 (59.8%)
Skin and subcutaneous tissue disorders/Any Term	15 (13.4%)	52 (46.4%)
Palmar-plantar erythrodysaesthesia syndrome	15 (13.4%)	50 (44.6%)
Rash	0 (0.0%)	3 (2.7%)
Blister	1 (0.9%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash erythematous	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	12 (10.7%)	8 (7.1%)
Mucosal inflammation	4 (3.6%)	1 (0.9%)
Fatigue	1 (0.9%)	2 (1.8%)
General physical health deterioration	2 (1.8%)	1 (0.9%)
Asthenia	2 (1.8%)	0 (0.0%)
Chest pain	1 (0.9%)	1 (0.9%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Oedema peripheral	1 (0.9%)	1 (0.9%)
Axillary pain	1 (0.9%)	0 (0.0%)
Disease progression	1 (0.9%)	0 (0.0%)
Facial pain	1 (0.9%)	0 (0.0%)
Heparin-induced thrombocytopenia	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Pain	1 (0.9%)	0 (0.0%)
Pyrexia	1 (0.9%)	0 (0.0%)
Gastrointestinal disorders/Any Term	7 (6.3%)	10 (8.9%)
Diarrhoea	5 (4.5%)	6 (5.4%)
Abdominal pain	1 (0.9%)	1 (0.9%)
Intestinal obstruction	2 (1.8%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_05_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Constipation	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	8 (7.1%)	8 (7.1%)
Neutropenia	3 (2.7%)	5 (4.5%)
Thrombocytopenia	5 (4.5%)	1 (0.9%)
Anaemia	1 (0.9%)	2 (1.8%)
Leukopenia	0 (0.0%)	2 (1.8%)
Febrile neutropenia	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	5 (4.5%)	8 (7.1%)
Dyspnoea	4 (3.6%)	5 (4.5%)
Pleural effusion	2 (1.8%)	3 (2.7%)
Respiratory failure	1 (0.9%)	3 (2.7%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_05_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	2 (1.8%)	5 (4.5%)
Pain in extremity	0 (0.0%)	3 (2.7%)
Musculoskeletal pain	0 (0.0%)	2 (1.8%)
Back pain	0 (0.0%)	1 (0.9%)
Groin pain	1 (0.9%)	0 (0.0%)
Musculoskeletal chest pain	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	3 (2.7%)	3 (2.7%)
Localised infection	1 (0.9%)	1 (0.9%)
Folliculitis	0 (0.0%)	1 (0.9%)
Pneumonia	0 (0.0%)	1 (0.9%)
Pyothorax	1 (0.9%)	0 (0.0%)
Sepsis	0 (0.0%)	1 (0.9%)
Septic shock	1 (0.9%)	0 (0.0%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	4 (3.6%)	2 (1.8%)
Metastases to central nervous system	2 (1.8%)	1 (0.9%)
Metastases to liver	0 (0.0%)	1 (0.9%)
Metastases to meninges	1 (0.9%)	0 (0.0%)
Metastases to ovary	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	4 (3.6%)	2 (1.8%)
Hypertension	2 (1.8%)	1 (0.9%)
Hypotension	2 (1.8%)	0 (0.0%)
Deep vein thrombosis	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	4 (3.6%)	1 (0.9%)
Cell death	2 (1.8%)	0 (0.0%)
Hypercalcaemia	1 (0.9%)	0 (0.0%)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Hypokalaemia	1 (0.9%)	0 (0.0%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hyponatraemia	1 (0.9%)	0 (0.0%)
Hepatobiliary disorders/Any Term	1 (0.9%)	3 (2.7%)
Hyperbilirubinaemia	0 (0.0%)	2 (1.8%)
Cholestasis	1 (0.9%)	0 (0.0%)
Hepatic vein occlusion	0 (0.0%)	1 (0.9%)
Jaundice	0 (0.0%)	1 (0.9%)
Investigations/Any Term	3 (2.7%)	1 (0.9%)
Aspartate aminotransferase increased	1 (0.9%)	1 (0.9%)
Blood amylase increased	1 (0.9%)	0 (0.0%)
Gamma-glutamyltransferase increased	1 (0.9%)	0 (0.0%)
Nervous system disorders/Any Term	1 (0.9%)	3 (2.7%)
Intracranial pressure increased	0 (0.0%)	1 (0.9%)
Neuropathy	0 (0.0%)	1 (0.9%)
Paraesthesia	0 (0.0%)	1 (0.9%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Syncope vasovagal	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	1 (0.9%)	1 (0.9%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure	0 (0.0%)	1 (0.9%)
Psychiatric disorders/Any Term	0 (0.0%)	2 (1.8%)
Confusional state	0 (0.0%)	2 (1.8%)
Renal and urinary disorders/Any Term	2 (1.8%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)
Ureteral disorder	1 (0.9%)	0 (0.0%)
Injury, poisoning and procedural complications/Any Term	1 (0.9%)	0 (0.0%)
Femur fracture	1 (0.9%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	0 (0.0%)	1 (0.9%)
Breast pain	0 (0.0%)	1 (0.9%)
Surgical and medical procedures/Any Term	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_05_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Bone operation	1 (0.9%)	0 (0.0%)

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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	28 (25.0%)	63 (56.3%)
Skin and subcutaneous tissue disorders/Any Term	15 (13.4%)	52 (46.4%)
Palmar-plantar erythrodysaesthesia syndrome	15 (13.4%)	50 (44.6%)
Rash	0 (0.0%)	3 (2.7%)
Blister	1 (0.9%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash erythematous	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	6 (5.4%)	10 (8.9%)
Diarrhoea	5 (4.5%)	6 (5.4%)
Abdominal pain	1 (0.9%)	1 (0.9%)
Abdominal pain upper	0 (0.0%)	1 (0.9%)
Constipation	0 (0.0%)	1 (0.9%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_06_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	6 (5.4%)	6 (5.4%)
Neutropenia	3 (2.7%)	5 (4.5%)
Thrombocytopenia	4 (3.6%)	1 (0.9%)
Anaemia	1 (0.9%)	1 (0.9%)
Leukopenia	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	5 (4.5%)	3 (2.7%)
Mucosal inflammation	3 (2.7%)	1 (0.9%)
Fatigue	1 (0.9%)	1 (0.9%)
Metaplasia	0 (0.0%)	1 (0.9%)
Oedema peripheral	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_06_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	2 (1.8%)	1 (0.9%)
Hypertension	2 (1.8%)	1 (0.9%)
Investigations/Any Term	1 (0.9%)	1 (0.9%)
Aspartate aminotransferase increased	0 (0.0%)	1 (0.9%)
Blood amylase increased	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	2 (1.8%)
Musculoskeletal pain	0 (0.0%)	1 (0.9%)
Pain in extremity	0 (0.0%)	1 (0.9%)
Nervous system disorders/Any Term	0 (0.0%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_06_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neuropathy	0 (0.0%)	1 (0.9%)
Paraesthesia	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	1 (0.9%)	0 (0.0%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Hepatobiliary disorders/Any Term	0 (0.0%)	1 (0.9%)
Hyperbilirubinaemia	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	0 (0.0%)	1 (0.9%)
Folliculitis	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_06_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.7 Incidence of On-study Deaths
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
On-study deaths	5 (4.5%)	5 (4.5%)
Cause		
Progressive disease	3 (2.7%)	2 (1.8%)
Toxicity due to study treatment (with at least one ae with outcome death)	1 (0.9%)	0 (0.0%)
Toxicity due to study treatment	1 (0.9%)	0 (0.0%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Other	0 (0.0%)	1 (0.9%)

Note: On-study death is defined as death occurred during the study treatment period or within 30 days post study treatment discontinuation.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_07_dead.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	30 (26.8%)	36 (32.1%)
Skin and subcutaneous tissue disorders/Any Term	5 (4.5%)	14 (12.5%)
Palmar-plantar erythrodysaesthesia syndrome	5 (4.5%)	14 (12.5%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	5 (4.5%)	8 (7.1%)
Pleural effusion	2 (1.8%)	4 (3.6%)
Dyspnoea	2 (1.8%)	3 (2.7%)
Respiratory failure	1 (0.9%)	2 (1.8%)
Pneumothorax	1 (0.9%)	0 (0.0%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	7 (6.3%)	5 (4.5%)
General physical health deterioration	2 (1.8%)	1 (0.9%)
Mucosal inflammation	2 (1.8%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_08_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Pyrexia	1 (0.9%)	1 (0.9%)
Asthenia	1 (0.9%)	0 (0.0%)
Disease progression	1 (0.9%)	0 (0.0%)
Facial pain	1 (0.9%)	0 (0.0%)
Heparin-induced thrombocytopenia	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Oedema peripheral	1 (0.9%)	0 (0.0%)
Gastrointestinal disorders/Any Term	7 (6.3%)	3 (2.7%)
Diarrhoea	4 (3.6%)	2 (1.8%)
Vomiting	3 (2.7%)	0 (0.0%)
Ascites	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_08_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Stomatitis	0 (0.0%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	5 (4.5%)	2 (1.8%)
Metastases to central nervous system	2 (1.8%)	1 (0.9%)
Colon cancer metastatic	1 (0.9%)	0 (0.0%)
Metastases to liver	0 (0.0%)	1 (0.9%)
Metastases to meninges	1 (0.9%)	0 (0.0%)
Metastases to ovary	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	3 (2.7%)	2 (1.8%)
Localised infection	1 (0.9%)	1 (0.9%)
Pneumonia	0 (0.0%)	1 (0.9%)
Pyothorax	1 (0.9%)	0 (0.0%)
Sepsis	0 (0.0%)	1 (0.9%)
Septic shock	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	3 (2.7%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_08_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neutropenia	1 (0.9%)	1 (0.9%)
Thrombocytopenia	2 (1.8%)	0 (0.0%)
Febrile neutropenia	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	4 (3.6%)	0 (0.0%)
Cell death	2 (1.8%)	0 (0.0%)
Hypokalaemia	2 (1.8%)	0 (0.0%)
Hypercalcaemia	1 (0.9%)	0 (0.0%)
Hyponatraemia	1 (0.9%)	0 (0.0%)
Nervous system disorders/Any Term	2 (1.8%)	2 (1.8%)
Cognitive disorder	0 (0.0%)	1 (0.9%)
Facial palsy	1 (0.9%)	0 (0.0%)
Intracranial pressure increased	0 (0.0%)	1 (0.9%)
Syncope vasovagal	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	3 (2.7%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_08_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hypotension	2 (1.8%)	0 (0.0%)
Deep vein thrombosis	0 (0.0%)	1 (0.9%)
Hypertension	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	1 (0.9%)	2 (1.8%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders/Any Term	1 (0.9%)	2 (1.8%)
Jaundice	1 (0.9%)	1 (0.9%)
Cholestasis	1 (0.9%)	0 (0.0%)
Hepatic vein occlusion	0 (0.0%)	1 (0.9%)
Investigations/Any Term	1 (0.9%)	1 (0.9%)
Aspartate aminotransferase increased	1 (0.9%)	0 (0.0%)
Lumbar puncture	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_08_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Musculoskeletal and connective tissue disorders/Any Term	1 (0.9%)	1 (0.9%)
Back pain	1 (0.9%)	0 (0.0%)
Pain in extremity	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	1 (0.9%)	1 (0.9%)
Breast pain	0 (0.0%)	1 (0.9%)
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)
Injury, poisoning and procedural complications/Any Term	1 (0.9%)	0 (0.0%)
Femur fracture	1 (0.9%)	0 (0.0%)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)
Surgical and medical procedures/Any Term	1 (0.9%)	0 (0.0%)
Bone operation	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_08_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.9 Incidence of Drug Related Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	11 (9.8%)	20 (17.9%)
Skin and subcutaneous tissue disorders/Any Term	5 (4.5%)	14 (12.5%)
Palmar-plantar erythrodysaesthesia syndrome	5 (4.5%)	14 (12.5%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	3 (2.7%)	3 (2.7%)
Diarrhoea	3 (2.7%)	2 (1.8%)
Vomiting	2 (1.8%)	0 (0.0%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Oedema peripheral	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_09_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.9 Incidence of Drug Related Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pyrexia	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	1 (0.9%)	1 (0.9%)
Neutropenia	1 (0.9%)	1 (0.9%)
Thrombocytopenia	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	1 (0.9%)	1 (0.9%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	1 (0.9%)
Dyspnoea	0 (0.0%)	1 (0.9%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	0 (0.0%)
Cell death	1 (0.9%)	0 (0.0%)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_09_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.9 Incidence of Drug Related Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Vascular disorders/Any Term	1 (0.9%)	0 (0.0%)
Hypertension	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_09_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.10 Incidence of Adverse Events Leading to Discontinuation of Study Treatment
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	9 (8.0%)	15 (13.4%)
Skin and subcutaneous tissue disorders/Any Term	2 (1.8%)	8 (7.1%)
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	8 (7.1%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	4 (3.6%)	2 (1.8%)
Diarrhoea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Asthenia	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_10_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.10 Incidence of Adverse Events Leading to Discontinuation of Study Treatment
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	1 (0.9%)	0 (0.0%)
Anaemia	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	1 (0.9%)	0 (0.0%)
Septic shock	1 (0.9%)	0 (0.0%)
Investigations/Any Term	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_10_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.10 Incidence of Adverse Events Leading to Discontinuation of Study Treatment
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Alanine aminotransferase increased	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	0 (0.0%)
Cell death	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	1 (0.9%)
Musculoskeletal pain	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	1 (0.9%)	0 (0.0%)
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_10_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ae.sas (Run Date: 17JUL2009 14:23)

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Table 14.3.11 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	8 (7.1%)	14 (12.5%)
Skin and subcutaneous tissue disorders/Any Term	2 (1.8%)	8 (7.1%)
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	8 (7.1%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	4 (3.6%)	2 (1.8%)
Diarrhoea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Asthenia	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_11_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ae.sas (Run Date: 17JUL2009 14:23)

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Table 14.3.11 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	1 (0.9%)	0 (0.0%)
Septic shock	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	0 (0.0%)
Cell death	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_11_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ae.sas (Run Date: 17JUL2009 14:23)

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Table 14.3.11 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Musculoskeletal pain	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	1 (0.9%)	0 (0.0%)
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_11_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ae.sas (Run Date: 17JUL2009 14:23)

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Table 14.3.12 Incidence of Adverse Events Leading to Discontinuation of Capecitabine
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	8 (7.1%)	14 (12.5%)
Skin and subcutaneous tissue disorders/Any Term	2 (1.8%)	7 (6.3%)
Palmar-plantar erythrodysaesthesia syndrome	2 (1.8%)	7 (6.3%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	4 (3.6%)	2 (1.8%)
Diarrhoea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Asthenia	1 (0.9%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_12_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ae.sas (Run Date: 17JUL2009 14:23)

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Table 14.3.12 Incidence of Adverse Events Leading to Discontinuation of Capecitabine
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	1 (0.9%)	0 (0.0%)
Anaemia	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	1 (0.9%)	0 (0.0%)
Septic shock	1 (0.9%)	0 (0.0%)
Investigations/Any Term	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_12_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ae.sas (Run Date: 17JUL2009 14:23)

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Table 14.3.12 Incidence of Adverse Events Leading to Discontinuation of Capecitabine
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Alanine aminotransferase increased	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	0 (0.0%)
Cell death	1 (0.9%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	1 (0.9%)
Musculoskeletal pain	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_12_ae.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_ae.sas (Run Date: 17JUL2009 14:23)

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Table 14.3.13 Incidence of Adverse Events Leading to Discontinuation of Capecitabine by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	0 (0.0%)	1 (0.9%)	5 (4.5%)	1 (0.9%)	1 (0.9%)	8 (7.1%)	0 (0.0%)	4 (3.6%)	10 (8.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Skin and subcutaneous tissue disorders/Any Term	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	0 (0.0%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Diarrhoea	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_13_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.13 Incidence of Adverse Events Leading to Discontinuation of Capecitabine by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Fatigue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthenia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Investigations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_13_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.13 Incidence of Adverse Events Leading to Discontinuation of Capecitabine by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
White blood cell count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Musculoskeletal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anaemia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cell death	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_13_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\adhoc_aeSEV.sas (Run Date: 17JUL2009 18:30)

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Table 14.3.14 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	0 (0.0%)	2 (1.8%)	4 (3.6%)	1 (0.9%)	1 (0.9%)	8 (7.1%)	0 (0.0%)	3 (2.7%)	11 (9.8%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Skin and subcutaneous tissue disorders/Any Term	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	8 (7.1%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	8 (7.1%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	0 (0.0%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Diarrhoea	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_14_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.14 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Fatigue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthenia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Musculoskeletal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_14_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\adhoc_aeSEV.sas (Run Date: 17JUL2009 18:30)

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Table 14.3.14 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cell death	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vaginal haemorrhage	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_3_14_aeSEV.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	109 (97.3%)	112 (100%)
Skin and subcutaneous tissue disorders/Any Term	84 (75.0%)	101 (90.2%)
Palmar-plantar erythrodysaesthesia syndrome	74 (66.1%)	101 (90.2%)
Alopecia	5 (4.5%)	36 (32.1%)
Rash	9 (8.0%)	25 (22.3%)
Dry skin	8 (7.1%)	11 (9.8%)
Pruritus	6 (5.4%)	7 (6.3%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Dermatitis	5 (4.5%)	4 (3.6%)
Nail disorder	4 (3.6%)	3 (2.7%)
Erythema	5 (4.5%)	0 (0.0%)
Onycholysis	2 (1.8%)	2 (1.8%)
Dermatitis acneiform	1 (0.9%)	2 (1.8%)

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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Rash erythematous	2 (1.8%)	1 (0.9%)
Rash generalised	0 (0.0%)	3 (2.7%)
Scar pain	1 (0.9%)	2 (1.8%)
Skin lesion	2 (1.8%)	1 (0.9%)
Skin toxicity	0 (0.0%)	3 (2.7%)
Dermal cyst	0 (0.0%)	2 (1.8%)
Hyperkeratosis	1 (0.9%)	1 (0.9%)
Nail bed bleeding	0 (0.0%)	2 (1.8%)
Nail toxicity	1 (0.9%)	1 (0.9%)
Skin ulcer	1 (0.9%)	1 (0.9%)
Subcutaneous nodule	0 (0.0%)	2 (1.8%)
Blister	1 (0.9%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hair colour changes	0 (0.0%)	1 (0.9%)
Hyperhidrosis	0 (0.0%)	1 (0.9%)
Ingrowing nail	0 (0.0%)	1 (0.9%)
Onychalgia	0 (0.0%)	1 (0.9%)
Pruritus generalised	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	1 (0.9%)
Rash maculo-papular	0 (0.0%)	1 (0.9%)
Rash papular	1 (0.9%)	0 (0.0%)
Rash vesicular	0 (0.0%)	1 (0.9%)
Skin chapped	1 (0.9%)	0 (0.0%)
Skin exfoliation	0 (0.0%)	1 (0.9%)
Skin fissures	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Skin hypopigmentation	0 (0.0%)	1 (0.9%)
Skin nodule	0 (0.0%)	1 (0.9%)
Urticaria	1 (0.9%)	0 (0.0%)
Venous ulcer pain	1 (0.9%)	0 (0.0%)
Xeroderma	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	64 (57.1%)	87 (77.7%)
Diarrhoea	34 (30.4%)	65 (58.0%)
Nausea	36 (32.1%)	32 (28.6%)
Vomiting	18 (16.1%)	28 (25.0%)
Constipation	12 (10.7%)	26 (23.2%)
Abdominal pain upper	13 (11.6%)	19 (17.0%)
Abdominal pain	12 (10.7%)	12 (10.7%)
Stomatitis	7 (6.3%)	10 (8.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Dyspepsia	5 (4.5%)	6 (5.4%)
Dry mouth	2 (1.8%)	3 (2.7%)
Abdominal distension	3 (2.7%)	1 (0.9%)
Flatulence	1 (0.9%)	3 (2.7%)
Gastritis	2 (1.8%)	2 (1.8%)
Odynophagia	1 (0.9%)	3 (2.7%)
Haemorrhoids	2 (1.8%)	1 (0.9%)
Mouth ulceration	1 (0.9%)	2 (1.8%)
Abdominal discomfort	1 (0.9%)	1 (0.9%)
Dysphagia	0 (0.0%)	2 (1.8%)
Gastrointestinal haemorrhage	1 (0.9%)	1 (0.9%)
Gastrooesophageal reflux disease	1 (0.9%)	1 (0.9%)
Intestinal obstruction	2 (1.8%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Aerophagia	0 (0.0%)	1 (0.9%)
Anal haemorrhage	0 (0.0%)	1 (0.9%)
Aphthous stomatitis	1 (0.9%)	0 (0.0%)
Ascites	1 (0.9%)	0 (0.0%)
Cheilitis	0 (0.0%)	1 (0.9%)
Enteritis	0 (0.0%)	1 (0.9%)
Gastrointestinal toxicity	0 (0.0%)	1 (0.9%)
Gingival bleeding	0 (0.0%)	1 (0.9%)
Gingival disorder	1 (0.9%)	0 (0.0%)
Gingivitis	0 (0.0%)	1 (0.9%)
Glossodynia	0 (0.0%)	1 (0.9%)
Lip oedema	0 (0.0%)	1 (0.9%)
Oesophagitis	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Oral pain	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Proctalgia	0 (0.0%)	1 (0.9%)
Sensitivity of teeth	1 (0.9%)	0 (0.0%)
Tongue discolouration	1 (0.9%)	0 (0.0%)
Toothache	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	69 (61.6%)	73 (65.2%)
Asthenia	31 (27.7%)	32 (28.6%)
Mucosal inflammation	23 (20.5%)	37 (33.0%)
Fatigue	14 (12.5%)	17 (15.2%)
Pyrexia	8 (7.1%)	14 (12.5%)
Chest pain	10 (8.9%)	10 (8.9%)
Oedema peripheral	9 (8.0%)	11 (9.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pain	6 (5.4%)	8 (7.1%)
Axillary pain	1 (0.9%)	2 (1.8%)
General physical health deterioration	2 (1.8%)	1 (0.9%)
Facial pain	1 (0.9%)	1 (0.9%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Chest discomfort	0 (0.0%)	1 (0.9%)
Chills	0 (0.0%)	1 (0.9%)
Disease progression	1 (0.9%)	0 (0.0%)
Face oedema	0 (0.0%)	1 (0.9%)
Heparin-induced thrombocytopenia	1 (0.9%)	0 (0.0%)
Localised oedema	1 (0.9%)	0 (0.0%)
Malaise	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Mucosal ulceration	1 (0.9%)	0 (0.0%)
Submandibular mass	0 (0.0%)	1 (0.9%)
Nervous system disorders/Any Term	40 (35.7%)	43 (38.4%)
Headache	18 (16.1%)	20 (17.9%)
Paraesthesia	10 (8.9%)	15 (13.4%)
Dizziness	4 (3.6%)	8 (7.1%)
Dysgeusia	5 (4.5%)	5 (4.5%)
Neuropathy	3 (2.7%)	1 (0.9%)
Hyperaesthesia	1 (0.9%)	2 (1.8%)
Memory impairment	1 (0.9%)	1 (0.9%)
Migraine	1 (0.9%)	1 (0.9%)
Neuropathy peripheral	2 (1.8%)	0 (0.0%)
Peripheral sensory neuropathy	2 (1.8%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Sciatica	1 (0.9%)	1 (0.9%)
Somnolence	1 (0.9%)	1 (0.9%)
Ageusia	0 (0.0%)	1 (0.9%)
Amnesia	1 (0.9%)	0 (0.0%)
Aphonia	1 (0.9%)	0 (0.0%)
Cognitive disorder	0 (0.0%)	1 (0.9%)
Convulsion	0 (0.0%)	1 (0.9%)
Cranial neuropathy	1 (0.9%)	0 (0.0%)
Dysaesthesia	1 (0.9%)	0 (0.0%)
Facial palsy	1 (0.9%)	0 (0.0%)
Intracranial pressure increased	0 (0.0%)	1 (0.9%)
Radicular syndrome	0 (0.0%)	1 (0.9%)
Syncope vasovagal	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Musculoskeletal and connective tissue disorders/Any Term	39 (34.8%)	43 (38.4%)
Back pain	13 (11.6%)	13 (11.6%)
Pain in extremity	9 (8.0%)	12 (10.7%)
Arthralgia	7 (6.3%)	9 (8.0%)
Musculoskeletal pain	4 (3.6%)	9 (8.0%)
Myalgia	6 (5.4%)	5 (4.5%)
Bone pain	6 (5.4%)	4 (3.6%)
Musculoskeletal chest pain	6 (5.4%)	3 (2.7%)
Neck pain	5 (4.5%)	4 (3.6%)
Muscle spasms	4 (3.6%)	3 (2.7%)
Flank pain	1 (0.9%)	1 (0.9%)
Groin pain	1 (0.9%)	0 (0.0%)
Joint stiffness	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Limb discomfort	1 (0.9%)	0 (0.0%)
Muscle contracture	0 (0.0%)	1 (0.9%)
Nodule on extremity	0 (0.0%)	1 (0.9%)
Osteoporosis	0 (0.0%)	1 (0.9%)
Sensation of heaviness	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	24 (21.4%)	38 (33.9%)
Dyspnoea	14 (12.5%)	14 (12.5%)
Cough	9 (8.0%)	16 (14.3%)
Pleural effusion	3 (2.7%)	8 (7.1%)
Dysphonia	1 (0.9%)	7 (6.3%)
Epistaxis	1 (0.9%)	4 (3.6%)
Productive cough	0 (0.0%)	5 (4.5%)
Respiratory failure	1 (0.9%)	2 (1.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Asthma	2 (1.8%)	0 (0.0%)
Pharyngolaryngeal pain	0 (0.0%)	2 (1.8%)
Bronchospasm	0 (0.0%)	1 (0.9%)
Haemoptysis	0 (0.0%)	1 (0.9%)
Increased bronchial secretion	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	1 (0.9%)
Pneumothorax	1 (0.9%)	0 (0.0%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Rhinitis allergic	1 (0.9%)	0 (0.0%)
Throat irritation	0 (0.0%)	1 (0.9%)
Tracheal stenosis	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	30 (26.8%)	29 (25.9%)
Influenza	6 (5.4%)	6 (5.4%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Upper respiratory tract infection	5 (4.5%)	5 (4.5%)
Nasopharyngitis	2 (1.8%)	4 (3.6%)
Urinary tract infection	4 (3.6%)	2 (1.8%)
Pneumonia	1 (0.9%)	4 (3.6%)
Rhinitis	2 (1.8%)	2 (1.8%)
Herpes zoster	2 (1.8%)	1 (0.9%)
Localised infection	1 (0.9%)	2 (1.8%)
Paronychia	1 (0.9%)	2 (1.8%)
Sinusitis	3 (2.7%)	0 (0.0%)
Bronchopneumonia	1 (0.9%)	1 (0.9%)
Fungal infection	1 (0.9%)	1 (0.9%)
Pharyngitis	1 (0.9%)	1 (0.9%)
Respiratory tract infection	1 (0.9%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Septic shock	1 (0.9%)	1 (0.9%)
Tonsillitis	1 (0.9%)	1 (0.9%)
Acarodermatitis	0 (0.0%)	1 (0.9%)
Cellulitis	0 (0.0%)	1 (0.9%)
Folliculitis	0 (0.0%)	1 (0.9%)
Furuncle	0 (0.0%)	1 (0.9%)
Genital herpes	0 (0.0%)	1 (0.9%)
Gingival abscess	0 (0.0%)	1 (0.9%)
Herpes virus infection	1 (0.9%)	0 (0.0%)
Labyrinthitis	0 (0.0%)	1 (0.9%)
Mastitis	0 (0.0%)	1 (0.9%)
Onychomycosis	1 (0.9%)	0 (0.0%)
Oral herpes	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Otitis media acute	0 (0.0%)	1 (0.9%)
Postoperative wound infection	0 (0.0%)	1 (0.9%)
Pyothorax	1 (0.9%)	0 (0.0%)
Sepsis	0 (0.0%)	1 (0.9%)
Tinea pedis	1 (0.9%)	0 (0.0%)
Tooth abscess	0 (0.0%)	1 (0.9%)
Tooth infection	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	19 (17.0%)	32 (28.6%)
Anorexia	13 (11.6%)	25 (22.3%)
Decreased appetite	2 (1.8%)	1 (0.9%)
Dehydration	0 (0.0%)	3 (2.7%)
Cell death	2 (1.8%)	0 (0.0%)
Hypertriglyceridaemia	0 (0.0%)	2 (1.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hypokalaemia	2 (1.8%)	0 (0.0%)
Diabetes mellitus	0 (0.0%)	1 (0.9%)
Hypercalcaemia	1 (0.9%)	0 (0.0%)
Hyperglycaemia	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Hypoalbuminaemia	0 (0.0%)	1 (0.9%)
Hypoglycaemia	1 (0.9%)	0 (0.0%)
Hyponatraemia	1 (0.9%)	0 (0.0%)
Hypophosphataemia	0 (0.0%)	1 (0.9%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Vascular disorders/Any Term	21 (18.8%)	29 (25.9%)
Hypertension	13 (11.6%)	20 (17.9%)
Hypotension	2 (1.8%)	3 (2.7%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_01_ae_te.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Deep vein thrombosis	1 (0.9%)	2 (1.8%)
Haematoma	2 (1.8%)	1 (0.9%)
Hot flush	0 (0.0%)	2 (1.8%)
Lymphoedema	2 (1.8%)	0 (0.0%)
Phlebitis	1 (0.9%)	1 (0.9%)
Flushing	0 (0.0%)	1 (0.9%)
Hypertensive crisis	1 (0.9%)	0 (0.0%)
Varicophlebitis	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	17 (15.2%)	26 (23.2%)
Anaemia	6 (5.4%)	12 (10.7%)
Neutropenia	4 (3.6%)	14 (12.5%)
Thrombocytopenia	6 (5.4%)	3 (2.7%)
Leukopenia	1 (0.9%)	4 (3.6%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Lymphopenia	0 (0.0%)	2 (1.8%)
Febrile neutropenia	1 (0.9%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Lymphadenitis	0 (0.0%)	1 (0.9%)
Lymphadenopathy	1 (0.9%)	0 (0.0%)
Investigations/Any Term	7 (6.3%)	24 (21.4%)
Weight decreased	0 (0.0%)	11 (9.8%)
Blood bilirubin increased	3 (2.7%)	3 (2.7%)
Alanine aminotransferase increased	0 (0.0%)	5 (4.5%)
Aspartate aminotransferase increased	2 (1.8%)	3 (2.7%)
Platelet count decreased	0 (0.0%)	3 (2.7%)
Aspartate aminotransferase abnormal	0 (0.0%)	2 (1.8%)
Blood amylase increased	2 (1.8%)	0 (0.0%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Haemoglobin decreased	0 (0.0%)	2 (1.8%)
White blood cell count decreased	0 (0.0%)	2 (1.8%)
Alanine aminotransferase abnormal	0 (0.0%)	1 (0.9%)
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)
Blood amylase abnormal	0 (0.0%)	1 (0.9%)
Blood creatinine increased	1 (0.9%)	0 (0.0%)
Blood uric acid increased	1 (0.9%)	0 (0.0%)
Gamma-glutamyltransferase increased	1 (0.9%)	0 (0.0%)
International normalised ratio increased	0 (0.0%)	1 (0.9%)
Lipase increased	0 (0.0%)	1 (0.9%)
Lumbar puncture	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Psychiatric disorders/Any Term	14 (12.5%)	16 (14.3%)
Insomnia	6 (5.4%)	9 (8.0%)
Anxiety	5 (4.5%)	3 (2.7%)
Depression	6 (5.4%)	2 (1.8%)
Confusional state	0 (0.0%)	3 (2.7%)
Affect lability	1 (0.9%)	0 (0.0%)
Agitation	0 (0.0%)	1 (0.9%)
Eye disorders/Any Term	19 (17.0%)	9 (8.0%)
Conjunctivitis	8 (7.1%)	1 (0.9%)
Lacrimation increased	7 (6.3%)	0 (0.0%)
Dry eye	1 (0.9%)	2 (1.8%)
Eye irritation	3 (2.7%)	0 (0.0%)
Vision blurred	1 (0.9%)	2 (1.8%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Blepharitis	1 (0.9%)	0 (0.0%)
Episcleritis	0 (0.0%)	1 (0.9%)
Eye pruritus	1 (0.9%)	0 (0.0%)
Eyelid oedema	0 (0.0%)	1 (0.9%)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)
Pupils unequal	0 (0.0%)	1 (0.9%)
Scleral discolouration	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	1 (0.9%)
Visual disturbance	1 (0.9%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	7 (6.3%)	13 (11.6%)
Vaginal haemorrhage	2 (1.8%)	3 (2.7%)
Breast pain	1 (0.9%)	3 (2.7%)
Pelvic pain	2 (1.8%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Breast haemorrhage	1 (0.9%)	1 (0.9%)
Dysmenorrhoea	0 (0.0%)	2 (1.8%)
Vaginal discharge	1 (0.9%)	1 (0.9%)
Breast discharge	0 (0.0%)	1 (0.9%)
Cervix oedema	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	1 (0.9%)
Uterine polyp	0 (0.0%)	1 (0.9%)
Vaginal inflammation	0 (0.0%)	1 (0.9%)
Ear and labyrinth disorders/Any Term	7 (6.3%)	6 (5.4%)
Ear pain	3 (2.7%)	2 (1.8%)
Vertigo	3 (2.7%)	2 (1.8%)
Tinnitus	2 (1.8%)	1 (0.9%)
Ear congestion	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Injury, poisoning and procedural complications/Any Term	6 (5.4%)	7 (6.3%)
Traumatic haematoma	1 (0.9%)	1 (0.9%)
Allergic transfusion reaction	0 (0.0%)	1 (0.9%)
Contusion	1 (0.9%)	0 (0.0%)
Fall	0 (0.0%)	1 (0.9%)
Femur fracture	1 (0.9%)	0 (0.0%)
Joint injury	0 (0.0%)	1 (0.9%)
Radius fracture	1 (0.9%)	0 (0.0%)
Rib fracture	1 (0.9%)	0 (0.0%)
Therapeutic agent toxicity	0 (0.0%)	1 (0.9%)
Thermal burn	0 (0.0%)	1 (0.9%)
Upper limb fracture	1 (0.9%)	0 (0.0%)
Wound dehiscence	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Wound secretion	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	5 (4.5%)	6 (5.4%)
Palpitations	1 (0.9%)	1 (0.9%)
Pericardial effusion	1 (0.9%)	1 (0.9%)
Tachycardia	1 (0.9%)	1 (0.9%)
Bradycardia	1 (0.9%)	0 (0.0%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Sinus tachycardia	0 (0.0%)	1 (0.9%)
Supraventricular tachycardia	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders/Any Term	3 (2.7%)	6 (5.4%)
Hyperbilirubinaemia	2 (1.8%)	4 (3.6%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Cholestasis	1 (0.9%)	1 (0.9%)
Jaundice	1 (0.9%)	1 (0.9%)
Bile duct obstruction	0 (0.0%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	5 (4.5%)	4 (3.6%)
Metastases to central nervous system	2 (1.8%)	1 (0.9%)
Metastases to meninges	1 (0.9%)	1 (0.9%)
Metastases to large intestine	1 (0.9%)	0 (0.0%)
Metastases to liver	0 (0.0%)	1 (0.9%)
Metastases to ovary	1 (0.9%)	0 (0.0%)
Thyroid neoplasm	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	3 (2.7%)	4 (3.6%)
Urinary retention	1 (0.9%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Dysuria	0 (0.0%)	1 (0.9%)
Haematuria	0 (0.0%)	1 (0.9%)
Renal failure	1 (0.9%)	0 (0.0%)
Renal failure acute	0 (0.0%)	1 (0.9%)
Ureteric obstruction	1 (0.9%)	0 (0.0%)
Immune system disorders/Any Term	1 (0.9%)	2 (1.8%)
Hypersensitivity	0 (0.0%)	2 (1.8%)
Food allergy	1 (0.9%)	0 (0.0%)
Surgical and medical procedures/Any Term	1 (0.9%)	2 (1.8%)
Bone operation	1 (0.9%)	0 (0.0%)
Muscle suture	0 (0.0%)	1 (0.9%)
Rib excision	0 (0.0%)	1 (0.9%)
Tooth extraction	0 (0.0%)	1 (0.9%)

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Table 14.3.1 Incidence of Treatment-emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Endocrine disorders/Any Term	0 (0.0%)	2 (1.8%)
Hypothyroidism	0 (0.0%)	2 (1.8%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	17 (15.2%)	41 (36.6%)	42 (37.5%)	2 (1.8%)	7 (6.3%)	109 (97.3%)	3 (2.7%)	39 (34.8%)	60 (53.6%)	1 (0.9%)	9 (8.0%)	112 (100%)
Skin and subcutaneous tissue disorders/Any Term	39 (34.8%)	28 (25.0%)	17 (15.2%)	0 (0.0%)	0 (0.0%)	84 (75.0%)	7 (6.3%)	43 (38.4%)	51 (45.5%)	0 (0.0%)	0 (0.0%)	101 (90.2%)
Palmar-plantar erythrodysaesthesia syndrome	33 (29.5%)	25 (22.3%)	16 (14.3%)	0 (0.0%)	0 (0.0%)	74 (66.1%)	8 (7.1%)	44 (39.3%)	49 (43.8%)	0 (0.0%)	0 (0.0%)	101 (90.2%)
Alopecia	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	33 (29.5%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (32.1%)
Rash	6 (5.4%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	13 (11.6%)	8 (7.1%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	25 (22.3%)
Dry skin	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	11 (9.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (9.8%)
Pruritus	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	6 (5.4%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Dermatitis	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Nail disorder	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Rash generalised	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dermal cyst	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Dermatitis acneiform	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Nail bed bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Onycholysis	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Scar pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Skin hyperpigmentation	8 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Subcutaneous nodule	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Hair colour changes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperhidrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperkeratosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Ingrowing nail	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Nail toxicity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Onychalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pruritus generalised	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash erythematous	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash maculo-papular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash vesicular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin exfoliation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin hypopigmentation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin lesion	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin nodule	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin ulcer	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Xeroderma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blister	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash papular	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin chapped	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin fissures	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urticaria	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Venous ulcer pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	33 (29.5%)	24 (21.4%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	64 (57.1%)	38 (33.9%)	37 (33.0%)	12 (10.7%)	0 (0.0%)	0 (0.0%)	87 (77.7%)
Diarrhoea	20 (17.9%)	9 (8.0%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	34 (30.4%)	36 (32.1%)	22 (19.6%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	65 (58.0%)
Nausea	30 (26.8%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (32.1%)	28 (25.0%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (28.6%)
Vomiting	8 (7.1%)	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	18 (16.1%)	21 (18.8%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (25.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Constipation	10 (8.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	20 (17.9%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	26 (23.2%)
Abdominal pain upper	9 (8.0%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.6%)	13 (11.6%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	19 (17.0%)
Abdominal pain	6 (5.4%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	6 (5.4%)	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	12 (10.7%)
Stomatitis	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	6 (5.4%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Dyspepsia	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Dry mouth	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Flatulence	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Odynophagia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dysphagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Gastritis	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Mouth ulceration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Abdominal discomfort	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Abdominal distension	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Aerophagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Anal haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cheilitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Enteritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal haemorrhage	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrooesophageal reflux disease	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gingival bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gingivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Glossodynia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haemorrhoids	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Lip oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oral pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Proctalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Toothache	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Aphthous stomatitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ascites	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gingival disorder	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oesophagitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensitivity of teeth	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue discolouration	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
General disorders and administration site conditions/Any Term	35 (31.3%)	21 (18.8%)	11 (9.8%)	1 (0.9%)	1 (0.9%)	69 (61.6%)	27 (24.1%)	36 (32.1%)	7 (6.3%)	0 (0.0%)	3 (2.7%)	73 (65.2%)
Mucosal inflammation	17 (15.2%)	2 (1.8%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	23 (20.5%)	23 (20.5%)	13 (11.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	37 (33.0%)
Asthenia	19 (17.0%)	9 (8.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	31 (27.7%)	19 (17.0%)	12 (10.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	32 (28.6%)
Fatigue	10 (8.9%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)	6 (5.4%)	8 (7.1%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	17 (15.2%)
Pyrexia	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	10 (8.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Oedema peripheral	7 (6.3%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	6 (5.4%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	11 (9.8%)
Chest pain	4 (3.6%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	2 (1.8%)	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Pain	4 (3.6%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	2 (1.8%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)
Axillary pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Multi-organ failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)
Chest discomfort	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Face oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Facial pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
General physical health deterioration	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Submandibular mass	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Disease progression	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Heparin-induced thrombocytopenia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Localised oedema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Malaise	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal ulceration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	17 (15.2%)	20 (17.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	39 (34.8%)	22 (19.6%)	15 (13.4%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	43 (38.4%)
Back pain	7 (6.3%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.6%)	6 (5.4%)	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	13 (11.6%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pain in extremity	7 (6.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	7 (6.3%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	12 (10.7%)
Arthralgia	3 (2.7%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	6 (5.4%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Musculoskeletal pain	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Myalgia	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Bone pain	3 (2.7%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	3 (2.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Neck pain	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Muscle spasms	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Musculoskeletal chest pain	1 (0.9%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Flank pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Muscle contracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Nodule on extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Osteoporosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Groin pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Joint stiffness	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Limb discomfort	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensation of heaviness	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders/Any Term	29 (25.9%)	10 (8.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	40 (35.7%)	26 (23.2%)	14 (12.5%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	43 (38.4%)
Headache	13 (11.6%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (16.1%)	14 (12.5%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (17.9%)
Paraesthesia	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	11 (9.8%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	15 (13.4%)
Dizziness	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)
Dysgeusia	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Hyperaesthesia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Ageusia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cognitive disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Convulsion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Intracranial pressure increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Memory impairment	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Migraine	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neuropathy	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Radicular syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Sciatica	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Somnolence	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Amnesia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Aphonia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cranial neuropathy	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dysaesthesia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Facial palsy	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy peripheral	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral sensory neuropathy	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Syncope vasovagal	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	12 (10.7%)	6 (5.4%)	2 (1.8%)	1 (0.9%)	3 (2.7%)	24 (21.4%)	19 (17.0%)	11 (9.8%)	5 (4.5%)	0 (0.0%)	3 (2.7%)	38 (33.9%)
Cough	7 (6.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	12 (10.7%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (14.3%)
Dyspnoea	7 (6.3%)	3 (2.7%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	14 (12.5%)	4 (3.6%)	5 (4.5%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Pleural effusion	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	3 (2.7%)	1 (0.9%)	3 (2.7%)	3 (2.7%)	0 (0.0%)	1 (0.9%)	8 (7.1%)
Dysphonia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Productive cough	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Epistaxis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Pharyngolaryngeal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Respiratory failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)
Bronchospasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haemoptysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Increased bronchial secretion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Throat irritation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthma	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pneumothorax	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rhinitis allergic	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tracheal stenosis	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	11 (9.8%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	19 (17.0%)	15 (13.4%)	14 (12.5%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	32 (28.6%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Anorexia	10 (8.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.6%)	15 (13.4%)	9 (8.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	25 (22.3%)
Dehydration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Hypertriglyceridaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Decreased appetite	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Diabetes mellitus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperglycaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypoalbuminaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypophosphataemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolic acidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Cell death	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypercalcaemia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hypoglycaemia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypokalaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyponatraemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations/Any Term	14 (12.5%)	13 (11.6%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	30 (26.8%)	12 (10.7%)	12 (10.7%)	3 (2.7%)	0 (0.0%)	2 (1.8%)	29 (25.9%)
Influenza	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Upper respiratory tract infection	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Nasopharyngitis	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Pneumonia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (3.6%)
Localised infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Paronychia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Rhinitis	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Urinary tract infection	1 (0.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Acarodermatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Bronchopneumonia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cellulitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Folliculitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Fungal infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Furuncle	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Genital herpes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gingival abscess	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Herpes zoster	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Labyrinthitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Mastitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Otitis media acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pharyngitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Postoperative wound infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Respiratory tract infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Sepsis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Tonsillitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Tooth abscess	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Herpes virus infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Onychomycosis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oral herpes	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyothorax	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sinusitis	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Tinea pedis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tooth infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders/Any Term	11 (9.8%)	6 (5.4%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	21 (18.8%)	11 (9.8%)	16 (14.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	29 (25.9%)
Hypertension	6 (5.4%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	13 (11.6%)	7 (6.3%)	12 (10.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	20 (17.9%)
Hypotension	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Deep vein thrombosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Hot flush	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Flushing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haematoma	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Phlebitis	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Varicophlebitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypertensive crisis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

	Placebo (N = 112)						Sorafenib (N = 112)					
MedDRA System Organ Class/ Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Lymphoedema	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	5 (4.5%)	4 (3.6%)	7 (6.3%)	1 (0.9%)	0 (0.0%)	17 (15.2%)	4 (3.6%)	11 (9.8%)	9 (8.0%)	2 (1.8%)	0 (0.0%)	26 (23.2%)
Neutropenia	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	8 (7.1%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	14 (12.5%)
Anaemia	3 (2.7%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	4 (3.6%)	4 (3.6%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	12 (10.7%)
Leukopenia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	6 (5.4%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Lymphopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Leukocytosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Lymphadenitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Febrile neutropenia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphadenopathy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations/Any Term	2 (1.8%)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	9 (8.0%)	12 (10.7%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	24 (21.4%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Weight decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (9.8%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Aspartate aminotransferase increased	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Blood bilirubin increased	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Platelet count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Aspartate aminotransferase abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Haemoglobin decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
White blood cell count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Alanine aminotransferase abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood amylase abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
International normalised ratio increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lipase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Lumbar puncture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood amylase increased	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood creatinine increased	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood uric acid increased	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gamma-glutamyltransferase increased	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders/Any Term	8 (7.1%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (12.5%)	10 (8.9%)	4 (3.6%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	16 (14.3%)
Insomnia	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	9 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Anxiety	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Confusional state	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	3 (2.7%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Depression	3 (2.7%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Agitation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Affect lability	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	2 (1.8%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	5 (4.5%)	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	13 (11.6%)
Breast pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Vaginal haemorrhage	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dysmenorrhoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Breast discharge	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Breast haemorrhage	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cervix oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pelvic pain	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Uterine polyp	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal discharge	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Eye disorders/Any Term	16 (14.3%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (17.0%)	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Dry eye	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Vision blurred	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Conjunctivitis	6 (5.4%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Episcleritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Eyelid oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pupils unequal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Scleral discolouration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blepharitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye irritation	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye pruritus	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lacrimation increased	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visual disturbance	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications/Any Term	2 (1.8%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	2 (1.8%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	7 (6.3%)
Allergic transfusion reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Fall	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Joint injury	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Therapeutic agent toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Thermal burn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Traumatic haematoma	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Wound dehiscence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Wound secretion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Contusion	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Femur fracture	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Radius fracture	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rib fracture	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Upper limb fracture	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders/Any Term	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	5 (4.5%)	1 (0.9%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Cardiac failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Palpitations	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pericardial effusion	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Sinus tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Supraventricular tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Tachycardia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Bradycardia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ear and labyrinth disorders/Any Term	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Ear pain	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Vertigo	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Ear congestion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Tinnitus	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders/Any Term	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	2 (1.8%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	6 (5.4%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hyperbilirubinaemia	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	4 (3.6%)
Bile duct obstruction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Cholestasis	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Jaundice	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	3 (2.7%)	5 (4.5%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	4 (3.6%)
Metastases to central nervous system	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Metastases to liver	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Metastases to meninges	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Thyroid neoplasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metastases to large intestine	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metastases to ovary	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (3.6%)
Dysuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haematuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Renal failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Urinary retention	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Renal failure	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ureteric obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endocrine disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Hypothyroidism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Immune system disorders/Any Term	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Food allergy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.2 Incidence of Treatment-emergent Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Surgical and medical procedures/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Muscle suture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rib excision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Tooth extraction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Bone operation	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	100 (89.3%)	109 (97.3%)
Skin and subcutaneous tissue disorders/Any Term	81 (72.3%)	101 (90.2%)
Palmar-plantar erythrodysaesthesia syndrome	74 (66.1%)	101 (90.2%)
Alopecia	4 (3.6%)	33 (29.5%)
Rash	9 (8.0%)	22 (19.6%)
Dry skin	7 (6.3%)	10 (8.9%)
Skin hyperpigmentation	8 (7.1%)	2 (1.8%)
Pruritus	5 (4.5%)	4 (3.6%)
Nail disorder	4 (3.6%)	3 (2.7%)
Dermatitis	3 (2.7%)	2 (1.8%)
Erythema	4 (3.6%)	0 (0.0%)
Onycholysis	2 (1.8%)	2 (1.8%)
Dermatitis acneiform	1 (0.9%)	2 (1.8%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Rash erythematous	2 (1.8%)	1 (0.9%)
Rash generalised	0 (0.0%)	3 (2.7%)
Skin toxicity	0 (0.0%)	3 (2.7%)
Hyperkeratosis	1 (0.9%)	1 (0.9%)
Nail bed bleeding	0 (0.0%)	2 (1.8%)
Nail toxicity	1 (0.9%)	1 (0.9%)
Blister	1 (0.9%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)
Hair colour changes	0 (0.0%)	1 (0.9%)
Hyperhidrosis	0 (0.0%)	1 (0.9%)
Onychalgia	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Rash maculo-papular	0 (0.0%)	1 (0.9%)
Rash papular	1 (0.9%)	0 (0.0%)
Rash vesicular	0 (0.0%)	1 (0.9%)
Skin chapped	1 (0.9%)	0 (0.0%)
Skin exfoliation	0 (0.0%)	1 (0.9%)
Skin fissures	1 (0.9%)	0 (0.0%)
Skin hypopigmentation	0 (0.0%)	1 (0.9%)
Subcutaneous nodule	0 (0.0%)	1 (0.9%)
Xeroderma	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	59 (52.7%)	81 (72.3%)
Diarrhoea	29 (25.9%)	64 (57.1%)
Nausea	33 (29.5%)	26 (23.2%)
Vomiting	15 (13.4%)	21 (18.8%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Abdominal pain upper	10 (8.9%)	16 (14.3%)
Constipation	7 (6.3%)	15 (13.4%)
Abdominal pain	8 (7.1%)	8 (7.1%)
Stomatitis	7 (6.3%)	9 (8.0%)
Dyspepsia	3 (2.7%)	4 (3.6%)
Dry mouth	2 (1.8%)	3 (2.7%)
Abdominal distension	3 (2.7%)	1 (0.9%)
Flatulence	0 (0.0%)	3 (2.7%)
Dysphagia	0 (0.0%)	2 (1.8%)
Mouth ulceration	0 (0.0%)	2 (1.8%)
Odynophagia	0 (0.0%)	2 (1.8%)
Abdominal discomfort	1 (0.9%)	0 (0.0%)
Aerophagia	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Aphthous stomatitis	1 (0.9%)	0 (0.0%)
Cheilitis	0 (0.0%)	1 (0.9%)
Gastritis	0 (0.0%)	1 (0.9%)
Gastrointestinal haemorrhage	1 (0.9%)	0 (0.0%)
Gastrointestinal toxicity	0 (0.0%)	1 (0.9%)
Gastrooesophageal reflux disease	1 (0.9%)	0 (0.0%)
Gingivitis	0 (0.0%)	1 (0.9%)
Glossodynia	0 (0.0%)	1 (0.9%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Lip oedema	0 (0.0%)	1 (0.9%)
Oral pain	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Tongue discolouration	1 (0.9%)	0 (0.0%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
General disorders and administration site conditions/Any Term	55 (49.1%)	62 (55.4%)
Mucosal inflammation	21 (18.8%)	37 (33.0%)
Asthenia	29 (25.9%)	28 (25.0%)
Fatigue	12 (10.7%)	17 (15.2%)
Pyrexia	3 (2.7%)	4 (3.6%)
Oedema peripheral	3 (2.7%)	3 (2.7%)
Pain	1 (0.9%)	3 (2.7%)
Chest pain	1 (0.9%)	1 (0.9%)
Chills	0 (0.0%)	1 (0.9%)
Face oedema	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal ulceration	1 (0.9%)	0 (0.0%)
Nervous system disorders/Any Term	26 (23.2%)	26 (23.2%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Paraesthesia	9 (8.0%)	14 (12.5%)
Headache	8 (7.1%)	9 (8.0%)
Dysgeusia	5 (4.5%)	5 (4.5%)
Neuropathy	3 (2.7%)	1 (0.9%)
Dizziness	2 (1.8%)	1 (0.9%)
Hyperaesthesia	1 (0.9%)	2 (1.8%)
Neuropathy peripheral	2 (1.8%)	0 (0.0%)
Aphonia	1 (0.9%)	0 (0.0%)
Dysaesthesia	1 (0.9%)	0 (0.0%)
Memory impairment	1 (0.9%)	0 (0.0%)
Peripheral sensory neuropathy	1 (0.9%)	0 (0.0%)
Somnolence	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	11 (9.8%)	22 (19.6%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neutropenia	4 (3.6%)	13 (11.6%)
Anaemia	3 (2.7%)	10 (8.9%)
Thrombocytopenia	5 (4.5%)	3 (2.7%)
Leukopenia	0 (0.0%)	4 (3.6%)
Lymphopenia	0 (0.0%)	2 (1.8%)
Lymphadenopathy	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	10 (8.9%)	20 (17.9%)
Anorexia	8 (7.1%)	17 (15.2%)
Decreased appetite	1 (0.9%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Hypertriglyceridaemia	0 (0.0%)	1 (0.9%)
Vascular disorders/Any Term	12 (10.7%)	18 (16.1%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hypertension	10 (8.9%)	18 (16.1%)
Deep vein thrombosis	1 (0.9%)	1 (0.9%)
Haematoma	1 (0.9%)	0 (0.0%)
Lymphoedema	1 (0.9%)	0 (0.0%)
Investigations/Any Term	4 (3.6%)	17 (15.2%)
Weight decreased	0 (0.0%)	6 (5.4%)
Alanine aminotransferase increased	0 (0.0%)	5 (4.5%)
Blood bilirubin increased	1 (0.9%)	3 (2.7%)
Aspartate aminotransferase increased	0 (0.0%)	3 (2.7%)
Platelet count decreased	0 (0.0%)	3 (2.7%)
Blood amylase increased	2 (1.8%)	0 (0.0%)
White blood cell count decreased	0 (0.0%)	2 (1.8%)
Aspartate aminotransferase abnormal	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)
Blood amylase abnormal	0 (0.0%)	1 (0.9%)
Blood creatinine increased	1 (0.9%)	0 (0.0%)
Haemoglobin decreased	0 (0.0%)	1 (0.9%)
Lipase increased	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	1 (0.9%)
Eye disorders/Any Term	14 (12.5%)	6 (5.4%)
Lacrimation increased	6 (5.4%)	0 (0.0%)
Conjunctivitis	4 (3.6%)	0 (0.0%)
Vision blurred	1 (0.9%)	2 (1.8%)
Dry eye	0 (0.0%)	2 (1.8%)
Eye irritation	2 (1.8%)	0 (0.0%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Blepharitis	1 (0.9%)	0 (0.0%)
Eye pruritus	1 (0.9%)	0 (0.0%)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)
Scleral discolouration	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	7 (6.3%)	10 (8.9%)
Myalgia	4 (3.6%)	4 (3.6%)
Arthralgia	2 (1.8%)	4 (3.6%)
Pain in extremity	0 (0.0%)	3 (2.7%)
Bone pain	0 (0.0%)	1 (0.9%)
Muscle spasms	1 (0.9%)	0 (0.0%)
Neck pain	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	5 (4.5%)	8 (7.1%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Dyspnoea	1 (0.9%)	4 (3.6%)
Cough	2 (1.8%)	1 (0.9%)
Epistaxis	1 (0.9%)	2 (1.8%)
Bronchospasm	0 (0.0%)	1 (0.9%)
Dysphonia	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	1 (0.9%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	6 (5.4%)	4 (3.6%)
Paronychia	1 (0.9%)	2 (1.8%)
Folliculitis	0 (0.0%)	1 (0.9%)
Fungal infection	1 (0.9%)	0 (0.0%)
Herpes zoster	1 (0.9%)	0 (0.0%)
Pneumonia	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Rhinitis	1 (0.9%)	0 (0.0%)
Tinea pedis	1 (0.9%)	0 (0.0%)
Upper respiratory tract infection	1 (0.9%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	2 (1.8%)	5 (4.5%)
Vaginal haemorrhage	1 (0.9%)	2 (1.8%)
Breast haemorrhage	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	1 (0.9%)
Pelvic pain	1 (0.9%)	0 (0.0%)
Vaginal inflammation	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders/Any Term	2 (1.8%)	4 (3.6%)
Hyperbilirubinaemia	2 (1.8%)	3 (2.7%)
Cholestasis	0 (0.0%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Ear and labyrinth disorders/Any Term	3 (2.7%)	2 (1.8%)
Vertigo	2 (1.8%)	2 (1.8%)
Tinnitus	2 (1.8%)	0 (0.0%)
Cardiac disorders/Any Term	2 (1.8%)	1 (0.9%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Tachycardia	1 (0.9%)	0 (0.0%)
Endocrine disorders/Any Term	0 (0.0%)	2 (1.8%)
Hypothyroidism	0 (0.0%)	2 (1.8%)
Psychiatric disorders/Any Term	1 (0.9%)	1 (0.9%)
Insomnia	1 (0.9%)	1 (0.9%)
Immune system disorders/Any Term	0 (0.0%)	1 (0.9%)
Hypersensitivity	0 (0.0%)	1 (0.9%)

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Table 14.3.3 Incidence of Drug Related Treatment-Emergent Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Injury, poisoning and procedural complications/Any Term	1 (0.9%)	0 (0.0%)
Traumatic haematoma	1 (0.9%)	0 (0.0%)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	31 (27.7%)	38 (33.9%)	28 (25.0%)	1 (0.9%)	2 (1.8%)	100 (89.3%)	2 (1.8%)	43 (38.4%)	63 (56.3%)	1 (0.9%)	0 (0.0%)	109 (97.3%)
Skin and subcutaneous tissue disorders/Any Term	37 (33.0%)	27 (24.1%)	17 (15.2%)	0 (0.0%)	0 (0.0%)	81 (72.3%)	7 (6.3%)	43 (38.4%)	51 (45.5%)	0 (0.0%)	0 (0.0%)	101 (90.2%)
Palmar-plantar erythrodysaesthesia syndrome	33 (29.5%)	25 (22.3%)	16 (14.3%)	0 (0.0%)	0 (0.0%)	74 (66.1%)	8 (7.1%)	44 (39.3%)	49 (43.8%)	0 (0.0%)	0 (0.0%)	101 (90.2%)
Alopecia	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	30 (26.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	33 (29.5%)
Rash	6 (5.4%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	11 (9.8%)	7 (6.3%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	22 (19.6%)
Dry skin	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	10 (8.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Pruritus	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	3 (2.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Nail disorder	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Rash generalised	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dermatitis	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dermatitis acneiform	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Nail bed bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Onycholysis	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Skin hyperpigmentation	8 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Hair colour changes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperhidrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperkeratosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Nail toxicity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Onychalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Purpura	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash erythematous	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash macular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash maculo-papular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Rash vesicular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin exfoliation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin hypopigmentation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Subcutaneous nodule	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Xeroderma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blister	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ecchymosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash papular	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin chapped	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin fissures	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	38 (33.9%)	15 (13.4%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	59 (52.7%)	39 (34.8%)	32 (28.6%)	10 (8.9%)	0 (0.0%)	0 (0.0%)	81 (72.3%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Diarrhoea	17 (15.2%)	7 (6.3%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	29 (25.9%)	35 (31.3%)	23 (20.5%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	64 (57.1%)
Nausea	28 (25.0%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	33 (29.5%)	24 (21.4%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (23.2%)
Vomiting	8 (7.1%)	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	15 (13.4%)	17 (15.2%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (18.8%)
Abdominal pain upper	7 (6.3%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	11 (9.8%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	16 (14.3%)
Constipation	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	12 (10.7%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	15 (13.4%)
Stomatitis	6 (5.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	5 (4.5%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Abdominal pain	3 (2.7%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	8 (7.1%)
Dyspepsia	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Dry mouth	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Flatulence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Dysphagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Mouth ulceration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Odynophagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Abdominal distension	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Aerophagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cheilitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gingivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Glossodynia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lip oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Oral pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal discomfort	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Aphthous stomatitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal haemorrhage	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrooesophageal reflux disease	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue discolouration	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	37 (33.0%)	13 (11.6%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	55 (49.1%)	29 (25.9%)	29 (25.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	62 (55.4%)
Mucosal inflammation	16 (14.3%)	2 (1.8%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	21 (18.8%)	23 (20.5%)	13 (11.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	37 (33.0%)
Asthenia	20 (17.9%)	9 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	29 (25.9%)	15 (13.4%)	12 (10.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	28 (25.0%)
Fatigue	9 (8.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	8 (7.1%)	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	17 (15.2%)
Pyrexia	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Oedema peripheral	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Chest pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Face oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Mucosal ulceration	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders/Any Term	22 (19.6%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (23.2%)	19 (17.0%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	26 (23.2%)
Paraesthesia	8 (7.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)	10 (8.9%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	14 (12.5%)
Headache	7 (6.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	7 (6.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Dysgeusia	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	5 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Hyperaesthesia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dizziness	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neuropathy	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Somnolence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Aphonia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dysaesthesia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Memory impairment	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy peripheral	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral sensory neuropathy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	2 (1.8%)	3 (2.7%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	11 (9.8%)	4 (3.6%)	11 (9.8%)	6 (5.4%)	1 (0.9%)	0 (0.0%)	22 (19.6%)
Neutropenia	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	7 (6.3%)	4 (3.6%)	1 (0.9%)	0 (0.0%)	13 (11.6%)
Anaemia	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	4 (3.6%)	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Leukopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	5 (4.5%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Lymphopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Lymphadenopathy	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	7 (6.3%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	11 (9.8%)	7 (6.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	20 (17.9%)
Anorexia	6 (5.4%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.1%)	11 (9.8%)	5 (4.5%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	17 (15.2%)
Decreased appetite	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperlipidaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypertriglyceridaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cell death	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders/Any Term	5 (4.5%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	12 (10.7%)	7 (6.3%)	10 (8.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	18 (16.1%)
Hypertension	3 (2.7%)	5 (4.5%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	10 (8.9%)	7 (6.3%)	10 (8.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	18 (16.1%)
Deep vein thrombosis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haematoma	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphoedema	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Investigations/Any Term	1 (0.9%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	4 (3.6%)	10 (8.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	17 (15.2%)
Weight decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Aspartate aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Blood bilirubin increased	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Platelet count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
White blood cell count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Aspartate aminotransferase abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood amylase abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Haemoglobin decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lipase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Neutrophil count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Transaminases increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood alkaline phosphatase increased	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood amylase increased	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood creatinine increased	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	7 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (6.3%)	8 (7.1%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Arthralgia	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Myalgia	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Pain in extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Bone pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Muscle spasms	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neck pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	5 (4.5%)	6 (5.4%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	8 (7.1%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Dyspnoea	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Epistaxis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Bronchospasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cough	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Dysphonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pharyngeal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye disorders/Any Term	13 (11.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (12.5%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)
Dry eye	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Vision blurred	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Scleral discolouration	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Visual acuity reduced	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blepharitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Conjunctivitis	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye irritation	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye pruritus	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lacrimation increased	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ocular hyperaemia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders/Any Term	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)
Vaginal haemorrhage	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Breast haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Menorrhagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Vaginal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pelvic pain	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hepatobiliary disorders/Any Term	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Hyperbilirubinaemia	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
Cholestasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cytolytic hepatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	4 (3.6%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.4%)	3 (2.7%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
Paronychia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Folliculitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pneumonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Fungal infection	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Herpes zoster	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rhinitis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tinea pedis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Upper respiratory tract infection	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ear and labyrinth disorders/Any Term	3 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Vertigo	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Tinnitus	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endocrine disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Hypothyroidism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachycardia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Immune system disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.4 Incidence of Drug Related Adverse Events by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Psychiatric disorders/Any Term	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Insomnia	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Traumatic haematoma	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal failure	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	51 (45.5%)	70 (62.5%)
Skin and subcutaneous tissue disorders/Any Term	17 (15.2%)	51 (45.5%)
Palmar-plantar erythrodysaesthesia syndrome	16 (14.3%)	49 (43.8%)
Rash	0 (0.0%)	4 (3.6%)
Blister	1 (0.9%)	0 (0.0%)
Onycholysis	1 (0.9%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash erythematous	0 (0.0%)	1 (0.9%)
Rash maculo-papular	0 (0.0%)	1 (0.9%)
Rash vesicular	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	13 (11.6%)	10 (8.9%)
Mucosal inflammation	4 (3.6%)	1 (0.9%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Asthenia	3 (2.7%)	1 (0.9%)
Fatigue	1 (0.9%)	3 (2.7%)
General physical health deterioration	2 (1.8%)	1 (0.9%)
Chest pain	1 (0.9%)	1 (0.9%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Oedema peripheral	1 (0.9%)	1 (0.9%)
Axillary pain	1 (0.9%)	0 (0.0%)
Disease progression	1 (0.9%)	0 (0.0%)
Facial pain	1 (0.9%)	0 (0.0%)
Heparin-induced thrombocytopenia	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Pain	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	8 (7.1%)	11 (9.8%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Neutropenia	3 (2.7%)	5 (4.5%)
Thrombocytopenia	5 (4.5%)	1 (0.9%)
Anaemia	1 (0.9%)	4 (3.6%)
Leukopenia	0 (0.0%)	2 (1.8%)
Febrile neutropenia	1 (0.9%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	7 (6.3%)	12 (10.7%)
Diarrhoea	5 (4.5%)	7 (6.3%)
Abdominal pain	1 (0.9%)	2 (1.8%)
Intestinal obstruction	2 (1.8%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	1 (0.9%)
Constipation	0 (0.0%)	1 (0.9%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	6 (5.4%)	8 (7.1%)
Dyspnoea	4 (3.6%)	5 (4.5%)
Pleural effusion	2 (1.8%)	4 (3.6%)
Respiratory failure	1 (0.9%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Tracheal stenosis	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	3 (2.7%)	5 (4.5%)
Localised infection	1 (0.9%)	1 (0.9%)
Septic shock	1 (0.9%)	1 (0.9%)
Folliculitis	0 (0.0%)	1 (0.9%)
Pneumonia	0 (0.0%)	1 (0.9%)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Postoperative wound infection	0 (0.0%)	1 (0.9%)
Pyothorax	1 (0.9%)	0 (0.0%)
Sepsis	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	2 (1.8%)	6 (5.4%)
Pain in extremity	0 (0.0%)	3 (2.7%)
Arthralgia	0 (0.0%)	1 (0.9%)
Back pain	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	1 (0.9%)
Groin pain	1 (0.9%)	0 (0.0%)
Musculoskeletal chest pain	1 (0.9%)	0 (0.0%)
Musculoskeletal pain	0 (0.0%)	1 (0.9%)
Investigations/Any Term	4 (3.6%)	3 (2.7%)
Aspartate aminotransferase increased	1 (0.9%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_05_ae_tegr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Blood amylase increased	2 (1.8%)	0 (0.0%)
Gamma-glutamyltransferase increased	1 (0.9%)	0 (0.0%)
Lipase increased	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	4 (3.6%)	3 (2.7%)
Cell death	2 (1.8%)	0 (0.0%)
Anorexia	0 (0.0%)	1 (0.9%)
Hypercalcaemia	1 (0.9%)	0 (0.0%)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Hypokalaemia	1 (0.9%)	0 (0.0%)
Hyponatraemia	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	4 (3.6%)	2 (1.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_05_ae_tegr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Metastases to central nervous system	2 (1.8%)	1 (0.9%)
Metastases to liver	0 (0.0%)	1 (0.9%)
Metastases to meninges	1 (0.9%)	0 (0.0%)
Metastases to ovary	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	4 (3.6%)	2 (1.8%)
Hypertension	2 (1.8%)	1 (0.9%)
Hypotension	2 (1.8%)	0 (0.0%)
Deep vein thrombosis	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders/Any Term	1 (0.9%)	3 (2.7%)
Hyperbilirubinaemia	0 (0.0%)	2 (1.8%)
Bile duct obstruction	0 (0.0%)	1 (0.9%)
Cholestasis	1 (0.9%)	0 (0.0%)
Jaundice	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_05_ae_tegr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Nervous system disorders/Any Term	1 (0.9%)	3 (2.7%)
Intracranial pressure increased	0 (0.0%)	1 (0.9%)
Neuropathy	0 (0.0%)	1 (0.9%)
Paraesthesia	0 (0.0%)	1 (0.9%)
Syncope vasovagal	1 (0.9%)	0 (0.0%)
Injury, poisoning and procedural complications/Any Term	2 (1.8%)	1 (0.9%)
Femur fracture	1 (0.9%)	0 (0.0%)
Radius fracture	1 (0.9%)	0 (0.0%)
Wound dehiscence	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	2 (1.8%)	1 (0.9%)
Renal failure	1 (0.9%)	0 (0.0%)
Renal failure acute	0 (0.0%)	1 (0.9%)
Ureteric obstruction	1 (0.9%)	0 (0.0%)

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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.5 Incidence of Treatment-emergent Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Cardiac disorders/Any Term	1 (0.9%)	1 (0.9%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure	0 (0.0%)	1 (0.9%)
Psychiatric disorders/Any Term	0 (0.0%)	2 (1.8%)
Confusional state	0 (0.0%)	2 (1.8%)
Reproductive system and breast disorders/Any Term	0 (0.0%)	1 (0.9%)
Breast pain	0 (0.0%)	1 (0.9%)
Surgical and medical procedures/Any Term	1 (0.9%)	0 (0.0%)
Bone operation	1 (0.9%)	0 (0.0%)

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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	31 (27.7%)	64 (57.1%)
Skin and subcutaneous tissue disorders/Any Term	17 (15.2%)	51 (45.5%)
Palmar-plantar erythrodysaesthesia syndrome	16 (14.3%)	49 (43.8%)
Rash	0 (0.0%)	4 (3.6%)
Blister	1 (0.9%)	0 (0.0%)
Onycholysis	1 (0.9%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash erythematous	0 (0.0%)	1 (0.9%)
Rash maculo-papular	0 (0.0%)	1 (0.9%)
Rash vesicular	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	6 (5.4%)	10 (8.9%)
Diarrhoea	5 (4.5%)	6 (5.4%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_06_ae_trgr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Abdominal pain	1 (0.9%)	1 (0.9%)
Abdominal pain upper	0 (0.0%)	1 (0.9%)
Constipation	0 (0.0%)	1 (0.9%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	6 (5.4%)	7 (6.3%)
Neutropenia	3 (2.7%)	5 (4.5%)
Thrombocytopenia	4 (3.6%)	1 (0.9%)
Anaemia	1 (0.9%)	2 (1.8%)
Leukopenia	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	5 (4.5%)	4 (3.6%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_06_ae_trgr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Mucosal inflammation	3 (2.7%)	1 (0.9%)
Fatigue	1 (0.9%)	1 (0.9%)
Asthenia	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	1 (0.9%)
Oedema peripheral	1 (0.9%)	0 (0.0%)
Investigations/Any Term	2 (1.8%)	3 (2.7%)
Blood amylase increased	2 (1.8%)	0 (0.0%)
Aspartate aminotransferase increased	0 (0.0%)	1 (0.9%)
Lipase increased	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	2 (1.8%)
Anorexia	0 (0.0%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_06_ae_trgr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hyperlipidaemia	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	2 (1.8%)	1 (0.9%)
Hypertension	2 (1.8%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	2 (1.8%)
Arthralgia	0 (0.0%)	1 (0.9%)
Pain in extremity	0 (0.0%)	1 (0.9%)
Nervous system disorders/Any Term	0 (0.0%)	2 (1.8%)
Neuropathy	0 (0.0%)	1 (0.9%)
Paraesthesia	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_06_ae_trgr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.6 Incidence of Drug Related Grade 3 or Higher Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Hepatobiliary disorders/Any Term	0 (0.0%)	1 (0.9%)
Hyperbilirubinaemia	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	0 (0.0%)	1 (0.9%)
Folliculitis	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_06_ae_trgr3.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.7 Incidence of Deaths
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Total deaths	65 (58.0%)	60 (53.6%)
Deceased within 30 days post treatment	5 (4.5%)	7 (6.3%)
Progressive disease	3 (2.7%)	2 (1.8%)
Toxicity due to study treatment (with at least one ae with outcome death)	1 (0.9%)	0 (0.0%)
Toxicity due to study treatment	1 (0.9%)	0 (0.0%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Other	0 (0.0%)	3 (2.7%)
Deceased beyond 30 days post treatment	60 (53.6%)	53 (47.3%)
Progressive disease	57 (50.9%)	51 (45.5%)
Other	3 (2.7%)	2 (1.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_07_dead.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_dead.sas (Run Date: 24SEP2010 9:49)

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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	31 (27.7%)	40 (35.7%)
Skin and subcutaneous tissue disorders/Any Term	5 (4.5%)	14 (12.5%)
Palmar-plantar erythrodysaesthesia syndrome	5 (4.5%)	14 (12.5%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	6 (5.4%)	8 (7.1%)
Pleural effusion	2 (1.8%)	5 (4.5%)
Dyspnoea	2 (1.8%)	3 (2.7%)
Respiratory failure	1 (0.9%)	2 (1.8%)
Pneumothorax	1 (0.9%)	0 (0.0%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Tracheal stenosis	1 (0.9%)	0 (0.0%)
General disorders and administration site conditions/Any Term	7 (6.3%)	5 (4.5%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
General physical health deterioration	2 (1.8%)	1 (0.9%)
Mucosal inflammation	2 (1.8%)	0 (0.0%)
Multi-organ failure	0 (0.0%)	2 (1.8%)
Pyrexia	1 (0.9%)	1 (0.9%)
Asthenia	1 (0.9%)	0 (0.0%)
Disease progression	1 (0.9%)	0 (0.0%)
Facial pain	1 (0.9%)	0 (0.0%)
Heparin-induced thrombocytopenia	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Oedema peripheral	1 (0.9%)	0 (0.0%)
Gastrointestinal disorders/Any Term	7 (6.3%)	3 (2.7%)
Diarrhoea	4 (3.6%)	2 (1.8%)
Vomiting	3 (2.7%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Ascites	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Any Term	5 (4.5%)	3 (2.7%)
Metastases to central nervous system	2 (1.8%)	1 (0.9%)
Metastases to meninges	1 (0.9%)	1 (0.9%)
Metastases to large intestine	1 (0.9%)	0 (0.0%)
Metastases to liver	0 (0.0%)	1 (0.9%)
Metastases to ovary	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	3 (2.7%)	4 (3.6%)
Localised infection	1 (0.9%)	1 (0.9%)
Septic shock	1 (0.9%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Mastitis	0 (0.0%)	1 (0.9%)
Pneumonia	0 (0.0%)	1 (0.9%)
Postoperative wound infection	0 (0.0%)	1 (0.9%)
Pyothorax	1 (0.9%)	0 (0.0%)
Sepsis	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	3 (2.7%)	3 (2.7%)
Neutropenia	1 (0.9%)	1 (0.9%)
Thrombocytopenia	2 (1.8%)	0 (0.0%)
Anaemia	0 (0.0%)	1 (0.9%)
Febrile neutropenia	1 (0.9%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	4 (3.6%)	2 (1.8%)
Cell death	2 (1.8%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hypokalaemia	2 (1.8%)	0 (0.0%)
Diabetes mellitus	0 (0.0%)	1 (0.9%)
Hypercalcaemia	1 (0.9%)	0 (0.0%)
Hyponatraemia	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Nervous system disorders/Any Term	2 (1.8%)	2 (1.8%)
Cognitive disorder	0 (0.0%)	1 (0.9%)
Facial palsy	1 (0.9%)	0 (0.0%)
Intracranial pressure increased	0 (0.0%)	1 (0.9%)
Syncope vasovagal	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	3 (2.7%)	1 (0.9%)
Hypotension	2 (1.8%)	0 (0.0%)
Deep vein thrombosis	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Hypertension	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	1 (0.9%)	2 (1.8%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders/Any Term	1 (0.9%)	2 (1.8%)
Jaundice	1 (0.9%)	1 (0.9%)
Bile duct obstruction	0 (0.0%)	1 (0.9%)
Cholestasis	1 (0.9%)	0 (0.0%)
Injury, poisoning and procedural complications/Any Term	2 (1.8%)	1 (0.9%)
Femur fracture	1 (0.9%)	0 (0.0%)
Radius fracture	1 (0.9%)	0 (0.0%)
Wound dehiscence	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Reproductive system and breast disorders/Any Term	1 (0.9%)	2 (1.8%)
Breast pain	0 (0.0%)	1 (0.9%)
Uterine polyp	0 (0.0%)	1 (0.9%)
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)
Investigations/Any Term	1 (0.9%)	1 (0.9%)
Aspartate aminotransferase increased	1 (0.9%)	0 (0.0%)
Lumbar puncture	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	1 (0.9%)	1 (0.9%)
Back pain	1 (0.9%)	0 (0.0%)
Pain in extremity	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	1 (0.9%)	1 (0.9%)
Renal failure	1 (0.9%)	0 (0.0%)
Renal failure acute	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.8 Incidence of Treatment-emergent Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Surgical and medical procedures/Any Term	1 (0.9%)	0 (0.0%)
Bone operation	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_08_ae_tes.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.9 Incidence of Drug Related Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	11 (9.8%)	20 (17.9%)
Skin and subcutaneous tissue disorders/Any Term	5 (4.5%)	14 (12.5%)
Palmar-plantar erythrodysaesthesia syndrome	5 (4.5%)	14 (12.5%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	3 (2.7%)	3 (2.7%)
Diarrhoea	3 (2.7%)	2 (1.8%)
Vomiting	2 (1.8%)	0 (0.0%)
Pancreatitis acute	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_09_ae_trs.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.9 Incidence of Drug Related Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Oedema peripheral	1 (0.9%)	0 (0.0%)
Pyrexia	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	1 (0.9%)	1 (0.9%)
Neutropenia	1 (0.9%)	1 (0.9%)
Thrombocytopenia	1 (0.9%)	0 (0.0%)
Cardiac disorders/Any Term	1 (0.9%)	1 (0.9%)
Cardiac arrest	1 (0.9%)	0 (0.0%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	1 (0.9%)
Dyspnoea	0 (0.0%)	1 (0.9%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	0 (0.0%)
Cell death	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_09_ae_trs.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.9 Incidence of Drug Related Serious Adverse Events
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Renal and urinary disorders/Any Term	1 (0.9%)	0 (0.0%)
Renal failure	1 (0.9%)	0 (0.0%)
Vascular disorders/Any Term	1 (0.9%)	0 (0.0%)
Hypertension	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_09_ae_trs.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.10 Incidence of Adverse Events Leading to Discontinuation of Study Treatment
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	11 (9.8%)	22 (19.6%)
Skin and subcutaneous tissue disorders/Any Term	4 (3.6%)	10 (8.9%)
Palmar-plantar erythrodysaesthesia syndrome	4 (3.6%)	9 (8.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	4 (3.6%)	2 (1.8%)
Diarrhoea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_10_ae_both.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.10 Incidence of Adverse Events Leading to Discontinuation of Study Treatment
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Blood and lymphatic system disorders/Any Term	1 (0.9%)	3 (2.7%)
Anaemia	1 (0.9%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Neutropenia	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_10_ae_both.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.10 Incidence of Adverse Events Leading to Discontinuation of Study Treatment
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	1 (0.9%)	1 (0.9%)
Septic shock	1 (0.9%)	1 (0.9%)
Investigations/Any Term	0 (0.0%)	2 (1.8%)
Alanine aminotransferase increased	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	2 (1.8%)
Arthralgia	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_10_ae_both.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.10 Incidence of Adverse Events Leading to Discontinuation of Study Treatment
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	1 (0.9%)
Wound dehiscence	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	0 (0.0%)	1 (0.9%)
Renal failure acute	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	1 (0.9%)	0 (0.0%)
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_10_ae_both.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.11 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	10 (8.9%)	20 (17.9%)
Skin and subcutaneous tissue disorders/Any Term	4 (3.6%)	10 (8.9%)
Palmar-plantar erythrodysaesthesia syndrome	4 (3.6%)	9 (8.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	4 (3.6%)	2 (1.8%)
Diarrhoea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_11_ae_db.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.11 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders/Any Term	0 (0.0%)	2 (1.8%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	1 (0.9%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_11_ae_db.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.11 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Septic shock	1 (0.9%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	2 (1.8%)
Arthralgia	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	1 (0.9%)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	1 (0.9%)
Wound dehiscence	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	0 (0.0%)	1 (0.9%)
Renal failure acute	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_11_ae_db.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.11 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Reproductive system and breast disorders/Any Term	1 (0.9%)	0 (0.0%)
Vaginal haemorrhage	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_11_ae_db.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.12 Incidence of Adverse Events Leading to Discontinuation of Capecitabine
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
All Systems/Any Term	10 (8.9%)	22 (19.6%)
Skin and subcutaneous tissue disorders/Any Term	4 (3.6%)	10 (8.9%)
Palmar-plantar erythrodysaesthesia syndrome	4 (3.6%)	9 (8.0%)
Pruritus	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	4 (3.6%)	2 (1.8%)
Diarrhoea	3 (2.7%)	1 (0.9%)
Abdominal pain	1 (0.9%)	0 (0.0%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)
Nausea	1 (0.9%)	0 (0.0%)
Stomatitis	0 (0.0%)	1 (0.9%)
Vomiting	1 (0.9%)	0 (0.0%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_12_ae_cap.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.12 Incidence of Adverse Events Leading to Discontinuation of Capecitabine
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Blood and lymphatic system disorders/Any Term	1 (0.9%)	3 (2.7%)
Anaemia	1 (0.9%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (0.9%)
Neutropenia	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions/Any Term	2 (1.8%)	2 (1.8%)
Asthenia	1 (0.9%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.9%)
General physical health deterioration	1 (0.9%)	0 (0.0%)
Metaplasia	0 (0.0%)	1 (0.9%)
Mucosal inflammation	1 (0.9%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders/Any Term	1 (0.9%)	2 (1.8%)
Dyspnoea	0 (0.0%)	2 (1.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_12_ae_cap.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.12 Incidence of Adverse Events Leading to Discontinuation of Capecitabine
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Pulmonary embolism	1 (0.9%)	0 (0.0%)
Infections and infestations/Any Term	1 (0.9%)	1 (0.9%)
Septic shock	1 (0.9%)	1 (0.9%)
Investigations/Any Term	0 (0.0%)	2 (1.8%)
Alanine aminotransferase increased	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	1 (0.9%)	1 (0.9%)
Cell death	1 (0.9%)	0 (0.0%)
Metabolic acidosis	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	2 (1.8%)
Arthralgia	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_12_ae_cap.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.12 Incidence of Adverse Events Leading to Discontinuation of Capecitabine
by System Organ Class and Preferred Term
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)	Sorafenib (N = 112)
Cardiac disorders/Any Term	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	1 (0.9%)
Wound dehiscence	0 (0.0%)	1 (0.9%)
Renal and urinary disorders/Any Term	0 (0.0%)	1 (0.9%)
Renal failure acute	0 (0.0%)	1 (0.9%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_12_ae_cap.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_ae.sas (Run Date: 24SEP2010 9:47)

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Table 14.3.13 Incidence of Adverse Events Leading to Discontinuation of Study Treatment by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	0 (0.0%)	3 (2.7%)	6 (5.4%)	1 (0.9%)	1 (0.9%)	11 (9.8%)	0 (0.0%)	9 (8.0%)	12 (10.7%)	0 (0.0%)	1 (0.9%)	22 (19.6%)
Skin and subcutaneous tissue disorders/Any Term	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	4 (3.6%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	3 (2.7%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	3 (2.7%)
Leukocytosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Neutropenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Anaemia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	0 (0.0%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_3_13_aeSEV.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_aeSEV.sas (Run Date: 24SEP2010 9:48)

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Table 14.3.13 Incidence of Adverse Events Leading to Discontinuation of Study Treatment by Worst NCI CTC Grade
(Safety Population)

	Placebo (N = 112)						Sorafenib (N = 112)					
MedDRA System Organ Class/ Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Diarrhoea	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Fatigue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthenia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.13 Incidence of Adverse Events Leading to Discontinuation of Study Treatment by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Investigations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.13 Incidence of Adverse Events Leading to Discontinuation of Study Treatment by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Infections and infestations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Wound dehiscence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Metabolic acidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Cell death	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Renal failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vaginal haemorrhage	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.14 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	0 (0.0%)	3 (2.7%)	5 (4.5%)	1 (0.9%)	1 (0.9%)	10 (8.9%)	0 (0.0%)	8 (7.1%)	11 (9.8%)	0 (0.0%)	1 (0.9%)	20 (17.9%)
Skin and subcutaneous tissue disorders/Any Term	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	4 (3.6%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	3 (2.7%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)
Leukocytosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal disorders/Any Term	0 (0.0%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Diarrhoea	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.14 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo by Worst NCI CTC Grade
(Safety Population)

	Placebo (N = 112)						Sorafenib (N = 112)					
MedDRA System Organ Class/ Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Abdominal pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Fatigue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthenia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.14 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Bone pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Infections and infestations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Wound dehiscence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Metabolic acidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)

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Table 14.3.14 Incidence of Adverse Events Leading to Discontinuation of Sorafenib/Placebo by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Cell death	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Renal failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Reproductive system and breast disorders/Any Term	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vaginal haemorrhage	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.15 Incidence of Adverse Events Leading to Discontinuation of Capecitabine by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All Systems/Any Term	0 (0.0%)	2 (1.8%)	6 (5.4%)	1 (0.9%)	1 (0.9%)	10 (8.9%)	1 (0.9%)	8 (7.1%)	12 (10.7%)	0 (0.0%)	1 (0.9%)	22 (19.6%)
Skin and subcutaneous tissue disorders/Any Term	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	3 (2.7%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	10 (8.9%)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	1 (0.9%)	2 (1.8%)	6 (5.4%)	0 (0.0%)	0 (0.0%)	9 (8.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Skin toxicity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Blood and lymphatic system disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	3 (2.7%)
Leukocytosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Neutropenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Anaemia	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders/Any Term	0 (0.0%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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Table 14.3.15 Incidence of Adverse Events Leading to Discontinuation of Capecitabine by Worst NCI CTC Grade
(Safety Population)

	Placebo (N = 112)						Sorafenib (N = 112)					
MedDRA System Organ Class/ Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Diarrhoea	0 (0.0%)	1 (0.9%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Abdominal pain	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Fatigue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metaplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Asthenia	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General physical health deterioration	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosal inflammation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Table 14.3.15 Incidence of Adverse Events Leading to Discontinuation of Capecitabine by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Investigations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Transaminases increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
White blood cell count decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Bone pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

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Table 14.3.15 Incidence of Adverse Events Leading to Discontinuation of Capecitabine by Worst NCI CTC Grade
(Safety Population)

MedDRA System Organ Class/ Preferred Term	Placebo (N = 112)						Sorafenib (N = 112)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Infections and infestations/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Injury, poisoning and procedural complications/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Wound dehiscence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Metabolism and nutrition disorders/Any Term	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Metabolic acidosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Cell death	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders/Any Term	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Renal failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)

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Table 14.3.16 Summary of Adverse Events
(Safety Population)

	Placebo (N = 112)	Sorafenib (N = 112)
Subjects With AE --Overall	109 (97.3%)	112 (100%)
-Grade 3+	51 (45.5%)	70 (62.5%)
Subjects With Treatment related AE	100 (89.3%)	109 (97.3%)
-Grade 3+	31 (27.7%)	64 (57.1%)
Subjects With SAE --Overall	31 (27.7%)	40 (35.7%)
Treatment related SAE	11 (9.8%)	20 (17.9%)
Subjects With AE Leading to Discontinuation of Sorafenib/Placebo	10 (8.9%)	20 (17.9%)
-Grade 3+	7 (6.3%)	12 (10.7%)
Subjects With AE Leading to Discontinuation of Capecitabine	10 (8.9%)	22 (19.6%)
-Grade 3+	8 (7.1%)	13 (11.6%)
Subjects With AE Leading to Discontinuation of Study Treatment	11 (9.8%)	22 (19.6%)
-Grade 3+	8 (7.1%)	13 (11.6%)

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14.4 Laboratory Data Summary Tables

Progression-free Survival Dataset

Overall Survival Dataset

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Baseline	N	111		111	
		Mean	12.8		12.5	
		SD	1.4		1.5	
		Median	13		13	
		Min	9		8	
		Max	16		16	
	Cycle 2	N	110	109	103	103
		Mean	12.5	-0.3	13.0	0.5
		SD	1.3	0.8	1.6	0.9
		Median	12	0	13	1
		Min	8	-5	9	-2
		Max	15	2	16	4
	Cycle 3	N	92	91	94	94
		Mean	12.5	-0.3	12.8	0.3
		SD	1.4	0.9	1.4	1.0
		Median	13	0	13	0
		Min	10	-2	10	-2
		Max	15	3	16	3

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
Hemoglobin (g/dL)	Cycle 4	N	79	78	87	87
		Mean	12.6	-0.3	12.7	0.3
		SD	1.3	0.9	1.6	1.1
		Median	13	0	13	0
		Min	10	-2	9	-3
		Max	15	2	16	2
	Cycle 5	N	68	67	77	77
		Mean	12.5	-0.3	12.7	0.3
		SD	1.3	1.1	1.6	1.1
		Median	12	0	13	0
		Min	9	-2	9	-2
		Max	15	3	16	3
	Cycle 6	N	61	60	70	70
		Mean	12.5	-0.4	12.8	0.3
		SD	1.3	1.1	1.6	1.1
		Median	12	0	13	0
		Min	9	-2	9	-2
		Max	15	3	16	3

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 7	N	49	48	60	60
		Mean	12.6	-0.3	12.8	0.2
		SD	1.2	1.1	1.6	1.4
		Median	13	-1	13	0
		Min	10	-2	10	-3
		Max	16	2	16	3
	Cycle 8	N	39	38	51	51
		Mean	12.9	-0.3	13.0	0.5
		SD	1.1	1.0	1.4	1.1
		Median	13	0	13	0
		Min	10	-3	10	-1
		Max	15	2	16	3
	Cycle 9	N	34	33	43	43
		Mean	12.9	-0.2	13.1	0.4
		SD	1.3	1.1	1.4	1.0
		Median	13	0	13	1
		Min	10	-3	9	-2
		Max	15	2	16	2

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 10	N	27	27	33	33
		Mean	12.7	-0.4	13.1	0.1
		SD	1.4	1.1	1.3	0.8
		Median	13	-1	13	0
		Min	10	-3	10	-2
		Max	15	1	15	2
	Cycle 11	N	23	22	32	32
		Mean	12.6	-0.6	13.1	0.1
		SD	1.4	1.3	1.6	1.3
		Median	13	0	13	0
		Min	10	-4	8	-4
		Max	15	2	15	2
	Cycle 12	N	18	18	22	22
		Mean	12.9	-0.3	13.2	0.1
		SD	1.4	1.0	1.3	1.0
		Median	13	0	13	0
		Min	10	-2	10	-2
		Max	16	1	16	2

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 13	N	14	14	21	21
		Mean	12.8	-0.4	13.1	0.1
		SD	1.3	0.9	1.2	1.1
		Median	13	0	13	0
		Min	10	-2	11	-2
		Max	15	2	15	2
	Cycle 14	N	9	9	14	14
		Mean	12.4	-0.6	13.0	0.2
		SD	1.5	0.8	1.3	1.2
		Median	13	0	13	0
		Min	9	-2	11	-2
		Max	15	0	15	3
	Cycle 15	N	6	6	10	10
		Mean	12.6	-0.5	12.9	0.2
		SD	1.6	0.8	1.4	1.3
		Median	13	0	13	0
		Min	10	-2	11	-2
		Max	14	0	15	3

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 16	N	2	2	6	6
		Mean	13.1	0.0	12.9	0.6
		SD	0.4	1.3	1.0	1.5
		Median	13	0	13	0
		Min	13	-1	11	-1
		Max	13	1	14	3
	Cycle 17	N	1	1	2	2
		Mean	13.1	0.7	12.9	2.2
		SD	-	-	1.3	0.5
		Median	13	1	13	2
		Min	13	1	12	2
		Max	13	1	14	3
	Cycle 18	N	1	1	1	1
		Mean	13.4	1.0	12.0	2.5
		SD	-	-	-	-
		Median	13	1	12	3
		Min	13	1	12	3
		Max	13	1	12	3

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 19	N	0	0	1	1
		Mean	-	-	12.5	3.0
		SD	-	-	-	-
		Median	-	-	13	3
		Min	-	-	13	3
		Max	-	-	13	3

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Baseline	N	111		111	
		Mean	38.1		37.7	
		SD	3.8		4.3	
		Median	38		39	
		Min	26		27	
		Max	49		48	
	Cycle 2	N	110	109	103	103
		Mean	37.2	-0.9	38.7	1.1
		SD	3.8	2.5	4.7	2.8
		Median	37	-1	39	1
		Min	26	-17	26	-5
		Max	46	4	48	9
	Cycle 3	N	92	91	94	94
		Mean	37.1	-1.2	38.5	0.9
		SD	3.9	2.8	4.2	3.0
		Median	37	-1	39	1
		Min	28	-8	28	-7
		Max	45	6	48	8

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 4	N	79	78	87	87
		Mean	37.2	-1.1	37.7	0.2
		SD	3.6	2.8	4.7	3.4
		Median	37	-1	37	0
		Min	30	-6	27	-11
		Max	46	8	49	7
	Cycle 5	N	68	67	77	77
		Mean	36.7	-1.3	37.6	0.1
		SD	3.5	3.3	4.5	3.5
		Median	36	-2	38	1
		Min	28	-7	28	-9
		Max	44	9	46	7
	Cycle 6	N	61	60	70	70
		Mean	36.6	-1.6	37.6	0.1
		SD	3.7	3.3	4.4	3.5
		Median	36	-2	38	0
		Min	27	-9	28	-8
		Max	44	8	47	9

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 7	N	49	48	60	60
		Mean	37.1	-1.1	37.9	-0.1
		SD	3.4	3.2	4.3	4.1
		Median	37	-2	38	-1
		Min	28	-7	29	-11
		Max	45	7	48	10
	Cycle 8	N	39	38	51	51
		Mean	37.7	-1.1	38.5	0.6
		SD	3.1	3.2	3.9	3.5
		Median	37	-1	39	1
		Min	31	-9	29	-9
		Max	45	6	47	9
	Cycle 9	N	34	33	43	43
		Mean	38.1	-0.7	38.7	0.3
		SD	3.9	3.6	4.2	3.2
		Median	38	0	38	1
		Min	30	-10	26	-7
		Max	45	6	46	6

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 10	N	27	27	33	33
		Mean	37.6	-1.3	38.3	-0.7
		SD	4.5	3.3	3.5	2.6
		Median	37	-2	39	0
		Min	28	-7	29	-7
		Max	50	6	44	5
	Cycle 11	N	23	22	32	32
		Mean	36.9	-2.2	38.3	-0.7
		SD	3.9	3.7	4.4	4.0
		Median	38	-2	39	0
		Min	30	-13	25	-14
		Max	43	4	48	6
	Cycle 12	N	17	17	22	22
		Mean	37.6	-1.7	38.6	-0.6
		SD	3.9	2.8	3.4	3.0
		Median	37	-1	38	0
		Min	31	-7	30	-7
		Max	47	3	45	6

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 13	N	14	14	21	21
		Mean	37.5	-1.7	38.4	-0.6
		SD	3.0	2.9	3.4	3.3
		Median	37	-1	38	0
		Min	31	-7	32	-6
		Max	42	2	45	5
	Cycle 14	N	9	9	14	14
		Mean	35.9	-2.7	37.8	-0.5
		SD	2.7	2.9	3.4	3.4
		Median	36	-2	38	-2
		Min	31	-7	32	-5
		Max	41	0	45	5
	Cycle 15	N	6	6	10	10
		Mean	36.8	-2.3	37.5	-0.6
		SD	3.0	3.0	3.5	3.9
		Median	37	-1	38	0
		Min	32	-7	31	-6
		Max	40	0	43	6

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 16	N	2	2	6	6
		Mean	39.3	-1.0	37.9	-0.2
		SD	3.2	5.7	2.3	4.5
		Median	39	-1	39	-1
		Min	37	-5	35	-5
		Max	42	3	41	8
	Cycle 17	N	1	1	2	2
		Mean	39.1	0.6	37.5	2.9
		SD	-	-	2.2	2.6
		Median	39	1	37	3
		Min	39	1	36	1
		Max	39	1	39	5
	Cycle 18	N	1	1	1	1
		Mean	40.9	2.4	36.4	5.2
		SD	-	-	-	-
		Median	41	2	36	5
		Min	41	2	36	5
		Max	41	2	36	5

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 19	N	0	0	1	1
		Mean	-	-	36.8	5.6
		SD	-	-	-	-
		Median	-	-	37	6
		Min	-	-	37	6
		Max	-	-	37	6

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (10^9/L)	Baseline	N	111		111	
		Mean	6.4		6.7	
		SD	2.2		2.7	
		Median	6		6	
		Min	3		3	
		Max	14		21	
	Cycle 2	N	110	109	103	103
		Mean	6.0	-0.5	5.5	-1.2
		SD	1.8	1.9	2.1	2.8
		Median	6	0	5	-1
		Min	2	-7	3	-18
		Max	12	4	16	8
	Cycle 3	N	92	91	94	94
		Mean	6.1	-0.4	5.2	-1.3
		SD	2.2	2.2	1.9	2.7
		Median	6	0	5	-1
		Min	3	-8	2	-18
		Max	19	11	16	9

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (10^9/L)	Cycle 4	N	79	78	87	87
		Mean	5.6	-0.8	5.3	-1.1
		SD	1.6	2.0	1.6	2.2
		Median	5	-1	5	-1
		Min	2	-10	2	-9
		Max	11	3	11	4
	Cycle 5	N	68	67	77	77
		Mean	5.7	-0.9	5.4	-1.0
		SD	2.0	2.4	1.6	2.1
		Median	6	-1	5	-1
		Min	3	-10	3	-8
		Max	16	9	11	4
	Cycle 6	N	61	60	70	70
		Mean	5.6	-0.9	5.3	-1.0
		SD	1.7	2.3	1.5	2.0
		Median	5	-1	5	-1
		Min	3	-10	3	-8
		Max	11	4	11	3

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (10^9/L)	Cycle 7	N	48	47	60	60
		Mean	6.0	-0.4	5.5	-0.9
		SD	2.5	2.8	1.6	2.2
		Median	5	-1	5	-1
		Min	3	-10	3	-9
		Max	17	10	11	6
	Cycle 8	N	39	38	51	51
		Mean	5.3	-1.0	5.3	-1.1
		SD	1.8	2.1	1.5	2.2
		Median	5	-1	5	-1
		Min	3	-9	3	-8
		Max	10	2	9	5
	Cycle 9	N	34	33	43	43
		Mean	5.8	-0.6	5.9	-0.4
		SD	2.5	2.6	2.5	2.8
		Median	5	-1	5	0
		Min	3	-9	3	-8
		Max	15	8	16	8

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (10^9/L)	Cycle 10	N	27	27	33	33
		Mean	5.3	-1.0	5.6	-0.8
		SD	1.7	2.2	1.6	2.4
		Median	5	-1	5	-1
		Min	2	-9	3	-8
		Max	11	3	12	4
	Cycle 11	N	23	22	32	32
		Mean	5.2	-1.0	5.2	-1.0
		SD	1.6	2.5	1.6	2.6
		Median	5	-1	5	-1
		Min	3	-10	2	-10
		Max	9	3	9	3
	Cycle 12	N	18	18	22	22
		Mean	6.1	0.0	5.3	-0.7
		SD	2.9	3.2	1.4	1.9
		Median	6	0	5	-1
		Min	3	-8	3	-6
		Max	15	8	8	5

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (10^9/L)	Cycle 13	N	14	14	21	21
		Mean	4.6	-1.5	5.1	-0.8
		SD	1.0	2.9	1.7	2.0
		Median	5	-1	5	-1
		Min	3	-11	3	-5
		Max	7	2	10	3
	Cycle 14	N	9	9	14	14
		Mean	4.6	-0.9	5.6	-0.4
		SD	1.4	1.8	1.6	2.0
		Median	5	-1	5	-1
		Min	3	-4	4	-4
		Max	7	2	8	4
	Cycle 15	N	6	6	10	10
		Mean	5.0	-0.2	5.6	-0.9
		SD	1.7	1.4	1.2	1.6
		Median	5	-1	5	-1
		Min	3	-1	4	-4
		Max	7	2	8	2

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (10^9/L)	Cycle 16	N	2	2	6	6
		Mean	5.0	-0.3	5.0	-1.3
		SD	1.0	0.4	1.5	1.8
		Median	5	0	5	-1
		Min	4	-1	4	-5
		Max	6	0	8	1
	Cycle 17	N	1	1	2	2
		Mean	6.7	0.5	4.9	-2.2
		SD	-	-	1.0	3.3
		Median	7	1	5	-2
		Min	7	1	4	-5
		Max	7	1	6	0
	Cycle 18	N	1	1	1	1
		Mean	5.7	-0.5	4.1	0.0
		SD	-	-	-	-
		Median	6	-1	4	0
		Min	6	-1	4	0
		Max	6	-1	4	0

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (10^9/L)	Cycle 19	N	0	0	1	1
		Mean	-	-	4.0	-0.1
		SD	-	-	-	-
		Median	-	-	4	0
		Min	-	-	4	-0
		Max	-	-	4	-0

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (10^9/L)	Baseline	N	111		111	
		Mean	4.2		4.4	
		SD	1.8		2.4	
		Median	4		4	
		Min	2		2	
		Max	12		19	
	Cycle 2	N	110	109	103	103
		Mean	3.7	-0.6	3.4	-1.1
		SD	1.4	1.6	1.8	2.5
		Median	3	-1	3	-1
		Min	1	-6	1	-17
		Max	9	3	13	8
	Cycle 3	N	92	91	94	94
		Mean	3.9	-0.4	3.2	-1.1
		SD	1.9	2.0	1.6	2.5
		Median	4	0	3	-1
		Min	2	-8	1	-17
		Max	16	10	14	9

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (10^9/L)	Cycle 4	N	79	78	87	87
		Mean	3.3	-0.9	3.2	-0.9
		SD	1.2	1.6	1.3	1.8
		Median	3	-1	3	-1
		Min	1	-9	1	-8
		Max	8	2	9	4
	Cycle 5	N	68	67	77	77
		Mean	3.6	-0.8	3.3	-0.8
		SD	1.8	2.2	1.2	1.7
		Median	3	-1	3	-1
		Min	2	-9	1	-7
		Max	14	8	7	3
	Cycle 6	N	61	60	70	70
		Mean	3.4	-0.9	3.3	-0.8
		SD	1.3	2.1	1.2	1.7
		Median	3	-1	3	-1
		Min	2	-9	1	-7
		Max	7	5	7	2

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (10^9/L)	Cycle 7	N	49	48	60	60
		Mean	3.8	-0.3	3.5	-0.7
		SD	2.4	2.7	1.2	1.9
		Median	3	0	3	-1
		Min	1	-9	1	-8
		Max	16	10	8	6
	Cycle 8	N	39	38	51	51
		Mean	3.1	-1.1	3.3	-0.9
		SD	1.2	1.8	1.3	1.9
		Median	3	-1	3	-1
		Min	1	-9	1	-8
		Max	7	2	8	5
	Cycle 9	N	34	33	43	43
		Mean	3.6	-0.5	3.8	-0.3
		SD	2.3	2.5	2.2	2.4
		Median	3	-1	3	0
		Min	1	-9	2	-8
		Max	14	8	11	7

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (10^9/L)	Cycle 10	N	27	27	33	33
		Mean	3.1	-1.0	3.4	-0.7
		SD	1.2	2.0	1.3	2.0
		Median	3	-1	3	-1
		Min	1	-8	2	-8
		Max	7	2	8	3
	Cycle 11	N	23	22	31	31
		Mean	3.0	-1.0	3.3	-0.4
		SD	1.2	2.3	1.2	1.6
		Median	3	-1	3	-1
		Min	1	-10	1	-5
		Max	6	2	6	3
	Cycle 12	N	18	18	22	22
		Mean	3.9	0.0	3.2	-0.5
		SD	2.8	3.0	1.3	1.7
		Median	3	0	3	0
		Min	2	-8	2	-4
		Max	13	7	7	4

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (10^9/L)	Cycle 13	N	14	14	21	21
		Mean	2.7	-1.4	3.2	-0.4
		SD	0.7	2.6	1.4	1.6
		Median	3	-1	3	0
		Min	2	-10	2	-3
		Max	4	1	6	3
	Cycle 14	N	9	9	14	14
		Mean	2.6	-0.8	3.5	-0.2
		SD	0.7	1.2	1.4	1.4
		Median	3	-1	3	0
		Min	1	-2	1	-3
		Max	3	1	7	2
	Cycle 15	N	6	6	10	10
		Mean	2.6	-0.5	3.4	-0.6
		SD	0.9	0.8	1.4	1.7
		Median	3	-1	3	0
		Min	2	-1	2	-3
		Max	4	1	6	3

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (10^9/L)	Cycle 16	N	2	2	6	6
		Mean	2.8	-0.4	2.7	-1.0
		SD	0.2	1.1	1.0	1.4
		Median	3	0	3	-1
		Min	3	-1	2	-4
		Max	3	0	4	0
	Cycle 17	N	1	1	2	2
		Mean	4.2	0.1	2.2	-2.1
		SD	-	-	0.8	2.6
		Median	4	0	2	-2
		Min	4	0	2	-4
		Max	4	0	3	-0
	Cycle 18	N	1	1	1	1
		Mean	3.1	-1.0	1.7	-0.2
		SD	-	-	-	-
		Median	3	-1	2	0
		Min	3	-1	2	-0
		Max	3	-1	2	-0

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (10^9/L)	Cycle 19	N	0	0	1	1
		Mean	-	-	1.8	-0.1
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	-0
		Max	-	-	2	-0

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (10^9/L)	Baseline	N	105		108	
		Mean	1.5		1.5	
		SD	0.6		0.6	
		Median	2		1	
		Min	0		0	
		Max	3		4	
	Cycle 2	N	105	103	98	98
		Mean	1.6	0.1	1.5	0.0
		SD	0.7	0.4	0.6	0.6
		Median	2	0	2	0
		Min	0	-1	0	-2
		Max	3	1	4	2
	Cycle 3	N	87	86	89	88
		Mean	1.6	0.0	1.5	-0.1
		SD	0.6	0.5	0.6	0.4
		Median	2	0	1	0
		Min	0	-2	0	-2
		Max	3	2	4	1

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
Lymphocytes absolute ct (10^9/L)	Cycle 4	N	74	73	80	79
		Mean	1.6	0.0	1.5	-0.1
		SD	0.7	0.6	0.6	0.6
		Median	2	0	1	0
		Min	1	-2	0	-2
		Max	4	2	4	3
	Cycle 5	N	64	62	72	72
		Mean	1.5	-0.1	1.4	-0.2
		SD	0.6	0.5	0.5	0.6
		Median	1	0	1	0
		Min	0	-2	0	-3
		Max	3	1	3	2
	Cycle 6	N	58	56	66	66
		Mean	1.5	-0.1	1.5	-0.1
		SD	0.7	0.6	0.5	0.5
		Median	1	0	1	0
		Min	0	-2	0	-2
		Max	3	1	3	1

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (10^9/L)	Cycle 7	N	49	46	55	55
		Mean	1.5	-0.1	1.5	-0.1
		SD	0.6	0.5	0.6	0.6
		Median	1	0	1	0
		Min	0	-1	1	-2
		Max	4	2	4	2
	Cycle 8	N	38	37	46	46
		Mean	1.6	0.0	1.5	-0.1
		SD	0.7	0.5	0.5	0.4
		Median	1	0	1	0
		Min	0	-1	1	-2
		Max	3	1	3	1
	Cycle 9	N	33	32	38	38
		Mean	1.5	-0.1	1.6	-0.1
		SD	0.6	0.5	0.5	0.5
		Median	1	0	2	0
		Min	0	-2	1	-1
		Max	3	1	3	1

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (10^9/L)	Cycle 10	N	26	26	29	28
		Mean	1.6	0.0	1.7	0.0
		SD	0.5	0.5	0.5	0.6
		Median	2	0	2	0
		Min	1	-1	1	-1
		Max	2	1	3	2
	Cycle 11	N	22	21	28	28
		Mean	1.5	0.0	1.5	-0.2
		SD	0.5	0.4	0.5	0.5
		Median	1	0	1	0
		Min	1	-1	1	-1
		Max	3	1	3	1
	Cycle 12	N	17	17	19	19
		Mean	1.6	0.1	1.6	-0.2
		SD	0.6	0.5	0.5	0.5
		Median	1	0	1	0
		Min	1	-1	1	-1
		Max	3	1	2	1

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (10^9/L)	Cycle 13	N	13	13	18	18
		Mean	1.4	-0.1	1.5	-0.3
		SD	0.7	0.4	0.5	0.6
		Median	1	0	1	0
		Min	1	-1	1	-2
		Max	3	1	2	1
	Cycle 14	N	8	8	12	12
		Mean	1.6	-0.1	1.6	0.0
		SD	1.0	0.8	0.5	0.8
		Median	1	0	2	0
		Min	1	-1	1	-1
		Max	4	1	2	2
	Cycle 15	N	6	5	9	8
		Mean	1.8	0.2	1.6	-0.2
		SD	1.0	0.8	0.8	0.7
		Median	1	0	1	0
		Min	1	-1	1	-1
		Max	4	2	3	1

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (10^9/L)	Cycle 16	N	2	2	6	6
		Mean	1.5	0.0	1.7	0.0
		SD	0.4	0.3	0.4	0.4
		Median	1	0	2	0
		Min	1	-0	1	-1
		Max	2	0	2	0
	Cycle 17	N	1	1	2	2
		Mean	1.6	0.1	2.2	0.1
		SD	-	-	0.1	0.4
		Median	2	0	2	0
		Min	2	0	2	-0
		Max	2	0	2	0
	Cycle 18	N	1	1	1	1
		Mean	1.7	0.1	2.1	0.2
		SD	-	-	-	-
		Median	2	0	2	0
		Min	2	0	2	0
		Max	2	0	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (10^9/L)	Cycle 19	N	0	0	1	1
		Mean	-	-	2.1	0.2
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	0
		Max	-	-	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (10^9/L)	Baseline	N	111		111	
		Mean	271.0		284.3	
		SD	70.0		94.0	
		Median	274		268	
		Min	104		140	
		Max	477		756	
	Cycle 2	N	110	109	103	103
		Mean	250.1	-24.1	207.3	-77.3
		SD	75.8	53.6	79.1	81.4
		Median	246	-20	193	-64
		Min	81	-198	82	-450
		Max	463	146	561	59
	Cycle 3	N	92	91	94	94
		Mean	238.1	-32.0	215.8	-65.8
		SD	73.9	55.1	76.5	91.8
		Median	237	-32	207	-60
		Min	47	-181	64	-415
		Max	558	217	445	173

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (10^9/L)	Cycle 4	N	79	78	87	87
		Mean	233.0	-35.0	219.9	-70.7
		SD	78.6	66.9	81.9	96.8
		Median	223	-36	196	-61
		Min	70	-208	79	-493
		Max	557	216	525	135
	Cycle 5	N	68	67	77	77
		Mean	236.2	-36.3	224.7	-54.1
		SD	83.7	69.9	80.8	81.6
		Median	225	-41	205	-59
		Min	82	-223	91	-295
		Max	661	320	508	216
	Cycle 6	N	60	59	70	70
		Mean	221.1	-52.8	208.6	-70.7
		SD	63.3	55.2	63.5	77.1
		Median	215	-56	196	-62
		Min	84	-214	107	-346
		Max	437	52	442	64

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (10^9/L)	Cycle 7	N	49	48	60	60
		Mean	245.1	-25.2	209.1	-70.3
		SD	97.7	87.2	69.8	89.5
		Median	223	-24	205	-61
		Min	86	-241	97	-370
		Max	704	363	537	78
	Cycle 8	N	39	38	51	51
		Mean	243.9	-18.1	204.8	-70.2
		SD	102.4	78.0	70.3	80.8
		Median	226	-26	200	-66
		Min	95	-132	97	-326
		Max	704	363	482	105
	Cycle 9	N	34	33	43	43
		Mean	235.2	-21.2	195.8	-73.6
		SD	109.6	86.1	55.5	76.4
		Median	207	-22	192	-64
		Min	96	-142	89	-335
		Max	733	392	342	53

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (10^9/L)	Cycle 10	N	27	27	33	33
		Mean	227.1	-20.3	191.3	-73.0
		SD	99.9	85.3	47.6	57.1
		Median	206	-25	191	-81
		Min	102	-121	82	-211
		Max	673	332	341	35
	Cycle 11	N	23	22	32	32
		Mean	211.9	-42.3	193.8	-70.3
		SD	61.6	45.5	70.3	64.3
		Median	204	-46	187	-67
		Min	96	-122	86	-229
		Max	402	59	469	40
	Cycle 12	N	18	18	22	22
		Mean	211.6	-34.7	184.9	-77.5
		SD	49.8	48.0	49.1	59.2
		Median	213	-42	186	-72
		Min	107	-114	77	-231
		Max	315	84	306	38

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (10^9/L)	Cycle 13	N	14	14	21	21
		Mean	202.6	-45.7	184.3	-73.3
		SD	53.4	41.5	42.1	57.7
		Median	210	-42	192	-74
		Min	103	-131	79	-203
		Max	280	9	251	14
	Cycle 14	N	9	9	14	14
		Mean	205.4	-50.4	175.3	-91.8
		SD	70.0	66.0	44.3	63.5
		Median	193	-32	181	-93
		Min	118	-172	85	-220
		Max	348	54	240	28
	Cycle 15	N	6	6	10	10
		Mean	205.3	-70.5	190.7	-87.2
		SD	67.9	21.1	65.7	71.2
		Median	196	-75	186	-93
		Min	114	-97	79	-188
		Max	311	-46	290	56

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (10^9/L)	Cycle 16	N	2	2	6	6
		Mean	248.5	-16.5	213.8	-102
		SD	40.3	0.7	60.7	97.2
		Median	249	-17	229	-112
		Min	220	-17	98	-256
		Max	277	-16	264	23
	Cycle 17	N	1	1	2	2
		Mean	352.0	58.0	199.0	-143
		SD	-	-	12.7	30.4
		Median	352	58	199	-143
		Min	352	58	190	-164
		Max	352	58	208	-121
	Cycle 18	N	1	1	1	1
		Mean	306.0	12.0	223.0	-106
		SD	-	-	-	-
		Median	306	12	223	-106
		Min	306	12	223	-106
		Max	306	12	223	-106

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (10^9/L)	Cycle 19	N	0	0	1	1
		Mean	-	-	240.0	-89.0
		SD	-	-	-	-
		Median	-	-	240	-89
		Min	-	-	240	-89
		Max	-	-	240	-89

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
PT (sec)	Baseline	N	100		104	
		Mean	12.8		12.5	
		SD	2.5		2.5	
		Median	12		12	
		Min	1		1	
		Max	26		21	
PTT (sec)	Baseline	N	21		16	
		Mean	24.4		31.6	
		SD	10.9		12.7	
		Median	26		30	
		Min	1		17	
		Max	49		74	
aPTT (sec)	Baseline	N	97		96	
		Mean	30.8		28.0	
		SD	15.7		8.9	
		Median	30		28	
		Min	1		1	
		Max	169		61	

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
PT, INR (None)	Baseline	N	108		107	
		Mean	1.0		1.0	
		SD	0.1		0.1	
		Median	1		1	
		Min	1		1	
		Max	2		1	

Note: PTT and INR were measured at baseline only.
Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabH.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Baseline	N	92		92	
		Mean	60.6		54.8	
		SD	31.0		29.3	
		Median	54		51	
		Min	1		1	
		Max	204		187	
	Cycle 2	N	84	79	77	72
		Mean	68.3	8.3	72.5	16.6
		SD	51.8	45.7	34.2	27.4
		Median	57	5	65	13
		Min	10	-148	1	-105
		Max	464	323	158	104
	Cycle 3	N	71	67	74	69
		Mean	61.7	1.7	58.8	5.6
		SD	29.8	28.4	28.0	30.0
		Median	54	4	60	7
		Min	1	-167	1	-135
		Max	166	89	152	83

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 4	N	63	59	64	60
		Mean	60.7	0.6	60.4	4.9
		SD	25.1	26.2	30.8	32.9
		Median	59	2	60	6
		Min	1	-156	16	-143
		Max	158	41	207	132
	Cycle 5	N	52	49	65	60
		Mean	61.1	-0.7	59.2	7.0
		SD	27.2	22.7	28.5	20.2
		Median	59	1	55	4
		Min	12	-114	1	-79
		Max	140	37	141	81
	Cycle 6	N	45	43	57	53
		Mean	60.8	-1.0	56.6	4.4
		SD	22.6	28.9	26.4	17.5
		Median	55	1	57	6
		Min	18	-144	2	-80
		Max	115	58	135	44

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 7	N	37	34	41	38
		Mean	61.5	-6.0	59.5	0.6
		SD	25.8	24.2	26.2	20.4
		Median	57	-3	62	5
		Min	18	-107	0	-85
		Max	134	31	149	43
	Cycle 8	N	27	25	37	33
		Mean	65.7	-3.8	59.0	2.0
		SD	29.3	34.2	31.7	26.0
		Median	59	1	57	5
		Min	37	-134	0	-106
		Max	182	79	145	47
	Cycle 9	N	23	21	33	28
		Mean	63.5	-4.9	56.4	-2.9
		SD	22.6	34.9	30.2	24.7
		Median	63	-1	55	1
		Min	30	-149	0	-89
		Max	121	18	132	39

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 10	N	18	17	26	22
		Mean	67.4	-2.4	64.6	5.3
		SD	26.7	34.8	42.4	38.6
		Median	62	1	58	3
		Min	36	-124	17	-91
		Max	144	41	226	142
	Cycle 11	N	14	13	25	22
		Mean	63.0	7.2	55.7	1.4
		SD	23.8	16.9	32.3	16.9
		Median	57	6	52	0
		Min	32	-26	2	-32
		Max	107	37	153	47
	Cycle 12	N	11	10	17	16
		Mean	66.4	10.1	64.6	-0.8
		SD	18.7	16.6	28.1	12.0
		Median	58	15	72	-2
		Min	39	-22	22	-31
		Max	94	32	114	22

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 13	N	8	7	18	16
		Mean	66.4	11.4	61.2	2.2
		SD	16.3	8.5	36.6	17.2
		Median	67	14	63	1
		Min	37	-1	2	-29
		Max	88	22	125	30
	Cycle 14	N	7	6	9	7
		Mean	76.7	24.5	53.5	1.0
		SD	48.4	43.3	35.8	3.5
		Median	63	11	45	-0
		Min	34	-2	1	-3
		Max	183	112	101	7
	Cycle 15	N	4	4	8	6
		Mean	71.5	12.5	56.4	-6.7
		SD	28.9	17.1	34.2	21.5
		Median	69	5	54	-6
		Min	39	3	17	-41
		Max	109	38	101	26

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 16	N	1	1	4	3
		Mean	54.0	-16.0	77.8	-7.3
		SD	-	-	13.1	18.9
		Median	54	-16	82	-14
		Min	54	-16	59	-22
		Max	54	-16	89	14
	Cycle 17	N	1	1	1	0
		Mean	66.0	-4.0	84.0	-
		SD	-	-	-	-
		Median	66	-4	84	-
		Min	66	-4	84	-
		Max	66	-4	84	-
	Cycle 18	N	1	1	1	0
		Mean	55.0	-15.0	84.0	-
		SD	-	-	-	-
		Median	55	-15	84	-
		Min	55	-15	84	-
		Max	55	-15	84	-

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 19	N	0	0	1	0
		Mean	-	-	90.0	-
		SD	-	-	-	-
		Median	-	-	90	-
		Min	-	-	90	-
		Max	-	-	90	-

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Baseline	N	108		109	
		Mean	22.4		23.7	
		SD	10.3		11.7	
		Median	20		22	
		Min	7		5	
		Max	59		58	
	Cycle 2	N	105	101	101	100
		Mean	21.9	-0.7	23.8	-0.4
		SD	10.8	6.8	12.4	7.2
		Median	21	0	20	-0
		Min	7	-22	5	-31
		Max	79	20	70	17
	Cycle 3	N	87	83	92	91
		Mean	23.1	0.2	21.5	-1.6
		SD	12.1	7.9	10.2	5.4
		Median	20	0	19	-1
		Min	7	-23	6	-17
		Max	75	39	47	10

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 4	N	78	75	84	83
		Mean	22.4	0.4	23.0	-0.3
		SD	10.7	6.7	11.3	6.5
		Median	20	0	20	-1
		Min	7	-20	4	-17
		Max	62	21	51	20
	Cycle 5	N	63	61	73	73
		Mean	23.1	0.2	23.6	-0.4
		SD	10.3	7.8	12.4	5.9
		Median	21	1	19	-1
		Min	7	-28	5	-13
		Max	45	18	56	14
	Cycle 6	N	57	55	68	68
		Mean	22.6	-0.0	22.7	-1.4
		SD	11.7	7.1	13.9	8.3
		Median	20	0	18	-1
		Min	8	-24	5	-17
		Max	64	16	89	45

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 7	N	47	46	56	55
		Mean	20.3	-1.5	24.9	-0.1
		SD	9.8	8.6	13.4	9.0
		Median	17	-1	22	-1
		Min	7	-28	4	-16
		Max	43	20	60	29
	Cycle 8	N	38	37	50	49
		Mean	19.8	-0.4	23.5	-0.1
		SD	9.3	6.5	12.8	6.8
		Median	17	0	19	-2
		Min	7	-18	5	-13
		Max	47	15	58	25
	Cycle 9	N	33	32	43	42
		Mean	20.0	-0.3	22.9	-1.8
		SD	10.6	6.5	13.1	7.1
		Median	16	-1	18	-3
		Min	8	-13	5	-13
		Max	55	20	65	17

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 10	N	26	26	34	34
		Mean	22.0	0.5	22.8	-1.6
		SD	8.5	7.4	11.2	6.2
		Median	19	1	21	-2
		Min	11	-20	5	-14
		Max	39	15	47	12
	Cycle 11	N	22	21	32	32
		Mean	21.5	0.0	23.5	-0.6
		SD	10.1	8.2	13.4	7.7
		Median	18	0	18	-0
		Min	9	-20	7	-20
		Max	48	21	50	18
	Cycle 12	N	17	17	22	22
		Mean	25.2	1.1	21.9	-1.8
		SD	10.7	9.0	11.3	10.4
		Median	24	1	16	-2
		Min	10	-14	6	-17
		Max	50	23	45	27

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 13	N	12	12	21	21
		Mean	23.7	1.2	24.3	0.2
		SD	9.9	7.4	12.6	7.6
		Median	23	0	22	1
		Min	10	-13	6	-16
		Max	41	19	49	13
	Cycle 14	N	9	9	13	13
		Mean	22.3	-1.1	23.8	-1.9
		SD	8.2	6.8	13.8	7.3
		Median	21	1	18	-2
		Min	12	-13	4	-13
		Max	34	9	42	11
	Cycle 15	N	6	6	9	9
		Mean	24.6	1.0	24.2	-1.0
		SD	8.7	7.7	13.3	10.1
		Median	26	1	17	-1
		Min	12	-9	11	-13
		Max	36	14	48	17

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 16	N	2	2	5	5
		Mean	31.0	5.0	28.0	3.9
		SD	2.8	8.5	13.7	7.5
		Median	31	5	29	2
		Min	29	-1	13	-2
		Max	33	11	48	16
	Cycle 17	N	1	1	2	2
		Mean	33.0	11.0	40.5	11.5
		SD	-	-	2.1	6.4
		Median	33	11	41	12
		Min	33	11	39	7
		Max	33	11	42	16
	Cycle 18	N	1	1	1	1
		Mean	14.0	-8.0	47.0	15.0
		SD	-	-	-	-
		Median	14	-8	47	15
		Min	14	-8	47	15
		Max	14	-8	47	15

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 19	N	0	0	1	1
		Mean	-	-	30.0	-2.0
		SD	-	-	-	-
		Median	-	-	30	-2
		Min	-	-	30	-2
		Max	-	-	30	-2

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Baseline	N	111		110	
		Mean	0.6		0.5	
		SD	0.3		0.3	
		Median	1		1	
		Min	0		0	
		Max	2		2	
	Cycle 2	N	107	106	100	99
		Mean	0.6	0.1	0.8	0.2
		SD	0.3	0.3	0.4	0.3
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	2	1	2	1
	Cycle 3	N	90	89	94	93
		Mean	0.8	0.2	0.8	0.3
		SD	0.4	0.4	0.4	0.3
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	2	2	2	1

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 4	N	79	78	86	85
		Mean	0.8	0.2	0.9	0.4
		SD	0.4	0.3	0.4	0.4
		Median	1	0	1	0
		Min	0	-1	0	-0
		Max	2	1	2	1
	Cycle 5	N	66	65	75	74
		Mean	0.8	0.3	0.9	0.4
		SD	0.5	0.5	0.5	0.4
		Median	1	0	1	0
		Min	0	-1	0	-0
		Max	2	1	3	2
	Cycle 6	N	61	60	69	68
		Mean	0.9	0.3	0.9	0.4
		SD	0.5	0.4	0.4	0.4
		Median	1	0	1	0
		Min	0	-0	0	-0
		Max	3	2	3	2

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 7	N	48	47	56	55
		Mean	0.9	0.3	0.9	0.3
		SD	0.5	0.4	0.5	0.4
		Median	1	0	1	0
		Min	0	-0	0	-0
		Max	2	1	3	2
	Cycle 8	N	38	37	50	49
		Mean	0.9	0.3	0.8	0.2
		SD	0.4	0.4	0.4	0.4
		Median	1	0	1	0
		Min	0	-1	0	-0
		Max	2	1	2	1
	Cycle 9	N	33	33	41	40
		Mean	0.9	0.3	0.9	0.3
		SD	0.5	0.4	0.5	0.4
		Median	1	0	1	0
		Min	0	-0	0	-0
		Max	2	2	2	1

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 10	N	27	27	34	34
		Mean	1.1	0.4	0.9	0.4
		SD	0.7	0.6	0.4	0.5
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	3	2	2	1
	Cycle 11	N	21	21	32	32
		Mean	1.1	0.5	0.9	0.4
		SD	0.6	0.6	0.5	0.4
		Median	1	1	1	0
		Min	0	-1	0	-1
		Max	2	2	3	1
	Cycle 12	N	16	16	22	22
		Mean	1.1	0.5	0.9	0.4
		SD	0.6	0.6	0.3	0.4
		Median	1	0	1	0
		Min	0	-0	0	-0
		Max	2	2	1	1

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 13	N	13	13	21	21
		Mean	1.1	0.4	0.9	0.3
		SD	0.6	0.6	0.3	0.2
		Median	1	1	1	0
		Min	0	-1	0	-0
		Max	2	1	2	1
	Cycle 14	N	9	9	14	14
		Mean	1.2	0.4	0.8	0.3
		SD	0.7	0.7	0.3	0.4
		Median	1	0	1	0
		Min	0	-0	0	-0
		Max	3	2	2	1
	Cycle 15	N	6	6	10	10
		Mean	1.2	0.3	0.8	0.3
		SD	0.5	0.6	0.3	0.3
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	2	1	1	1

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 16	N	2	2	5	5
		Mean	1.4	0.4	1.0	0.4
		SD	0.0	0.5	0.3	0.4
		Median	1	0	1	0
		Min	1	0	1	-0
		Max	1	1	1	1
	Cycle 17	N	1	1	2	2
		Mean	1.1	-0.3	0.8	0.5
		SD	-	-	0.5	0.5
		Median	1	-0	1	0
		Min	1	-0	0	0
		Max	1	-0	1	1
	Cycle 18	N	1	1	1	1
		Mean	1.8	0.4	0.4	0.0
		SD	-	-	-	-
		Median	2	0	0	0
		Min	2	0	0	0
		Max	2	0	0	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 19	N	0	0	1	1
		Mean	-	-	0.4	0.1
		SD	-	-	-	-
		Median	-	-	0	0
		Min	-	-	0	0
		Max	-	-	0	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Baseline	N	111		111	
		Mean	0.8		0.8	
		SD	0.2		0.2	
		Median	1		1	
		Min	1		0	
		Max	2		2	
	Cycle 2	N	110	109	103	103
		Mean	0.8	-0.0	0.8	-0.0
		SD	0.2	0.2	0.2	0.1
		Median	1	0	1	0
		Min	0	-1	0	-0
		Max	1	1	1	1
	Cycle 3	N	91	90	95	95
		Mean	0.8	0.0	0.8	-0.0
		SD	0.2	0.2	0.2	0.1
		Median	1	0	1	0
		Min	0	-0	0	-0
		Max	2	1	1	0

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 4	N	79	78	87	87
		Mean	0.8	0.0	0.8	-0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	-0	0	-0
		Max	2	0	1	0
	Cycle 5	N	67	66	77	77
		Mean	0.8	0.0	0.8	-0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	-0
		Min	0	-0	0	-0
		Max	2	1	1	0
	Cycle 6	N	60	59	70	70
		Mean	0.8	0.0	0.8	-0.0
		SD	0.2	0.1	0.2	0.1
		Median	1	0	1	-0
		Min	1	-0	0	-0
		Max	2	1	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 7	N	49	48	57	57
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	-0
		Min	1	-0	1	-0
		Max	2	0	2	1
	Cycle 8	N	39	38	50	50
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	-0	1	-0
		Max	1	0	1	1
	Cycle 9	N	33	33	43	43
		Mean	0.8	-0.0	0.8	-0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	0
		Min	0	-0	0	-0
		Max	2	0	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 10	N	27	27	34	34
		Mean	0.8	0.0	0.7	-0.0
		SD	0.3	0.2	0.2	0.1
		Median	1	0	1	-0
		Min	0	-0	0	-0
		Max	2	1	1	0
	Cycle 11	N	23	22	32	32
		Mean	0.8	0.0	0.8	-0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	-0
		Min	1	-0	0	-1
		Max	1	0	1	1
	Cycle 12	N	18	18	22	22
		Mean	0.8	0.1	0.8	-0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	-0
		Min	1	-0	1	-0
		Max	1	0	1	1

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 13	N	13	13	21	21
		Mean	0.8	0.1	0.8	-0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	-0
		Min	1	-0	1	-0
		Max	1	0	1	1
	Cycle 14	N	9	9	14	14
		Mean	0.8	-0.0	0.8	-0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	-0
		Min	0	-0	1	-0
		Max	1	0	1	0
	Cycle 15	N	6	6	10	10
		Mean	0.8	0.0	0.8	-0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	-0
		Min	1	-0	1	-0
		Max	1	0	1	0

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 16	N	2	2	6	6
		Mean	1.0	0.2	0.7	-0.1
		SD	0.1	0.1	0.1	0.1
		Median	1	0	1	-0
		Min	1	0	1	-0
		Max	1	0	1	0
	Cycle 17	N	1	1	2	2
		Mean	1.0	0.1	0.7	0.0
		SD	-	-	0.1	0.2
		Median	1	0	1	0
		Min	1	0	1	-0
		Max	1	0	1	0
	Cycle 18	N	1	1	1	1
		Mean	0.9	0.0	0.6	-0.1
		SD	-	-	-	-
		Median	1	0	1	-0
		Min	1	0	1	-0
		Max	1	0	1	-0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 19	N	0	0	1	1
		Mean	-	-	0.6	-0.2
		SD	-	-	-	-
		Median	-	-	1	-0
		Min	-	-	1	-0
		Max	-	-	1	-0

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Baseline	N	35		40	
		Mean	88.3		82.0	
		SD	85.6		88.7	
		Median	55		40	
		Min	6		2	
		Max	282		326	
	Cycle 2	N	28	25	27	23
		Mean	105.2	-6.3	136.0	50.3
		SD	97.9	56.6	155.0	119.9
		Median	69	-1	74	36
		Min	3	-192	3	-288
		Max	409	127	692	409
	Cycle 3	N	23	20	28	20
		Mean	89.3	-13.9	97.7	35.7
		SD	83.5	56.7	108.2	94.1
		Median	48	1	50	18
		Min	6	-194	0	-217
		Max	281	32	385	294

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 4	N	26	22	22	18
		Mean	97.4	3.8	96.3	21.4
		SD	87.6	40.2	185.0	168.9
		Median	75	4	45	6
		Min	7	-143	0	-281
		Max	270	89	882	599
	Cycle 5	N	19	17	19	14
		Mean	103.9	12.6	78.1	16.7
		SD	97.2	34.6	95.0	36.9
		Median	71	5	41	12
		Min	8	-72	0	-53
		Max	295	94	355	83
	Cycle 6	N	19	16	17	14
		Mean	88.3	-10.2	78.9	13.4
		SD	83.3	40.4	107.5	56.1
		Median	39	2	37	3
		Min	2	-132	0	-106
		Max	264	25	399	120

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
Lipase (U/L)	Cycle 7	N	18	13	16	12
		Mean	84.4	-2.8	80.8	-7.4
		SD	86.0	50.0	115.0	106.4
		Median	37	-4	37	1
		Min	9	-136	0	-281
		Max	315	64	416	133
	Cycle 8	N	13	9	15	12
		Mean	99.4	1.9	94.9	3.9
		SD	77.2	29.7	136.0	115.4
		Median	94	0	43	12
		Min	14	-60	0	-259
		Max	207	36	527	244
	Cycle 9	N	13	10	13	8
		Mean	89.3	5.7	57.2	-58.4
		SD	74.6	35.4	44.1	117.3
		Median	68	9	48	3
		Min	20	-84	0	-278
		Max	229	55	135	50

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 10	N	12	11	11	7
		Mean	73.2	-20.2	65.3	0.8
		SD	53.8	65.8	54.0	45.3
		Median	62	3	35	23
		Min	17	-177	16	-97
		Max	183	40	177	33
	Cycle 11	N	10	7	8	6
		Mean	72.6	-26.1	72.4	0.4
		SD	53.7	75.0	55.0	55.3
		Median	48	3	55	9
		Min	17	-179	25	-76
		Max	175	37	198	62
	Cycle 12	N	9	7	4	4
		Mean	93.7	-7.3	75.7	-14.4
		SD	65.3	41.5	70.2	54.6
		Median	102	0	51	10
		Min	13	-98	22	-96
		Max	208	24	178	19

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 13	N	6	4	5	4
		Mean	115.5	-8.8	82.2	-3.8
		SD	82.7	23.5	91.0	21.1
		Median	117	3	47	-1
		Min	17	-44	17	-32
		Max	211	3	242	18
	Cycle 14	N	4	3	3	2
		Mean	92.3	-3.3	91.0	-36.0
		SD	90.7	18.8	73.6	87.7
		Median	65	7	50	-36
		Min	21	-25	47	-98
		Max	219	8	176	26
	Cycle 15	N	1	1	3	2
		Mean	114.0	26.0	73.0	-53.0
		SD	-	-	53.6	124.5
		Median	114	26	56	-53
		Min	114	26	30	-141
		Max	114	26	133	35

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
Lipase (U/L)	Cycle 16	N	1	1	1	1
		Mean	118.0	30.0	145.0	-129
		SD	-	-	-	-
		Median	118	30	145	-129
		Min	118	30	145	-129
		Max	118	30	145	-129
	Cycle 17	N	0	0	1	1
		Mean	-	-	196.0	-78.0
		SD	-	-	-	-
		Median	-	-	196	-78
		Min	-	-	196	-78
		Max	-	-	196	-78
	Cycle 18	N	0	0	0	0
		Mean	-	-	-	-
		SD	-	-	-	-
		Median	-	-	-	-
		Min	-	-	-	-
		Max	-	-	-	-

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
Lipase (U/L)	Cycle 19	N	0	0	0	0
		Mean	-	-	-	-
		SD	-	-	-	-
		Median	-	-	-	-
		Min	-	-	-	-
		Max	-	-	-	-

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Baseline	N	111		111	
		Mean	34.4		31.3	
		SD	27.4		21.7	
		Median	27		24	
		Min	14		12	
		Max	201		126	
	Cycle 2	N	108	107	101	101
		Mean	30.8	-3.1	33.1	2.3
		SD	20.0	13.7	16.2	16.4
		Median	25	-1	29	4
		Min	13	-69	13	-83
		Max	132	33	102	31
	Cycle 3	N	91	90	94	94
		Mean	27.5	-4.9	33.1	2.7
		SD	11.1	19.8	13.0	17.7
		Median	24	0	31	5
		Min	14	-120	15	-72
		Max	81	26	68	33

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 4	N	78	77	87	87
		Mean	27.8	-4.9	35.6	4.7
		SD	12.0	22.6	15.3	22.1
		Median	24	-2	32	5
		Min	14	-131	11	-75
		Max	70	30	96	70
	Cycle 5	N	67	66	76	76
		Mean	28.8	-4.7	36.5	6.0
		SD	21.7	20.0	16.8	24.8
		Median	24	-1	34	6
		Min	10	-116	12	-73
		Max	182	41	87	67
	Cycle 6	N	61	60	69	69
		Mean	26.6	-4.1	36.9	5.8
		SD	12.6	21.9	15.8	21.9
		Median	23	0	34	9
		Min	12	-117	14	-75
		Max	75	58	89	56

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 7	N	49	48	56	56
		Mean	28.0	-3.1	37.4	8.2
		SD	11.9	22.1	29.4	29.8
		Median	25	0	31	5
		Min	12	-113	14	-46
		Max	69	49	216	190
	Cycle 8	N	38	37	50	50
		Mean	26.7	-6.4	35.3	4.8
		SD	9.5	23.0	16.7	22.2
		Median	24	-1	33	5
		Min	14	-114	12	-81
		Max	55	26	92	52
	Cycle 9	N	34	33	43	43
		Mean	29.0	-3.5	36.3	6.2
		SD	13.6	25.3	19.6	24.4
		Median	26	0	32	5
		Min	14	-113	13	-83
		Max	79	62	108	60

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 10	N	27	27	34	34
		Mean	28.1	-5.4	32.7	2.9
		SD	12.1	26.5	12.9	21.3
		Median	26	0	32	6
		Min	15	-116	15	-88
		Max	68	43	62	39
	Cycle 11	N	21	20	32	32
		Mean	32.9	-3.2	32.6	3.0
		SD	19.5	31.7	10.8	21.1
		Median	27	2	33	7
		Min	18	-109	15	-92
		Max	108	43	50	32
	Cycle 12	N	18	18	22	22
		Mean	36.3	6.9	30.4	5.2
		SD	36.4	35.5	12.1	12.7
		Median	28	4	28	6
		Min	15	-44	12	-24
		Max	179	131	65	34

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 13	N	13	13	21	21
		Mean	28.3	-2.0	32.1	7.2
		SD	9.9	17.9	14.2	15.0
		Median	26	0	28	7
		Min	16	-42	15	-21
		Max	44	24	63	40
	Cycle 14	N	9	9	14	14
		Mean	29.1	2.8	37.0	10.4
		SD	8.0	16.8	18.7	18.7
		Median	29	4	32	7
		Min	17	-34	14	-18
		Max	43	26	76	45
	Cycle 15	N	6	6	10	10
		Mean	27.7	1.3	39.0	9.7
		SD	6.9	17.5	19.9	16.8
		Median	27	2	36	6
		Min	20	-29	18	-16
		Max	39	22	79	48

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 16	N	2	2	6	6
		Mean	28.0	7.5	43.5	9.2
		SD	11.3	4.9	22.0	7.0
		Median	28	8	34	11
		Min	20	4	31	-1
		Max	36	11	87	17
	Cycle 17	N	1	1	2	2
		Mean	28.0	12.0	47.5	-2.5
		SD	-	-	21.9	10.6
		Median	28	12	48	-3
		Min	28	12	32	-10
		Max	28	12	63	5
	Cycle 18	N	1	1	1	1
		Mean	19.0	3.0	33.0	6.0
		SD	-	-	-	-
		Median	19	3	33	6
		Min	19	3	33	6
		Max	19	3	33	6

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 19	N	0	0	1	1
		Mean	-	-	28.0	1.0
		SD	-	-	-	-
		Median	-	-	28	1
		Min	-	-	28	1
		Max	-	-	28	1

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Baseline	N	111		111	
		Mean	29.9		26.2	
		SD	21.3		17.2	
		Median	23		20	
		Min	9		5	
		Max	128		101	
	Cycle 2	N	110	109	101	101
		Mean	25.9	-3.7	29.0	3.1
		SD	16.2	14.3	15.7	17.1
		Median	21	-2	24	4
		Min	6	-77	8	-83
		Max	99	29	106	56
	Cycle 3	N	91	90	94	94
		Mean	26.0	-2.7	32.4	6.2
		SD	14.1	16.7	17.7	18.2
		Median	23	-1	27	7
		Min	7	-87	12	-48
		Max	90	41	121	88

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 4	N	79	78	87	87
		Mean	24.9	-3.9	34.8	8.4
		SD	11.6	17.3	20.6	22.5
		Median	22	-2	29	7
		Min	5	-88	12	-65
		Max	63	40	109	78
	Cycle 5	N	67	66	77	77
		Mean	25.5	-3.6	36.6	11.1
		SD	13.0	22.0	25.1	28.2
		Median	22	-1	28	7
		Min	10	-98	8	-50
		Max	71	56	133	121
	Cycle 6	N	61	60	70	70
		Mean	25.5	-4.2	36.1	10.1
		SD	16.8	24.6	22.0	21.5
		Median	21	-2	31	9
		Min	9	-100	10	-44
		Max	110	95	123	92

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 7	N	49	48	57	57
		Mean	27.3	-2.0	35.7	10.6
		SD	15.1	23.9	24.4	21.9
		Median	24	-2	27	7
		Min	7	-98	8	-48
		Max	82	67	143	118
	Cycle 8	N	38	37	50	50
		Mean	26.1	-5.1	31.1	6.7
		SD	14.9	23.0	15.3	19.6
		Median	20	-3	27	7
		Min	10	-99	12	-55
		Max	66	38	78	48
	Cycle 9	N	34	33	43	43
		Mean	26.7	-3.0	30.5	6.1
		SD	18.3	24.4	15.5	19.8
		Median	22	-2	27	9
		Min	8	-99	11	-59
		Max	93	78	70	32

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 10	N	27	27	34	34
		Mean	26.3	-2.3	28.4	4.5
		SD	15.6	25.0	12.9	17.4
		Median	25	-1	25	8
		Min	9	-94	8	-49
		Max	82	67	66	33
	Cycle 11	N	21	20	32	32
		Mean	27.0	-2.2	29.9	6.1
		SD	17.6	29.1	12.9	17.7
		Median	22	-3	29	8
		Min	10	-92	10	-49
		Max	77	62	63	32
	Cycle 12	N	18	18	22	22
		Mean	28.4	2.5	25.9	6.4
		SD	16.4	17.7	10.0	11.0
		Median	20	1	26	9
		Min	10	-31	8	-19
		Max	70	55	45	28

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 13	N	13	13	21	21
		Mean	25.6	-0.2	26.4	7.8
		SD	10.5	14.9	9.3	11.4
		Median	24	-1	27	10
		Min	11	-25	10	-18
		Max	50	33	42	26
	Cycle 14	N	9	9	14	14
		Mean	26.4	3.7	28.9	10.2
		SD	9.0	12.3	14.1	12.6
		Median	26	1	26	9
		Min	16	-14	8	-11
		Max	42	25	58	30
	Cycle 15	N	6	6	10	10
		Mean	25.5	3.8	26.7	5.9
		SD	10.0	14.1	13.0	13.4
		Median	25	-1	26	3
		Min	14	-13	8	-15
		Max	38	23	41	26

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 16	N	2	2	6	6
		Mean	21.0	2.0	30.8	5.2
		SD	4.2	7.1	11.3	10.5
		Median	21	2	29	6
		Min	18	-3	16	-11
		Max	24	7	45	19
	Cycle 17	N	1	1	2	2
		Mean	17.0	0.0	34.0	1.0
		SD	-	-	4.2	25.5
		Median	17	0	34	1
		Min	17	0	31	-17
		Max	17	0	37	19
	Cycle 18	N	1	1	1	1
		Mean	16.0	-1.0	32.0	20.0
		SD	-	-	-	-
		Median	16	-1	32	20
		Min	16	-1	32	20
		Max	16	-1	32	20

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 19	N	0	0	1	1
		Mean	-	-	26.0	14.0
		SD	-	-	-	-
		Median	-	-	26	14
		Min	-	-	26	14
		Max	-	-	26	14

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabC.sas (Run Date: 17JUL2009 14:24)

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Table 14.4.3 Incidence of Laboratory Values of CTCAE Toxicity Grade 3 and 4
(Safety Population)

	Placebo (N=112)		Sorafenib (N=112)	
Laboratory Test	Grade 3 n/N(%)	Grade 4 n/N(%)	Grade 3 n/N(%)	Grade 4 n/N(%)
Hemoglobin	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
Lymphocytes	7/108 (6.5%)	0/108 (0%)	2/103 (1.9%)	0/103 (0%)
Neutrophils	0/110 (0%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Platelets	1/110 (0.9%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
WBC	1/110 (0.9%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
PTINR	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Amylase	2/91 (2.2%)	0/91 (0%)	1/90 (1.1%)	0/90 (0%)
Lipase	0/38 (0%)	0/38 (0%)	3/46 (6.5%)	1/46 (2.2%)
Bilirubin, total	0/109 (0%)	0/109 (0%)	0/104 (0%)	0/104 (0%)
Creatinine	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
SGOT/AST	2/109 (1.8%)	0/109 (0%)	1/104 (1.0%)	0/104 (0%)
SGPT/ALT	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)

Note: Grade in this table represents the worst post-baseline grade reported for the subject.
Note: n=number of subjects with the grade being the worst post baseline toxicity; N=total number of subjects with the laboratory measurement reported post baseline.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_03_LabGrd.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Amylase (U/L)	-1	3	1
	0	76	64
	1	5	12
	2	1	3
	3	1	0
	Unk	26	32
Bilirubin, total (mg/dL)	-1	3	1
	0	78	60
	1	20	32
	2	7	10
	Unk	4	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabX.sas (Run Date: 17JUL2009 14:25)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Creatinine (mg/dL)	-1	1	2
	0	102	93
	1	4	8
	2	2	0
	Unk	3	9
Hemoglobin (g/dL)	-2	0	1
	-1	5	3
	0	76	77
	1	25	20
	2	3	2
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabX.sas (Run Date: 17JUL2009 14:25)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Lipase (U/L)	-3	1	0
	-2	0	1
	0	27	21
	1	4	5
	2	0	2
	3	0	3
	Unk	80	80
Lymphocytes absolute ct (GIGA/L)	-3	0	1
	-2	0	1
	-1	0	3
	0	80	66
	1	16	21
	2	6	8
	3	2	1
	Unk	8	11

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabX.sas (Run Date: 17JUL2009 14:25)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Neutrophils absolute ct (GIGA/L)	-1	2	2
	0	91	79
	1	14	16
	2	2	5
	3	0	1
	Unk	3	9
Platelets (GIGA/L)	0	100	74
	1	7	28
	2	2	1
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_LabX.sas (Run Date: 17JUL2009 14:25)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
SGOT/AST (U/L)	-2	0	1
	-1	9	5
	0	79	55
	1	18	40
	2	2	1
	3	0	1
	Unk	4	9
SGPT/ALT (U/L)	-1	8	4
	0	81	63
	1	18	29
	2	2	7
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
WBC (GIGA/L)	-1	1	0
	0	84	65
	1	19	30
	2	4	8
	3	1	0
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	110	79.4	10.2	60.0	123.0
	Cycle2	106	78.8	10.4	52.0	108.0
	Cycle3	91	78.1	10.2	57.0	110.0
	Cycle4	72	79.5	10.5	54.0	105.0
	Cycle5	62	78.3	12.4	50.0	120.0
	Cycle6	59	77.6	12.1	56.0	130.0
	Cycle7	49	78.1	9	60.0	94.0
	Cycle8	39	79.4	11	60.0	100.0
	Cycle9	34	82.9	9.9	66.0	110.0
	Cycle10	26	78	9.2	60.0	90.0
	Cycle11	23	76.7	9.2	60.0	90.0
	Cycle12	17	77.3	8.5	60.0	90.0
	Cycle13	13	80.6	8.9	70.0	101.0
	Cycle14	10	77.7	3.9	70.0	80.0
	Cycle15	6	80	3.9	75.0	87.0
	Cycle16	2	75	7.1	70.0	80.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_vital.sas (Run Date: 20JUL2009 13:07)

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle17	1	80		80.0	80.0
	Cycle18	1	70		70.0	70.0
	End of treatment	71	80.7	8.7	62.0	100.0
	Change from baseline: cycle2	104	-1.1	9.6	-22.0	22.0
	Change from baseline: cycle3	90	-1.3	10.6	-34.0	26.0
	Change from baseline: cycle4	72	0.2	11.9	-43.0	30.0
	Change from baseline: cycle5	62	-1.3	12.8	-40.0	30.0
	Change from baseline: cycle6	59	-1.2	10.7	-30.0	30.0
	Change from baseline: cycle7	49	-0.9	10.5	-26.0	20.0
	Change from baseline: cycle8	39	0.2	11.1	-25.0	25.0
	Change from baseline: cycle9	34	2.6	11.3	-17.0	30.0
	Change from baseline: cycle10	26	-2.3	11.4	-30.0	19.0
	Change from baseline: cycle11	23	-4.8	13.2	-30.0	20.0
	Change from baseline: cycle12	17	-3.1	12.2	-30.0	10.0
	Change from baseline: cycle13	13	1.4	11.1	-20.0	16.0
	Change from baseline: cycle14	10	1.3	9.7	-20.0	10.0
	Change from baseline: cycle15	6	3.3	9.7	-15.0	10.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: cycle16	2	-5	21.2	-20.0	10.0
	Change from baseline: cycle17	1	10		10.0	10.0
	Change from baseline: cycle18	1	0		0.0	0.0
	Change from baseline: end of treatment	71	-0.3	11.7	-32.0	35.0
Sorafenib	Baseline	112	77.9	10.5	50.0	103.0
	Cycle2	100	81.9	12.3	45.0	110.0
	Cycle3	94	82.1	11.2	60.0	120.0
	Cycle4	84	82	10.1	60.0	120.0
	Cycle5	74	81	8.7	54.0	105.0
	Cycle6	69	80.9	11.1	59.0	110.0
	Cycle7	56	82	11.7	60.0	133.0
	Cycle8	49	79.8	11.3	57.0	103.0
	Cycle9	40	81.5	8.5	65.0	100.0
	Cycle10	29	81	6.9	70.0	91.0
	Cycle11	28	81	8.6	60.0	93.0
	Cycle12	22	82	9.7	70.0	101.0
	Cycle13	21	83.2	8.3	70.0	100.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_vital.sas (Run Date: 20JUL2009 13:07)

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle14	12	79.6	11.9	60.0	97.0
	Cycle15	9	80.1	8.9	70.0	95.0
	Cycle16	6	83.5	13.9	60.0	100.0
	Cycle17	2	88	11.3	80.0	96.0
	Cycle18	1	91		91.0	91.0
	Cycle19	1	90		90.0	90.0
	End of treatment	62	80.8	10.2	54.0	110.0
	Change from baseline: cycle2	100	3.7	11.9	-23.0	39.0
	Change from baseline: cycle3	94	3.7	11.2	-20.0	30.0
	Change from baseline: cycle4	84	3.5	11.7	-23.0	50.0
	Change from baseline: cycle5	74	2.3	12	-34.0	30.0
	Change from baseline: cycle6	69	1.8	13.3	-30.0	33.0
	Change from baseline: cycle7	56	2.1	11.7	-30.0	41.0
	Change from baseline: cycle8	49	0.8	12.2	-40.0	21.0
	Change from baseline: cycle9	40	2.1	9.8	-20.0	20.0
	Change from baseline: cycle10	29	0.5	10.4	-20.0	21.0
	Change from baseline: cycle11	28	0.3	11.5	-20.0	40.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: cycle12	22	2.4	13.3	-20.0	30.0
	Change from baseline: cycle13	21	3.4	11.8	-20.0	30.0
	Change from baseline: cycle14	12	-0.3	13.5	-20.0	20.0
	Change from baseline: cycle15	9	-1.9	12.2	-20.0	20.0
	Change from baseline: cycle16	6	1.7	6.8	-10.0	10.0
	Change from baseline: cycle17	2	1.5	16.3	-10.0	13.0
	Change from baseline: cycle18	1	8		8.0	8.0
	Change from baseline: cycle19	1	7		7.0	7.0
	Change from baseline: end of treatment	62	3.2	10.8	-30.0	36.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_vital.sas (Run Date: 20JUL2009 13:07)

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	110	128.7	17.7	95.0	180.0
	Cycle2	106	125.5	17.5	90.0	171.0
	Cycle3	91	125.7	15	90.0	170.0
	Cycle4	72	126.9	15.5	85.0	165.0
	Cycle5	62	125.7	16.7	87.0	180.0
	Cycle6	59	126.3	18.1	90.0	190.0
	Cycle7	49	124.6	14	100.0	180.0
	Cycle8	39	127.7	14.9	100.0	160.0
	Cycle9	34	129.3	14.5	100.0	160.0
	Cycle10	26	122.4	13.9	90.0	144.0
	Cycle11	23	121	15.9	90.0	150.0
	Cycle12	17	118	12	100.0	140.0
	Cycle13	13	121.7	8.8	110.0	139.0
	Cycle14	10	125.8	9.5	110.0	140.0
	Cycle15	6	120	5.6	110.0	127.0
	Cycle16	2	125	7.1	120.0	130.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
Program: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\tblpgm\t_vital.sas (Run Date: 20JUL2009 13:07)

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle17	1	120		120.0	120.0
	Cycle18	1	110		110.0	110.0
	End of treatment	71	126.4	18.4	100.0	190.0
	Change from baseline: cycle2	104	-2.7	13.9	-40.0	40.0
	Change from baseline: cycle3	90	-1.6	15.9	-40.0	40.0
	Change from baseline: cycle4	72	-1.1	18	-60.0	50.0
	Change from baseline: cycle5	62	-3.1	19.6	-60.0	33.0
	Change from baseline: cycle6	59	-1	18.2	-74.0	40.0
	Change from baseline: cycle7	49	-3.5	18.1	-70.0	40.0
	Change from baseline: cycle8	39	0.2	19.3	-60.0	30.0
	Change from baseline: cycle9	34	-0.8	16.5	-47.0	40.0
	Change from baseline: cycle10	26	-3.7	17.6	-51.0	36.0
	Change from baseline: cycle11	23	-6.6	18.6	-40.0	40.0
	Change from baseline: cycle12	17	-6.6	17	-30.0	30.0
	Change from baseline: cycle13	13	-1.3	10	-20.0	16.0
	Change from baseline: cycle14	10	4.1	16.1	-20.0	40.0
	Change from baseline: cycle15	6	0.7	14.8	-20.0	20.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: cycle16	2	10	14.1	0.0	20.0
	Change from baseline: cycle17	1	20		20.0	20.0
	Change from baseline: cycle18	1	10		10.0	10.0
	Change from baseline: end of treatment	71	-3	18.5	-50.0	50.0
Sorafenib	Baseline	112	124	16.7	90.0	168.0
	Cycle2	100	128.2	16.8	89.0	174.0
	Cycle3	94	128.9	19.3	100.0	220.0
	Cycle4	84	127.9	16.9	100.0	180.0
	Cycle5	74	127.3	17.7	90.0	180.0
	Cycle6	69	126.7	16.8	95.0	170.0
	Cycle7	56	129.7	15.9	100.0	166.0
	Cycle8	49	124.1	15.8	93.0	160.0
	Cycle9	40	125.3	14.2	100.0	170.0
	Cycle10	29	127.6	11.1	100.0	147.0
	Cycle11	28	129.2	13.4	100.0	150.0
	Cycle12	22	125.5	14.9	100.0	150.0
	Cycle13	21	125.9	13.3	102.0	160.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle14	12	122	19.1	100.0	150.0
	Cycle15	9	122.1	15.6	97.0	154.0
	Cycle16	6	127	16	100.0	145.0
	Cycle17	2	135.5	7.8	130.0	141.0
	Cycle18	1	139		139.0	139.0
	Cycle19	1	130		130.0	130.0
	End of treatment	62	122.2	15	96.0	160.0
	Change from baseline: cycle2	100	3.1	16.5	-45.0	40.0
	Change from baseline: cycle3	94	4.2	19.5	-35.0	80.0
	Change from baseline: cycle4	84	2.4	20.2	-39.0	53.0
	Change from baseline: cycle5	74	1.6	21.7	-53.0	60.0
	Change from baseline: cycle6	69	1.3	19.7	-48.0	50.0
	Change from baseline: cycle7	56	3.3	17.9	-30.0	50.0
	Change from baseline: cycle8	49	-0.4	17.5	-45.0	34.0
	Change from baseline: cycle9	40	1.6	18.6	-43.0	31.0
	Change from baseline: cycle10	29	4.7	18.8	-31.0	40.0
	Change from baseline: cycle11	28	5.9	16.9	-35.0	42.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: cycle12	22	3	20.7	-37.0	40.0
	Change from baseline: cycle13	21	4.7	17.4	-33.0	40.0
	Change from baseline: cycle14	12	0.2	19.7	-40.0	36.0
	Change from baseline: cycle15	9	-5	23	-35.0	44.0
	Change from baseline: cycle16	6	-3	11.5	-15.0	17.0
	Change from baseline: cycle17	2	10.5	29	-10.0	31.0
	Change from baseline: cycle18	1	29		29.0	29.0
	Change from baseline: cycle19	1	20		20.0	20.0
	Change from baseline: end of treatment	62	-1.7	15.6	-38.0	45.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	112	67.3	12.6	37.0	116.0
	Cycle2	109	67.1	12.8	37.5	114.0
	Cycle3	91	67.3	12.6	38.3	110.0
	Cycle4	77	66.3	11.7	36.5	109.0
	Cycle5	67	66.6	11.3	45.0	107.0
	Cycle6	60	67.6	11.4	50.0	107.0
	Cycle7	50	68.8	12.2	50.0	110.5
	Cycle8	39	69.3	13.2	52.1	110.5
	Cycle9	34	69.8	13.4	53.3	110.0
	Cycle10	27	68.5	13.1	52.2	110.0
	Cycle11	23	70.9	15.2	51.9	111.0
	Cycle12	18	69.9	15	51.1	111.0
	Cycle13	14	69.4	11.2	56.0	90.0
	Cycle14	9	67.9	9.2	55.0	82.4
	Cycle15	6	69.4	9.1	60.0	84.1
	Cycle16	2	78.7	3.7	76.1	81.3

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle17	1	82		82.0	82.0
	Cycle18	1	81.6		81.6	81.6
	End of treatment	73	68.9	13.9	45.0	111.0
	Change from baseline: cycle2	109	-0.1	1.1	-3.7	4.0
	Change from baseline: cycle3	91	0.2	1.9	-7.1	5.0
	Change from baseline: cycle4	77	0.3	1.7	-3.3	4.2
	Change from baseline: cycle5	67	0.3	2.1	-4.7	5.5
	Change from baseline: cycle6	60	0.7	2.5	-6.0	6.9
	Change from baseline: cycle7	50	1.1	2.8	-5.8	7.0
	Change from baseline: cycle8	39	1.1	3.2	-7.3	11.0
	Change from baseline: cycle9	34	1.6	3.9	-8.7	16.2
	Change from baseline: cycle10	27	1.3	3.5	-10.5	9.0
	Change from baseline: cycle11	23	1.8	2.7	-1.5	10.0
	Change from baseline: cycle12	18	2.3	2.9	-2.2	8.0
	Change from baseline: cycle13	14	2.5	2.8	-1.7	8.0
	Change from baseline: cycle14	9	1.9	3.1	-2.0	7.2
	Change from baseline: cycle15	6	2.4	2.4	-0.7	4.7

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: cycle16	2	2.7	1.3	1.8	3.6
	Change from baseline: cycle17	1	2.5		2.5	2.5
	Change from baseline: cycle18	1	2.1		2.1	2.1
	Change from baseline: end of treatment	73	0.6	3	-7.6	15.0
Sorafenib	Baseline	112	66.7	13.5	42.0	103.0
	Cycle2	103	65.8	13.6	41.6	100.3
	Cycle3	94	65.8	14.3	36.4	104.0
	Cycle4	88	65.6	14	42.5	105.0
	Cycle5	76	66.6	13.7	43.0	103.7
	Cycle6	71	66.9	14.2	41.2	104.0
	Cycle7	59	67	14	42.5	102.6
	Cycle8	51	64.8	12.6	41.0	100.7
	Cycle9	42	66	11.4	40.5	101.3
	Cycle10	32	66	9.7	40.0	92.3
	Cycle11	32	65.6	9.8	38.5	90.8
	Cycle12	23	65.5	8.6	46.0	91.0
	Cycle13	21	68.2	11.5	56.5	105.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle14	14	66.9	9.8	57.5	95.1
	Cycle15	10	64.5	6	58.0	77.0
	Cycle16	6	64	3	60.0	68.0
	Cycle17	2	63.5	2.1	62.0	65.0
	Cycle18	1	62		62.0	62.0
	Cycle19	1	61		61.0	61.0
	End of treatment	65	62.2	12.7	36.4	101.9
	Change from baseline: cycle2	103	-1.4	2	-13.7	4.0
	Change from baseline: cycle3	94	-1.8	2.7	-13.8	3.3
	Change from baseline: cycle4	88	-2.7	6.1	-51.9	4.0
	Change from baseline: cycle5	76	-2.4	3.4	-16.0	4.2
	Change from baseline: cycle6	71	-2.4	3.8	-16.0	5.2
	Change from baseline: cycle7	59	-2.5	3.7	-15.0	6.1
	Change from baseline: cycle8	51	-3.1	4.3	-15.0	5.0
	Change from baseline: cycle9	42	-2.5	5	-15.0	9.6
	Change from baseline: cycle10	32	-3.3	5.8	-14.8	5.5
	Change from baseline: cycle11	32	-3.2	5.3	-15.0	6.7

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: cycle12	23	-3.9	5.7	-16.0	7.4
	Change from baseline: cycle13	21	-2	8.2	-16.0	22.0
	Change from baseline: cycle14	14	-4	5.9	-15.5	2.9
	Change from baseline: cycle15	10	-5.2	6.1	-16.0	2.8
	Change from baseline: cycle16	6	-6.8	7.5	-15.0	5.0
	Change from baseline: cycle17	2	2.8	3.2	0.5	5.0
	Change from baseline: cycle18	1	0.5		0.5	0.5
	Change from baseline: cycle19	1	-0.5		-0.5	-0.5
	Change from baseline: end of treatment	65	-3	4	-14.4	4.7

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Height (cm)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	112	158.4	7.1	140.0	176.0
Sorafenib	Baseline	112	158.5	6.7	144.0	187.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	111	1.6882	0.14952	1.2	2.1
	Cycle2	109	1.68183	0.1531	1.2	2.1
	Cycle3	92	1.67913	0.15285	1.3	2.1
	Cycle4	78	1.66949	0.14778	1.2	2.1
	Cycle5	68	1.67515	0.14187	1.3	2.0
	Cycle6	61	1.68902	0.13729	1.4	2.1
	Cycle7	50	1.7018	0.14016	1.4	2.1
	Cycle8	39	1.70462	0.14802	1.4	2.1
	Cycle9	34	1.70912	0.15316	1.4	2.1
	Cycle10	27	1.7	0.15704	1.4	2.0
	Cycle11	23	1.7213	0.17227	1.4	2.1
	Cycle12	18	1.71	0.17263	1.4	2.1
	Cycle13	14	1.71857	0.14469	1.5	2.0
	Cycle14	9	1.68222	0.13227	1.5	2.0
	Cycle15	6	1.71833	0.14784	1.5	2.0
	Cycle16	2	1.87	0.09899	1.8	1.9

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle17	1	1.94		1.9	1.9
	Cycle18	1	1.94		1.9	1.9
	Change from baseline: cycle2	108	-0.00278	0.01289	-0.1	0.0
	Change from baseline: cycle3	92	-0.00152	0.02127	-0.1	0.1
	Change from baseline: cycle4	78	-0.00038	0.02177	-0.1	0.1
	Change from baseline: cycle5	68	-0.00206	0.0236	-0.1	0.0
	Change from baseline: cycle6	61	0.0018	0.02784	-0.1	0.1
	Change from baseline: cycle7	50	0.006	0.03117	-0.1	0.1
	Change from baseline: cycle8	39	0.00359	0.03065	-0.1	0.1
	Change from baseline: cycle9	34	0.00971	0.0268	-0.1	0.1
	Change from baseline: cycle10	27	0.01185	0.03151	-0.1	0.1
	Change from baseline: cycle11	23	0.01261	0.03333	-0.1	0.1
	Change from baseline: cycle12	18	0.01722	0.04142	-0.1	0.1
	Change from baseline: cycle13	14	0.02071	0.04428	-0.1	0.1
	Change from baseline: cycle14	9	0.01	0.04664	-0.1	0.1
	Change from baseline: cycle15	6	0.01667	0.02875	-0.0	0.1
	Change from baseline: cycle16	2	0.005	0.02121	-0.0	0.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: cycle17	1	0.02		0.0	0.0
	Change from baseline: cycle18	1	0.02		0.0	0.0
Sorafenib	Baseline	112	1.67705	0.16428	1.3	2.2
	Cycle2	103	1.66922	0.16736	1.3	2.2
	Cycle3	94	1.6733	0.17409	1.2	2.2
	Cycle4	88	1.68102	0.1699	1.4	2.3
	Cycle5	76	1.68461	0.16625	1.4	2.2
	Cycle6	71	1.68761	0.17009	1.3	2.2
	Cycle7	59	1.69153	0.17625	1.3	2.2
	Cycle8	51	1.66353	0.15042	1.3	2.0
	Cycle9	43	1.67581	0.14161	1.4	2.0
	Cycle10	32	1.67625	0.12998	1.3	1.9
	Cycle11	32	1.67625	0.13119	1.3	1.9
	Cycle12	23	1.68522	0.12176	1.4	1.9
	Cycle13	21	1.7	0.11036	1.5	1.9
	Cycle14	14	1.70929	0.12755	1.6	2.0
	Cycle15	10	1.695	0.1203	1.6	1.9

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle16	6	1.705	0.09752	1.6	1.9
	Cycle17	2	1.635	0.02121	1.6	1.7
	Cycle18	1	1.65		1.7	1.7
	Cycle19	1	1.65		1.7	1.7
	Change from baseline: cycle2	103	-0.01379	0.02331	-0.1	0.1
	Change from baseline: cycle3	94	-0.01436	0.03102	-0.2	0.1
	Change from baseline: cycle4	88	-0.01682	0.03292	-0.1	0.1
	Change from baseline: cycle5	76	-0.02171	0.03782	-0.1	0.1
	Change from baseline: cycle6	71	-0.02127	0.03609	-0.1	0.1
	Change from baseline: cycle7	59	-0.01712	0.0468	-0.2	0.2
	Change from baseline: cycle8	51	-0.02784	0.04424	-0.1	0.1
	Change from baseline: cycle9	43	-0.02442	0.054	-0.2	0.1
	Change from baseline: cycle10	32	-0.03438	0.06777	-0.2	0.1
	Change from baseline: cycle11	32	-0.03188	0.06874	-0.3	0.1
	Change from baseline: cycle12	23	-0.03304	0.05834	-0.2	0.1
	Change from baseline: cycle13	21	-0.03	0.06641	-0.2	0.1
	Change from baseline: cycle14	14	-0.02714	0.05136	-0.1	0.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: cycle15	10	-0.028	0.04984	-0.1	0.0
	Change from baseline: cycle16	6	-0.05333	0.08116	-0.2	0.1
	Change from baseline: cycle17	2	0.025	0.03536	0.0	0.1
	Change from baseline: cycle18	1	0		0.0	0.0
	Change from baseline: cycle19	1	0		0.0	0.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	109	80.7	12.7	54.0	126.0
	Cycle2	106	81.7	11.8	53.0	118.0
	Cycle3	90	80	11.3	52.0	108.0
	Cycle4	71	80.8	12.4	58.0	112.0
	Cycle5	63	79.2	10.8	44.0	112.0
	Cycle6	59	78.2	13	43.0	116.0
	Cycle7	49	79.6	12	54.0	112.0
	Cycle8	39	78.1	11.9	55.0	106.0
	Cycle9	34	80.2	11.7	50.0	104.0
	Cycle10	26	77.3	10.1	56.0	101.0
	Cycle11	23	78	13.1	55.0	106.0
	Cycle12	17	78.5	12.3	63.0	110.0
	Cycle13	13	75	12.5	60.0	108.0
	Cycle14	9	73.6	3.7	68.0	80.0
	Cycle15	6	75	13.6	64.0	102.0
	Cycle16	2	72	2.8	70.0	74.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle17	1	76		76.0	76.0
	Cycle18	1	67		67.0	67.0
	End of treatment	71	83.7	12.4	50.0	122.0
	Change from baseline: cycle2	103	0.2	11.7	-32.0	31.0
	Change from baseline: cycle3	89	-0.1	12.1	-30.0	34.0
	Change from baseline: cycle4	70	1.6	14.9	-38.0	34.0
	Change from baseline: cycle5	62	0.2	14.2	-40.0	28.0
	Change from baseline: cycle6	58	0.1	14.6	-41.0	34.0
	Change from baseline: cycle7	48	2.2	14.5	-30.0	28.0
	Change from baseline: cycle8	39	0.7	12.2	-28.0	32.0
	Change from baseline: cycle9	34	2.2	11.2	-23.0	30.0
	Change from baseline: cycle10	26	2.2	9.8	-16.0	20.0
	Change from baseline: cycle11	23	2.5	11.3	-16.0	25.0
	Change from baseline: cycle12	17	2.9	12.6	-24.0	24.0
	Change from baseline: cycle13	13	-0.5	8.8	-16.0	14.0
	Change from baseline: cycle14	9	1.4	8.8	-16.0	10.0
	Change from baseline: cycle15	6	6.3	12.8	-11.0	28.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: cycle16	2	0	14.1	-10.0	10.0
	Change from baseline: cycle17	1	12		12.0	12.0
	Change from baseline: cycle18	1	3		3.0	3.0
	Change from baseline: end of treatment	70	1.3	12.9	-36.0	35.0
Sorafenib	Baseline	111	84.2	14.1	53.0	132.0
	Cycle2	94	82.5	13.6	54.0	120.0
	Cycle3	91	82.7	12.2	54.0	122.0
	Cycle4	84	83.1	13.6	56.0	122.0
	Cycle5	74	81.4	13.4	55.0	123.0
	Cycle6	69	83	16.6	50.0	130.0
	Cycle7	56	82.1	13.6	59.0	120.0
	Cycle8	49	81.4	12.3	64.0	116.0
	Cycle9	40	79.8	11.4	59.0	110.0
	Cycle10	29	82.7	13.9	64.0	117.0
	Cycle11	28	83.1	12	61.0	108.0
	Cycle12	22	83.5	15.7	62.0	122.0
	Cycle13	21	82	10.7	70.0	109.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle14	12	84.6	15.3	68.0	117.0
	Cycle15	9	86.4	15.7	62.0	109.0
	Cycle16	6	88.2	16.3	68.0	112.0
	Cycle17	2	92	33.9	68.0	116.0
	Cycle18	1	85		85.0	85.0
	Cycle19	1	72		72.0	72.0
	End of treatment	61	87.7	14	57.0	122.0
	Change from baseline: cycle2	94	-1.6	12.3	-37.0	32.0
	Change from baseline: cycle3	91	-1.1	13.4	-43.0	44.0
	Change from baseline: cycle4	83	-1.1	14.3	-45.0	36.0
	Change from baseline: cycle5	73	-1.2	11.2	-41.0	26.0
	Change from baseline: cycle6	69	0.6	13.7	-29.0	32.0
	Change from baseline: cycle7	56	-0.3	12.9	-32.0	31.0
	Change from baseline: cycle8	49	0	10.6	-24.0	28.0
	Change from baseline: cycle9	40	-2.3	11.1	-22.0	20.0
	Change from baseline: cycle10	29	-1.1	10.8	-25.0	17.0
	Change from baseline: cycle11	28	0.8	10.2	-22.0	29.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: cycle12	22	0.3	10.3	-28.0	22.0
	Change from baseline: cycle13	21	-0.6	11.8	-20.0	26.0
	Change from baseline: cycle14	12	2.3	11.3	-17.0	26.0
	Change from baseline: cycle15	9	4	14.1	-18.0	31.0
	Change from baseline: cycle16	6	2.2	11.4	-12.0	13.0
	Change from baseline: cycle17	2	2	19.8	-12.0	16.0
	Change from baseline: cycle18	1	-15		-15.0	-15.0
	Change from baseline: cycle19	1	-28		-28.0	-28.0
	Change from baseline: end of treatment	61	2.9	16	-34.0	36.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	107	36.3	0.5	35.0	37.7
	Cycle2	102	36.3	0.4	34.7	37.4
	Cycle3	90	36.2	0.4	35.0	37.3
	Cycle4	70	36.2	0.5	34.3	37.4
	Cycle5	62	36.3	0.4	35.0	37.4
	Cycle6	58	36.3	0.3	35.6	37.2
	Cycle7	49	36.3	0.4	35.4	37.0
	Cycle8	39	36.3	0.5	35.0	37.3
	Cycle9	34	36.3	0.4	35.0	37.1
	Cycle10	26	36.3	0.4	34.8	37.1
	Cycle11	23	36.5	0.4	36.0	37.6
	Cycle12	17	36.3	0.4	35.7	37.1
	Cycle13	13	36.4	0.4	36.0	37.1
	Cycle14	9	36.4	0.3	36.0	37.1
	Cycle15	5	36.2	0.5	35.4	36.5
	Cycle16	2	36.6	0.4	36.3	36.8

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle17	1	36.1		36.1	36.1
	Cycle18	1	36		36.0	36.0
	End of treatment	70	36.3	0.4	34.8	37.2
	Change from baseline: cycle2	97	0	0.4	-1.3	1.1
	Change from baseline: cycle3	88	0	0.5	-1.5	1.4
	Change from baseline: cycle4	68	-0.1	0.4	-1.7	1.2
	Change from baseline: cycle5	60	0	0.4	-0.8	1.2
	Change from baseline: cycle6	56	0	0.5	-1.2	1.5
	Change from baseline: cycle7	47	-0.1	0.4	-1.0	1.1
	Change from baseline: cycle8	38	-0.1	0.4	-0.9	1.0
	Change from baseline: cycle9	33	-0.1	0.4	-1.2	0.6
	Change from baseline: cycle10	25	0	0.4	-0.7	0.8
	Change from baseline: cycle11	22	0.1	0.3	-0.4	1.1
	Change from baseline: cycle12	17	0	0.5	-0.9	1.1
	Change from baseline: cycle13	13	0.1	0.4	-0.7	1.1
	Change from baseline: cycle14	9	0.1	0.3	-0.3	0.7
	Change from baseline: cycle15	5	-0.1	0.5	-0.8	0.5

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: cycle16	2	0.4	0.1	0.3	0.4
	Change from baseline: cycle17	1	0.1		0.1	0.1
	Change from baseline: cycle18	1	0		0.0	0.0
	Change from baseline: end of treatment	67	0.1	0.5	-0.7	1.5
Sorafenib	Baseline	110	36.4	0.5	35.0	37.5
	Cycle2	93	36.3	0.4	35.4	37.5
	Cycle3	91	36.3	0.4	35.2	37.3
	Cycle4	82	36.3	0.5	35.0	37.5
	Cycle5	72	36.3	0.4	35.5	37.2
	Cycle6	67	36.3	0.3	35.4	37.1
	Cycle7	55	36.3	0.4	35.5	37.5
	Cycle8	49	36.2	0.4	35.5	37.4
	Cycle9	40	36.2	0.4	34.7	37.2
	Cycle10	29	36.1	0.5	34.1	36.8
	Cycle11	27	36.3	0.4	35.5	37.1
	Cycle12	22	36.3	0.5	35.5	37.4
	Cycle13	20	36.3	0.5	35.5	37.5

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle14	12	36.3	0.5	35.5	36.9
	Cycle15	9	36.4	0.4	36.0	37.2
	Cycle16	6	36.4	0.4	36.0	37.0
	Cycle17	2	36.4	0.6	36.0	36.8
	Cycle18	1	36		36.0	36.0
	Cycle19	1	36		36.0	36.0
	End of treatment	60	36.3	0.5	34.8	38.0
	Change from baseline: cycle2	92	-0.1	0.4	-1.0	1.1
	Change from baseline: cycle3	89	-0.1	0.4	-1.6	1.0
	Change from baseline: cycle4	80	0	0.4	-1.1	1.1
	Change from baseline: cycle5	70	-0.1	0.4	-1.5	0.7
	Change from baseline: cycle6	66	0	0.5	-1.6	1.5
	Change from baseline: cycle7	54	0	0.4	-0.9	1.0
	Change from baseline: cycle8	48	-0.1	0.4	-0.9	1.0
	Change from baseline: cycle9	40	-0.1	0.5	-2.3	0.8
	Change from baseline: cycle10	29	-0.2	0.6	-2.0	0.7
	Change from baseline: cycle11	27	0	0.4	-0.9	1.0

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.5 Vital Signals – Descriptive Statistics
(Safety Population)

Variable= Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: cycle12	22	-0.1	0.5	-0.9	1.6
	Change from baseline: cycle13	20	-0.1	0.6	-1.0	1.7
	Change from baseline: cycle14	12	0	0.5	-0.8	1.0
	Change from baseline: cycle15	9	0.1	0.5	-0.5	1.0
	Change from baseline: cycle16	6	-0.1	0.3	-0.5	0.3
	Change from baseline: cycle17	2	0.2	0.9	-0.5	0.8
	Change from baseline: cycle18	1	-0.5		-0.5	-0.5
	Change from baseline: cycle19	1	-0.5		-0.5	-0.5
	Change from baseline: end of treatment	59	-0.1	0.6	-2.2	1.7

Note: Baseline vital signs are measured within 1 week of randomization. Vital signs during treatment period are measured within 48 hours of cycle start.

Source: E:\BioMetrics\Rand\Bay43-9006\Breast\PhaseIIb\CSR\Baselga\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 27MAR09, Download: 08JUN09)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Baseline	N	111		111	
		Mean	12.8		12.5	
		SD	1.4		1.5	
		Median	13		13	
		Min	9		8	
		Max	16		16	
	Cycle 2	N	110	109	103	103
		Mean	12.5	-0.3	13.0	0.5
		SD	1.3	0.8	1.6	0.9
		Median	12	0	13	1
		Min	8	-5	9	-2
		Max	15	2	16	4
	Cycle 3	N	92	91	94	94
		Mean	12.5	-0.3	12.8	0.3
		SD	1.4	0.9	1.4	1.0
		Median	13	0	13	0
		Min	10	-2	10	-2
		Max	15	3	16	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 4	N	79	78	87	87
		Mean	12.6	-0.3	12.7	0.3
		SD	1.3	0.9	1.6	1.1
		Median	13	0	13	0
		Min	10	-2	9	-3
		Max	15	2	16	2
	Cycle 5	N	69	68	77	77
		Mean	12.6	-0.3	12.7	0.3
		SD	1.3	1.1	1.6	1.1
		Median	13	0	13	0
		Min	9	-2	9	-2
		Max	15	3	16	3
	Cycle 6	N	63	62	73	73
		Mean	12.5	-0.4	12.7	0.3
		SD	1.3	1.1	1.6	1.1
		Median	12	0	13	0
		Min	9	-2	9	-2
		Max	15	3	16	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 7	N	54	53	65	65
		Mean	12.6	-0.3	12.8	0.2
		SD	1.2	1.1	1.6	1.3
		Median	13	-1	13	0
		Min	10	-2	10	-3
		Max	16	2	16	3
	Cycle 8	N	45	44	61	61
		Mean	12.7	-0.2	13.0	0.4
		SD	1.2	1.1	1.4	1.1
		Median	13	0	13	0
		Min	10	-3	9	-2
		Max	15	2	16	3
	Cycle 9	N	42	41	56	56
		Mean	12.8	-0.1	13.1	0.5
		SD	1.3	1.1	1.4	1.0
		Median	13	0	13	1
		Min	10	-3	9	-2
		Max	16	2	16	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 10	N	36	36	49	49
		Mean	12.5	-0.2	13.0	0.2
		SD	1.3	1.2	1.4	1.2
		Median	12	-1	13	0
		Min	10	-3	10	-4
		Max	15	2	16	4
	Cycle 11	N	30	29	48	48
		Mean	12.5	-0.3	13.0	0.2
		SD	1.3	1.4	1.5	1.2
		Median	12	0	13	0
		Min	10	-4	8	-4
		Max	15	2	16	4
	Cycle 12	N	25	25	39	39
		Mean	12.8	-0.1	12.9	0.1
		SD	1.3	1.2	1.4	1.3
		Median	13	0	13	0
		Min	10	-2	10	-3
		Max	16	3	16	4

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 13	N	20	20	36	36
		Mean	12.7	-0.2	12.9	0.1
		SD	1.2	0.9	1.4	1.4
		Median	13	0	13	0
		Min	10	-2	11	-4
		Max	15	2	15	3
	Cycle 14	N	16	16	35	35
		Mean	12.4	-0.3	13.0	0.1
		SD	1.3	0.9	1.5	1.8
		Median	12	0	13	0
		Min	9	-2	10	-4
		Max	15	1	17	7
	Cycle 15	N	14	14	33	33
		Mean	12.8	0.1	12.8	0.0
		SD	1.4	0.9	1.4	1.3
		Median	13	0	13	0
		Min	10	-2	10	-3
		Max	15	2	16	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 16	N	7	7	30	30
		Mean	13.0	0.1	12.8	0.1
		SD	1.6	0.8	1.3	1.3
		Median	13	0	13	0
		Min	10	-1	11	-3
		Max	15	1	16	3
	Cycle 17	N	7	7	25	25
		Mean	12.8	-0.1	12.9	0.3
		SD	1.7	0.8	1.6	1.6
		Median	13	0	13	0
		Min	10	-1	11	-2
		Max	15	1	17	4
	Cycle 18	N	6	6	21	21
		Mean	12.7	0.0	12.9	0.3
		SD	1.7	1.2	1.9	1.7
		Median	13	0	13	1
		Min	10	-2	7	-5
		Max	15	2	15	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 19	N	4	4	19	19
		Mean	12.2	-0.3	12.9	0.5
		SD	2.4	1.0	1.4	1.6
		Median	13	0	13	0
		Min	9	-1	11	-2
		Max	14	1	16	3
	Cycle 20	N	3	3	18	18
		Mean	12.8	-0.4	13.2	0.7
		SD	1.4	1.2	1.3	1.5
		Median	13	0	13	0
		Min	11	-2	11	-1
		Max	14	1	16	4
	Cycle 21	N	3	3	15	15
		Mean	13.1	-0.1	12.8	0.5
		SD	0.7	1.8	1.2	1.4
		Median	14	-1	13	0
		Min	12	-2	11	-2
		Max	14	2	15	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 22	N	2	2	14	14
		Mean	13.9	-0.7	12.9	0.6
		SD	0.0	0.6	1.2	1.6
		Median	14	-1	13	0
		Min	14	-1	11	-2
		Max	14	0	15	4
	Cycle 23	N	2	2	13	13
		Mean	13.5	-1.1	12.6	0.6
		SD	0.1	0.6	1.3	1.8
		Median	13	-1	13	0
		Min	13	-2	11	-2
		Max	14	-1	15	4
	Cycle 24	N	1	1	11	11
		Mean	14.0	-1.0	12.4	0.4
		SD	-	-	1.4	1.7
		Median	14	-1	13	0
		Min	14	-1	10	-2
		Max	14	-1	15	4

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 25	N	1	1	10	10
		Mean	13.0	-2.0	12.3	0.4
		SD	-	-	1.3	1.6
		Median	13	-2	13	0
		Min	13	-2	10	-2
		Max	13	-2	14	3
	Cycle 26	N	1	1	10	10
		Mean	14.2	-0.8	12.5	0.6
		SD	-	-	1.4	1.9
		Median	14	-1	13	1
		Min	14	-1	9	-3
		Max	14	-1	14	4
	Cycle 27	N	1	1	10	10
		Mean	13.0	-2.0	12.7	0.7
		SD	-	-	1.6	2.2
		Median	13	-2	13	1
		Min	13	-2	9	-3
		Max	13	-2	14	4

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 28	N	0	0	9	9
		Mean	-	-	12.6	0.7
		SD	-	-	1.6	2.1
		Median	-	-	13	0
		Min	-	-	9	-3
		Max	-	-	15	4
	Cycle 29	N	0	0	9	9
		Mean	-	-	12.5	0.6
		SD	-	-	1.1	1.9
		Median	-	-	13	0
		Min	-	-	10	-2
		Max	-	-	14	4
	Cycle 30	N	0	0	7	7
		Mean	-	-	12.9	0.5
		SD	-	-	0.9	1.7
		Median	-	-	13	0
		Min	-	-	12	-1
		Max	-	-	14	4

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 31	N	0	0	6	6
		Mean	-	-	13.8	1.3
		SD	-	-	0.6	1.1
		Median	-	-	14	1
		Min	-	-	13	0
		Max	-	-	15	3
	Cycle 32	N	0	0	5	5
		Mean	-	-	13.6	1.1
		SD	-	-	0.4	1.8
		Median	-	-	14	1
		Min	-	-	13	-1
		Max	-	-	14	4
	Cycle 33	N	0	0	5	5
		Mean	-	-	13.4	1.0
		SD	-	-	0.6	1.5
		Median	-	-	14	1
		Min	-	-	13	0
		Max	-	-	14	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 34	N	0	0	4	4
		Mean	-	-	13.5	1.2
		SD	-	-	0.4	1.7
		Median	-	-	13	1
		Min	-	-	13	-1
		Max	-	-	14	4
	Cycle 35	N	0	0	1	1
		Mean	-	-	12.9	3.4
		SD	-	-	-	-
		Median	-	-	13	3
		Min	-	-	13	3
		Max	-	-	13	3
	Cycle 36	N	0	0	1	1
		Mean	-	-	12.3	2.8
		SD	-	-	-	-
		Median	-	-	12	3
		Min	-	-	12	3
		Max	-	-	12	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hemoglobin (g/dL)	Cycle 37	N	0	0	1	1
		Mean	-	-	13.0	3.5
		SD	-	-	-	-
		Median	-	-	13	4
		Min	-	-	13	4
		Max	-	-	13	4
	Cycle 38	N	0	0	1	1
		Mean	-	-	13.1	3.6
		SD	-	-	-	-
		Median	-	-	13	4
		Min	-	-	13	4
		Max	-	-	13	4
	Cycle 39	N	0	0	1	1
		Mean	-	-	12.4	2.9
		SD	-	-	-	-
		Median	-	-	12	3
		Min	-	-	12	3
		Max	-	-	12	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Baseline	N	111		111	
		Mean	38.1		37.7	
		SD	3.8		4.3	
		Median	38		39	
		Min	26		27	
		Max	49		48	
	Cycle 2	N	110	109	103	103
		Mean	37.2	-0.9	38.7	1.1
		SD	3.8	2.5	4.7	2.8
		Median	37	-1	39	1
		Min	26	-17	26	-5
		Max	46	4	48	9
	Cycle 3	N	92	91	94	94
		Mean	37.1	-1.2	38.5	0.9
		SD	3.9	2.8	4.2	3.0
		Median	37	-1	39	1
		Min	28	-8	28	-7
		Max	45	6	48	8

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 4	N	79	78	87	87
		Mean	37.2	-1.1	37.7	0.2
		SD	3.6	2.8	4.7	3.4
		Median	37	-1	37	0
		Min	30	-6	27	-11
		Max	46	8	49	7
	Cycle 5	N	69	68	77	77
		Mean	36.7	-1.3	37.6	0.1
		SD	3.5	3.3	4.5	3.5
		Median	36	-2	38	1
		Min	28	-7	28	-9
		Max	44	9	46	7
	Cycle 6	N	63	62	73	73
		Mean	36.6	-1.6	37.5	0.0
		SD	3.7	3.3	4.3	3.5
		Median	36	-2	38	0
		Min	27	-9	28	-8
		Max	44	8	47	9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 7	N	54	53	65	65
		Mean	37.2	-1.2	37.9	-0.1
		SD	3.3	3.2	4.3	4.0
		Median	37	-2	38	0
		Min	28	-7	29	-11
		Max	45	7	48	10
	Cycle 8	N	45	44	61	61
		Mean	37.2	-1.1	38.4	0.6
		SD	3.3	3.3	4.0	3.6
		Median	37	-1	39	1
		Min	31	-9	29	-9
		Max	45	6	47	9
	Cycle 9	N	42	41	56	56
		Mean	37.8	-0.6	38.7	0.7
		SD	4.1	3.8	4.1	3.3
		Median	38	0	38	1
		Min	30	-10	26	-7
		Max	48	6	46	8

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 10	N	36	36	49	49
		Mean	36.9	-1.0	38.4	-0.1
		SD	4.2	3.7	4.0	3.7
		Median	37	-2	39	0
		Min	28	-7	29	-8
		Max	50	6	48	12
	Cycle 11	N	30	29	48	48
		Mean	36.6	-1.7	38.3	-0.3
		SD	3.6	3.7	4.2	3.9
		Median	36	-1	39	0
		Min	30	-13	25	-14
		Max	43	4	48	8
	Cycle 12	N	24	24	39	39
		Mean	37.2	-1.1	38.0	-0.6
		SD	3.6	3.1	3.8	3.7
		Median	37	-1	38	-1
		Min	31	-7	30	-8
		Max	47	5	45	9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 13	N	20	20	36	36
		Mean	37.4	-1.1	38.0	-0.8
		SD	2.9	3.1	3.9	4.0
		Median	37	-1	38	0
		Min	31	-7	31	-11
		Max	42	4	45	7
	Cycle 14	N	16	16	35	35
		Mean	36.5	-1.5	38.1	-0.7
		SD	3.0	3.0	4.5	5.2
		Median	37	-1	38	-2
		Min	31	-7	30	-12
		Max	41	2	53	19
	Cycle 15	N	14	14	33	33
		Mean	37.2	-0.9	37.6	-1.0
		SD	3.0	2.7	3.8	3.6
		Median	38	-1	37	-2
		Min	32	-7	30	-6
		Max	42	4	46	9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 16	N	7	7	30	30
		Mean	37.6	-0.2	37.9	-0.6
		SD	4.1	3.1	3.8	3.9
		Median	39	0	38	-1
		Min	30	-5	30	-9
		Max	42	4	47	8
	Cycle 17	N	7	7	25	25
		Mean	36.9	-0.9	38.4	0.0
		SD	4.2	2.5	3.9	4.0
		Median	39	-1	38	-1
		Min	29	-5	32	-6
		Max	40	3	47	8
	Cycle 18	N	6	6	21	21
		Mean	36.8	-0.6	38.4	-0.1
		SD	4.1	4.2	4.8	4.2
		Median	37	-1	38	-1
		Min	30	-7	23	-13
		Max	41	5	44	6

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 19	N	4	4	19	19
		Mean	35.0	-0.9	39.0	1.1
		SD	5.6	3.2	3.9	3.9
		Median	36	-1	37	0
		Min	28	-4	33	-4
		Max	40	3	49	10
	Cycle 20	N	3	3	18	18
		Mean	35.8	-1.4	39.1	1.1
		SD	3.4	2.4	3.9	4.1
		Median	38	-2	38	0
		Min	32	-3	35	-4
		Max	38	1	49	9
	Cycle 21	N	3	3	15	15
		Mean	38.1	0.8	37.8	0.1
		SD	0.5	6.2	3.0	3.7
		Median	38	-3	37	-1
		Min	38	-3	33	-4
		Max	39	8	44	7

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 22	N	2	2	14	14
		Mean	39.0	-1.6	38.6	1.0
		SD	0.4	0.6	2.8	3.8
		Median	39	-2	39	0
		Min	39	-2	34	-4
		Max	39	-1	44	9
	Cycle 23	N	2	2	13	13
		Mean	38.0	-2.6	38.2	1.1
		SD	0.0	0.1	3.6	4.3
		Median	38	-3	38	1
		Min	38	-3	33	-4
		Max	38	-3	44	9
	Cycle 24	N	1	1	11	11
		Mean	38.8	-1.9	37.5	0.2
		SD	-	-	3.6	4.3
		Median	39	-2	39	-1
		Min	39	-2	30	-8
		Max	39	-2	42	9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 25	N	1	1	10	10
		Mean	38.2	-2.5	36.8	-0.4
		SD	-	-	3.4	4.2
		Median	38	-3	38	0
		Min	38	-3	30	-8
		Max	38	-3	41	6
	Cycle 26	N	1	1	10	10
		Mean	39.7	-1.0	37.8	0.6
		SD	-	-	3.1	4.4
		Median	40	-1	38	0
		Min	40	-1	31	-7
		Max	40	-1	42	9
	Cycle 27	N	1	1	10	10
		Mean	37.4	-3.3	38.0	0.8
		SD	-	-	3.9	5.6
		Median	37	-3	38	0
		Min	37	-3	29	-9
		Max	37	-3	42	10

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 28	N	0	0	9	9
		Mean	-	-	37.8	0.6
		SD	-	-	4.2	6.2
		Median	-	-	39	1
		Min	-	-	30	-8
		Max	-	-	43	11
	Cycle 29	N	0	0	9	9
		Mean	-	-	37.9	0.7
		SD	-	-	3.3	5.6
		Median	-	-	38	0
		Min	-	-	32	-6
		Max	-	-	44	11
	Cycle 30	N	0	0	7	7
		Mean	-	-	38.7	0.3
		SD	-	-	2.9	4.5
		Median	-	-	39	-1
		Min	-	-	36	-4
		Max	-	-	44	9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 31	N	0	0	6	6
		Mean	-	-	41.1	2.6
		SD	-	-	3.1	2.8
		Median	-	-	41	3
		Min	-	-	37	-2
		Max	-	-	46	6
	Cycle 32	N	0	0	5	5
		Mean	-	-	40.9	2.7
		SD	-	-	1.8	4.9
		Median	-	-	42	1
		Min	-	-	39	-2
		Max	-	-	43	11
	Cycle 33	N	0	0	5	5
		Mean	-	-	39.1	0.8
		SD	-	-	1.9	3.4
		Median	-	-	40	1
		Min	-	-	36	-3
		Max	-	-	41	5

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 34	N	0	0	4	4
		Mean	-	-	39.8	1.7
		SD	-	-	0.9	4.3
		Median	-	-	40	0
		Min	-	-	39	-1
		Max	-	-	41	8
	Cycle 35	N	0	0	1	1
		Mean	-	-	38.9	7.7
		SD	-	-	-	-
		Median	-	-	39	8
		Min	-	-	39	8
		Max	-	-	39	8
	Cycle 36	N	0	0	1	1
		Mean	-	-	35.1	3.9
		SD	-	-	-	-
		Median	-	-	35	4
		Min	-	-	35	4
		Max	-	-	35	4

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Hematocrit (%)	Cycle 37	N	0	0	1	1
		Mean	-	-	39.5	8.3
		SD	-	-	-	-
		Median	-	-	40	8
		Min	-	-	40	8
		Max	-	-	40	8
	Cycle 38	N	0	0	1	1
		Mean	-	-	39.9	8.7
		SD	-	-	-	-
		Median	-	-	40	9
		Min	-	-	40	9
		Max	-	-	40	9
	Cycle 39	N	0	0	1	1
		Mean	-	-	38.0	6.8
		SD	-	-	-	-
		Median	-	-	38	7
		Min	-	-	38	7
		Max	-	-	38	7

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Baseline	N	111		111	
		Mean	6.4		6.7	
		SD	2.2		2.7	
		Median	6		6	
		Min	3		3	
		Max	14		21	
	Cycle 2	N	110	109	103	103
		Mean	6.0	-0.5	5.5	-1.2
		SD	1.8	1.9	2.1	2.8
		Median	6	0	5	-1
		Min	2	-7	3	-18
		Max	12	4	16	8
	Cycle 3	N	92	91	94	94
		Mean	6.1	-0.4	5.2	-1.3
		SD	2.2	2.2	1.9	2.7
		Median	6	0	5	-1
		Min	3	-8	2	-18
		Max	19	11	16	9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 4	N	79	78	87	87
		Mean	5.6	-0.8	5.3	-1.1
		SD	1.6	2.0	1.6	2.2
		Median	5	-1	5	-1
		Min	2	-10	2	-9
		Max	11	3	11	4
	Cycle 5	N	69	68	77	77
		Mean	5.6	-0.9	5.4	-1.0
		SD	2.0	2.4	1.6	2.1
		Median	6	-1	5	-1
		Min	3	-10	3	-8
		Max	16	9	11	4
	Cycle 6	N	63	62	73	73
		Mean	5.6	-0.8	5.3	-1.1
		SD	1.7	2.3	1.5	2.0
		Median	5	-1	5	-1
		Min	3	-10	3	-8
		Max	11	4	11	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 7	N	53	52	65	65
		Mean	6.0	-0.3	5.5	-1.0
		SD	2.4	2.8	1.6	2.3
		Median	6	0	5	-1
		Min	3	-10	3	-9
		Max	17	10	11	6
	Cycle 8	N	45	44	61	61
		Mean	5.3	-1.0	5.4	-1.1
		SD	1.7	2.0	1.4	2.1
		Median	5	-1	6	-1
		Min	3	-9	3	-8
		Max	10	2	9	5
	Cycle 9	N	42	41	56	56
		Mean	5.7	-0.6	5.8	-0.7
		SD	2.3	2.4	2.3	2.7
		Median	5	-1	5	-1
		Min	3	-9	3	-8
		Max	15	8	16	8

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 10	N	36	36	49	49
		Mean	5.3	-0.9	5.7	-0.8
		SD	1.6	2.0	1.9	2.6
		Median	5	-1	5	-1
		Min	2	-9	3	-8
		Max	11	3	15	9
	Cycle 11	N	30	29	48	48
		Mean	5.0	-1.0	5.2	-1.4
		SD	1.4	2.3	1.4	2.5
		Median	5	-1	5	-1
		Min	3	-10	2	-10
		Max	9	3	9	3
	Cycle 12	N	25	25	39	39
		Mean	5.9	0.0	5.2	-1.2
		SD	2.6	2.7	1.2	2.2
		Median	5	0	5	-1
		Min	3	-8	3	-8
		Max	15	8	8	5

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 13	N	20	20	36	36
		Mean	5.0	-1.0	5.2	-1.2
		SD	1.3	2.7	1.5	2.3
		Median	5	-1	5	-1
		Min	3	-11	3	-8
		Max	9	2	10	3
	Cycle 14	N	16	16	35	35
		Mean	4.8	-1.2	5.5	-0.9
		SD	1.4	2.8	1.5	2.3
		Median	5	-1	5	0
		Min	3	-10	3	-9
		Max	7	2	9	4
	Cycle 15	N	14	14	33	33
		Mean	4.9	-1.1	5.4	-0.8
		SD	1.3	2.8	1.3	1.6
		Median	4	-1	5	-1
		Min	3	-10	3	-4
		Max	7	2	8	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 16	N	7	7	30	30
		Mean	5.6	0.1	5.5	-0.6
		SD	1.6	1.7	2.1	2.5
		Median	6	0	5	-1
		Min	3	-3	4	-5
		Max	8	3	14	8
	Cycle 17	N	7	7	25	25
		Mean	5.8	0.2	5.5	-0.7
		SD	1.7	1.9	1.6	2.1
		Median	7	1	5	0
		Min	3	-3	3	-5
		Max	8	2	9	3
	Cycle 18	N	6	6	21	21
		Mean	5.3	-0.4	5.5	-0.7
		SD	2.3	2.4	1.5	2.3
		Median	5	-1	5	-1
		Min	3	-4	4	-4
		Max	9	3	9	4

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 19	N	4	4	19	19
		Mean	5.6	-0.4	5.5	-0.8
		SD	1.3	2.1	1.2	2.2
		Median	6	0	6	0
		Min	4	-3	4	-4
		Max	7	2	8	4
	Cycle 20	N	3	3	18	18
		Mean	5.5	-0.1	5.5	-0.7
		SD	2.2	3.4	1.9	2.6
		Median	5	-1	5	-1
		Min	4	-3	4	-4
		Max	8	3	11	7
	Cycle 21	N	3	3	15	15
		Mean	4.7	-1.0	5.2	-1.1
		SD	1.7	3.2	1.5	2.2
		Median	4	-1	5	-1
		Min	4	-4	3	-5
		Max	7	2	8	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 22	N	2	2	14	14
		Mean	5.3	0.9	5.2	-1.0
		SD	2.5	2.3	1.2	2.3
		Median	5	1	5	0
		Min	4	-1	4	-5
		Max	7	3	7	2
	Cycle 23	N	2	2	13	13
		Mean	5.4	1.0	4.9	-1.3
		SD	3.4	3.1	1.3	1.5
		Median	5	1	5	-1
		Min	3	-1	4	-4
		Max	8	3	8	1
	Cycle 24	N	1	1	11	11
		Mean	8.5	3.9	4.6	-1.5
		SD	-	-	0.8	2.3
		Median	9	4	5	-1
		Min	9	4	3	-5
		Max	9	4	6	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 25	N	1	1	10	10
		Mean	6.3	1.7	4.7	-1.5
		SD	-	-	1.1	2.0
		Median	6	2	4	-1
		Min	6	2	3	-4
		Max	6	2	6	3
	Cycle 26	N	1	1	10	10
		Mean	9.2	4.6	5.1	-1.1
		SD	-	-	1.5	1.6
		Median	9	5	5	-1
		Min	9	5	4	-3
		Max	9	5	9	1
	Cycle 27	N	1	1	10	10
		Mean	7.0	2.4	5.0	-1.2
		SD	-	-	1.9	1.7
		Median	7	2	4	0
		Min	7	2	3	-4
		Max	7	2	10	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 28	N	0	0	9	9
		Mean	-	-	5.2	-1.1
		SD	-	-	1.2	1.8
		Median	-	-	5	-1
		Min	-	-	3	-4
		Max	-	-	7	2
	Cycle 29	N	0	0	9	9
		Mean	-	-	5.6	-0.7
		SD	-	-	2.5	1.6
		Median	-	-	4	0
		Min	-	-	4	-4
		Max	-	-	11	1
	Cycle 30	N	0	0	7	7
		Mean	-	-	4.6	-1.6
		SD	-	-	1.3	2.1
		Median	-	-	5	-1
		Min	-	-	3	-5
		Max	-	-	7	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 31	N	0	0	6	6
		Mean	-	-	4.3	-1.2
		SD	-	-	0.6	1.9
		Median	-	-	4	0
		Min	-	-	4	-4
		Max	-	-	5	0
	Cycle 32	N	0	0	5	5
		Mean	-	-	4.1	-1.0
		SD	-	-	0.1	1.8
		Median	-	-	4	0
		Min	-	-	4	-4
		Max	-	-	4	0
	Cycle 33	N	0	0	5	5
		Mean	-	-	4.5	-0.7
		SD	-	-	0.4	1.6
		Median	-	-	5	0
		Min	-	-	4	-4
		Max	-	-	5	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 34	N	0	0	4	4
		Mean	-	-	4.8	-0.3
		SD	-	-	0.7	1.9
		Median	-	-	5	0
		Min	-	-	4	-3
		Max	-	-	5	1
	Cycle 35	N	0	0	1	1
		Mean	-	-	4.5	0.4
		SD	-	-	-	-
		Median	-	-	5	0
		Min	-	-	5	0
		Max	-	-	5	0
	Cycle 36	N	0	0	1	1
		Mean	-	-	4.0	-0.1
		SD	-	-	-	-
		Median	-	-	4	0
		Min	-	-	4	0
		Max	-	-	4	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
WBC (GIGA/L)	Cycle 37	N	0	0	1	1
		Mean	-	-	3.6	-0.5
		SD	-	-	-	-
		Median	-	-	4	0
		Min	-	-	4	0
		Max	-	-	4	0
	Cycle 38	N	0	0	1	1
		Mean	-	-	4.7	0.6
		SD	-	-	-	-
		Median	-	-	5	1
		Min	-	-	5	1
		Max	-	-	5	1
	Cycle 39	N	0	0	1	1
		Mean	-	-	4.9	0.8
		SD	-	-	-	-
		Median	-	-	5	1
		Min	-	-	5	1
		Max	-	-	5	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Baseline	N	111		111	
		Mean	4.2		4.4	
		SD	1.8		2.4	
		Median	4		4	
		Min	2		2	
		Max	12		19	
	Cycle 2	N	110	109	103	103
		Mean	3.7	-0.6	3.4	-1.1
		SD	1.4	1.6	1.8	2.5
		Median	3	-1	3	-1
		Min	1	-6	1	-17
		Max	9	3	13	8
	Cycle 3	N	92	91	94	94
		Mean	3.9	-0.4	3.2	-1.1
		SD	1.9	2.0	1.6	2.5
		Median	4	0	3	-1
		Min	2	-8	1	-17
		Max	16	10	14	9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 4	N	79	78	87	87
		Mean	3.3	-0.9	3.2	-0.9
		SD	1.2	1.6	1.3	1.8
		Median	3	-1	3	-1
		Min	1	-9	1	-8
		Max	8	2	9	4
	Cycle 5	N	69	68	77	77
		Mean	3.6	-0.8	3.3	-0.8
		SD	1.8	2.2	1.2	1.7
		Median	3	-1	3	-1
		Min	2	-9	1	-7
		Max	14	8	7	3
	Cycle 6	N	63	62	73	73
		Mean	3.5	-0.8	3.3	-0.8
		SD	1.3	2.1	1.2	1.7
		Median	4	-1	3	-1
		Min	2	-9	1	-7
		Max	7	5	7	2

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 7	N	54	53	65	65
		Mean	3.9	-0.2	3.4	-0.7
		SD	2.3	2.6	1.2	1.9
		Median	3	0	3	-1
		Min	1	-9	1	-8
		Max	16	10	8	6
	Cycle 8	N	45	44	61	61
		Mean	3.1	-1.0	3.4	-0.8
		SD	1.1	1.7	1.3	1.9
		Median	3	-1	3	-1
		Min	1	-9	1	-8
		Max	7	2	8	5
	Cycle 9	N	42	41	56	56
		Mean	3.6	-0.4	3.6	-0.5
		SD	2.1	2.3	2.0	2.3
		Median	3	0	3	-1
		Min	1	-9	2	-8
		Max	14	8	11	7

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 10	N	36	36	49	49
		Mean	3.1	-0.9	3.5	-0.6
		SD	1.1	1.8	1.7	2.4
		Median	3	-1	3	-1
		Min	1	-8	2	-8
		Max	7	2	12	10
	Cycle 11	N	30	29	47	47
		Mean	2.9	-1.0	3.3	-0.8
		SD	1.1	2.1	1.1	2.0
		Median	3	-1	3	-1
		Min	1	-10	1	-8
		Max	6	2	6	3
	Cycle 12	N	25	25	39	39
		Mean	3.8	0.0	3.3	-0.9
		SD	2.5	2.6	1.1	2.0
		Median	3	0	3	-1
		Min	2	-8	2	-8
		Max	13	7	7	4

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 13	N	20	20	36	36
		Mean	3.0	-0.9	3.2	-0.8
		SD	1.0	2.3	1.2	2.0
		Median	3	-1	3	-1
		Min	2	-10	1	-8
		Max	7	1	6	3
	Cycle 14	N	16	16	35	35
		Mean	3.0	-1.0	3.6	-0.5
		SD	1.1	2.5	1.4	2.2
		Median	3	-1	3	0
		Min	1	-9	1	-9
		Max	5	2	7	3
	Cycle 15	N	14	14	33	33
		Mean	2.9	-1.0	3.4	-0.5
		SD	1.2	2.3	1.2	1.5
		Median	3	0	3	0
		Min	2	-9	2	-3
		Max	5	1	6	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 16	N	7	7	30	30
		Mean	3.2	-0.2	3.6	-0.2
		SD	1.2	1.1	1.9	2.3
		Median	3	0	3	0
		Min	2	-2	2	-4
		Max	6	1	11	9
	Cycle 17	N	7	7	25	25
		Mean	3.3	-0.1	3.4	-0.4
		SD	1.6	1.2	1.3	1.7
		Median	3	0	3	0
		Min	2	-2	2	-4
		Max	6	1	6	3
	Cycle 18	N	6	6	21	21
		Mean	3.0	-0.6	3.6	-0.4
		SD	1.8	1.0	1.3	1.8
		Median	3	-1	3	0
		Min	1	-2	2	-3
		Max	6	1	6	3

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 19	N	4	4	19	19
		Mean	3.1	-0.6	3.5	-0.5
		SD	1.2	1.5	1.0	1.6
		Median	3	0	3	0
		Min	2	-3	2	-3
		Max	5	1	6	3
	Cycle 20	N	3	3	18	18
		Mean	2.7	-0.5	3.4	-0.4
		SD	1.0	2.1	1.6	2.0
		Median	3	-1	3	0
		Min	2	-3	2	-3
		Max	4	2	8	6
	Cycle 21	N	3	3	15	15
		Mean	2.5	-0.7	3.3	-0.6
		SD	0.8	1.4	1.3	1.9
		Median	3	-1	3	0
		Min	2	-2	2	-4
		Max	3	1	6	2

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 22	N	2	2	14	14
		Mean	2.3	0.0	3.2	-0.7
		SD	0.9	1.1	1.1	1.8
		Median	2	0	3	0
		Min	2	-1	2	-4
		Max	3	1	5	2
	Cycle 23	N	2	2	13	13
		Mean	2.5	0.3	3.0	-0.8
		SD	1.5	1.7	1.1	1.2
		Median	2	0	3	0
		Min	1	-1	2	-3
		Max	4	1	5	1
	Cycle 24	N	1	1	11	11
		Mean	3.0	0.9	2.7	-1.2
		SD	-	-	0.9	1.9
		Median	3	1	2	-1
		Min	3	1	2	-4
		Max	3	1	5	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 25	N	1	1	10	10
		Mean	2.3	0.2	3.0	-1.1
		SD	-	-	1.2	1.7
		Median	2	0	3	-1
		Min	2	0	1	-3
		Max	2	0	4	2
	Cycle 26	N	1	1	10	10
		Mean	4.0	1.8	3.3	-0.7
		SD	-	-	1.4	1.2
		Median	4	2	3	0
		Min	4	2	1	-3
		Max	4	2	6	1
	Cycle 27	N	1	1	10	10
		Mean	3.2	1.1	3.2	-0.8
		SD	-	-	1.7	1.5
		Median	3	1	2	0
		Min	3	1	2	-4
		Max	3	1	7	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 28	N	0	0	9	9
		Mean	-	-	3.5	-0.5
		SD	-	-	1.5	1.7
		Median	-	-	3	-1
		Min	-	-	1	-2
		Max	-	-	6	3
	Cycle 29	N	0	0	9	9
		Mean	-	-	3.8	-0.2
		SD	-	-	2.6	1.6
		Median	-	-	2	0
		Min	-	-	2	-3
		Max	-	-	8	2
	Cycle 30	N	0	0	7	7
		Mean	-	-	2.6	-1.2
		SD	-	-	1.0	1.7
		Median	-	-	3	-1
		Min	-	-	2	-4
		Max	-	-	4	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 31	N	0	0	6	6
		Mean	-	-	2.4	-0.9
		SD	-	-	0.4	1.7
		Median	-	-	2	0
		Min	-	-	2	-3
		Max	-	-	3	0
	Cycle 32	N	0	0	5	5
		Mean	-	-	2.2	-0.7
		SD	-	-	0.4	1.5
		Median	-	-	2	0
		Min	-	-	2	-3
		Max	-	-	3	0
	Cycle 33	N	0	0	5	5
		Mean	-	-	2.4	-0.5
		SD	-	-	0.4	1.6
		Median	-	-	2	0
		Min	-	-	2	-3
		Max	-	-	3	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 34	N	0	0	4	4
		Mean	-	-	2.9	-0.2
		SD	-	-	0.5	1.5
		Median	-	-	3	0
		Min	-	-	2	-2
		Max	-	-	3	1
	Cycle 35	N	0	0	1	1
		Mean	-	-	2.4	0.5
		SD	-	-	-	-
		Median	-	-	2	1
		Min	-	-	2	1
		Max	-	-	2	1
	Cycle 36	N	0	0	1	1
		Mean	-	-	2.0	0.1
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	0
		Max	-	-	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Neutrophils absolute ct (GIGA/L)	Cycle 37	N	0	0	1	1
		Mean	-	-	0.6	-1.3
		SD	-	-	-	-
		Median	-	-	1	-1
		Min	-	-	1	-1
		Max	-	-	1	-1
	Cycle 38	N	0	0	1	1
		Mean	-	-	2.7	0.8
		SD	-	-	-	-
		Median	-	-	3	1
		Min	-	-	3	1
		Max	-	-	3	1
	Cycle 39	N	0	0	1	1
		Mean	-	-	2.3	0.4
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	0
		Max	-	-	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Baseline	N	105		108	
		Mean	1.5		1.5	
		SD	0.6		0.6	
		Median	2		1	
		Min	0		0	
		Max	3		4	
	Cycle 2	N	105	103	98	98
		Mean	1.6	0.1	1.5	0.0
		SD	0.7	0.4	0.6	0.6
		Median	2	0	2	0
		Min	0	-1	0	-2
		Max	3	1	4	2
	Cycle 3	N	87	86	89	88
		Mean	1.6	0.0	1.5	-0.1
		SD	0.6	0.5	0.6	0.4
		Median	2	0	1	0
		Min	0	-2	0	-2
		Max	3	2	4	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 4	N	74	73	80	79
		Mean	1.6	0.0	1.5	-0.1
		SD	0.7	0.6	0.6	0.6
		Median	2	0	1	0
		Min	1	-2	0	-2
		Max	4	2	4	3
	Cycle 5	N	65	63	72	72
		Mean	1.5	-0.1	1.4	-0.2
		SD	0.6	0.5	0.5	0.6
		Median	1	0	1	0
		Min	0	-2	0	-3
		Max	3	1	3	2
	Cycle 6	N	60	58	69	69
		Mean	1.5	-0.1	1.5	-0.1
		SD	0.7	0.6	0.6	0.5
		Median	1	0	1	0
		Min	0	-2	0	-2
		Max	3	1	3	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 7	N	54	51	60	60
		Mean	1.5	-0.1	1.5	-0.1
		SD	0.6	0.5	0.6	0.6
		Median	1	0	1	0
		Min	0	-1	1	-2
		Max	4	2	4	2
	Cycle 8	N	44	42	56	56
		Mean	1.5	0.0	1.4	-0.1
		SD	0.6	0.5	0.5	0.5
		Median	1	0	1	0
		Min	0	-1	0	-2
		Max	3	1	3	1
	Cycle 9	N	40	39	51	51
		Mean	1.5	-0.1	1.5	-0.1
		SD	0.6	0.5	0.5	0.5
		Median	1	0	1	0
		Min	0	-2	1	-1
		Max	3	1	3	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 10	N	35	34	45	44
		Mean	1.5	0.0	1.6	-0.1
		SD	0.5	0.4	0.5	0.7
		Median	2	0	2	0
		Min	1	-1	1	-2
		Max	3	1	3	2
	Cycle 11	N	29	28	44	44
		Mean	1.5	-0.1	1.5	-0.2
		SD	0.5	0.4	0.5	0.5
		Median	1	0	1	0
		Min	1	-1	1	-2
		Max	3	1	3	1
	Cycle 12	N	24	24	36	36
		Mean	1.5	0.0	1.4	-0.2
		SD	0.5	0.5	0.5	0.6
		Median	1	0	1	0
		Min	1	-1	0	-2
		Max	3	1	2	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 13	N	19	19	33	33
		Mean	1.4	-0.1	1.5	-0.2
		SD	0.6	0.4	0.6	0.6
		Median	1	0	1	0
		Min	1	-1	0	-2
		Max	3	1	3	1
	Cycle 14	N	15	15	33	33
		Mean	1.4	-0.2	1.4	-0.3
		SD	0.7	0.6	0.5	0.8
		Median	1	0	1	0
		Min	1	-1	1	-2
		Max	4	1	2	2
	Cycle 15	N	14	13	32	31
		Mean	1.5	0.0	1.4	-0.2
		SD	0.8	0.7	0.6	0.7
		Median	1	0	1	0
		Min	0	-2	0	-2
		Max	4	2	3	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 16	N	7	6	30	30
		Mean	1.8	0.3	1.4	-0.2
		SD	1.0	0.8	0.5	0.5
		Median	1	0	1	0
		Min	1	-1	1	-2
		Max	4	2	3	1
	Cycle 17	N	6	6	25	25
		Mean	2.0	0.3	1.5	-0.1
		SD	1.0	0.7	0.6	0.5
		Median	2	0	1	0
		Min	1	0	1	-1
		Max	4	2	3	1
	Cycle 18	N	6	5	21	21
		Mean	1.8	0.2	1.4	-0.2
		SD	1.3	1.2	0.5	0.4
		Median	1	0	1	0
		Min	1	-1	0	-1
		Max	4	2	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 19	N	4	3	19	19
		Mean	1.9	0.2	1.5	-0.1
		SD	0.8	0.6	0.5	0.6
		Median	2	0	2	0
		Min	1	0	1	-2
		Max	3	1	2	1
	Cycle 20	N	3	2	18	18
		Mean	2.4	0.8	1.6	0.0
		SD	1.3	1.2	0.5	0.5
		Median	2	1	2	0
		Min	2	0	1	-1
		Max	4	2	3	1
	Cycle 21	N	2	2	15	15
		Mean	1.9	-0.2	1.4	-0.2
		SD	2.0	1.7	0.4	0.4
		Median	2	0	1	0
		Min	0	-1	1	-1
		Max	3	1	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 22	N	2	1	14	14
		Mean	2.7	1.6	1.5	-0.1
		SD	1.6	-	0.4	0.4
		Median	3	2	1	0
		Min	2	2	1	-1
		Max	4	2	2	1
	Cycle 23	N	1	1	13	13
		Mean	3.9	1.7	1.4	-0.1
		SD	-	-	0.4	0.3
		Median	4	2	1	0
		Min	4	2	1	-1
		Max	4	2	2	0
	Cycle 24	N	1	1	11	11
		Mean	5.4	3.2	1.4	-0.1
		SD	-	-	0.5	0.3
		Median	5	3	2	0
		Min	5	3	1	-1
		Max	5	3	2	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	□□□ñ□□□□	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 25	N	1	1	10	10
		Mean	3.7	1.4	1.3	-0.2
		SD	-	-	0.4	0.3
		Median	4	1	1	0
		Min	4	1	1	-1
		Max	4	1	2	0
	Cycle 26	N	1	1	10	10
		Mean	4.5	2.3	1.3	-0.2
		SD	-	-	0.4	0.3
		Median	5	2	1	0
		Min	5	2	1	-1
		Max	5	2	2	0
	Cycle 27	N	1	1	10	10
		Mean	3.3	1.0	1.4	-0.2
		SD	-	-	0.5	0.2
		Median	3	1	1	0
		Min	3	1	1	-1
		Max	3	1	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 28	N	0	0	9	9
		Mean	-	-	1.3	-0.3
		SD	-	-	0.6	0.5
		Median	-	-	1	0
		Min	-	-	1	-1
		Max	-	-	3	1
	Cycle 29	N	0	0	9	9
		Mean	-	-	1.4	-0.2
		SD	-	-	0.5	0.4
		Median	-	-	1	0
		Min	-	-	1	-1
		Max	-	-	2	0
	Cycle 30	N	0	0	7	7
		Mean	-	-	1.6	-0.1
		SD	-	-	0.7	0.5
		Median	-	-	2	0
		Min	-	-	1	-1
		Max	-	-	2	1

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 31	N	0	0	6	6
		Mean	-	-	1.4	-0.2
		SD	-	-	0.4	0.3
		Median	-	-	1	0
		Min	-	-	1	-1
		Max	-	-	2	0
	Cycle 32	N	0	0	5	5
		Mean	-	-	1.5	-0.2
		SD	-	-	0.5	0.3
		Median	-	-	2	0
		Min	-	-	1	-1
		Max	-	-	2	0
	Cycle 33	N	0	0	5	5
		Mean	-	-	1.5	-0.2
		SD	-	-	0.4	0.3
		Median	-	-	2	0
		Min	-	-	1	-1
		Max	-	-	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 34	N	0	0	4	4
		Mean	-	-	1.5	-0.2
		SD	-	-	0.7	0.5
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	3	1
	Cycle 35	N	0	0	1	1
		Mean	-	-	1.8	-0.1
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	0
		Max	-	-	2	0
	Cycle 36	N	0	0	1	1
		Mean	-	-	1.8	-0.1
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	0
		Max	-	-	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lymphocytes absolute ct (GIGA/L)	Cycle 37	N	0	0	1	1
		Mean	-	-	2.8	0.9
		SD	-	-	-	-
		Median	-	-	3	1
		Min	-	-	3	1
		Max	-	-	3	1
	Cycle 38	N	0	0	1	1
		Mean	-	-	1.8	-0.1
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	0
		Max	-	-	2	0
	Cycle 39	N	0	0	1	1
		Mean	-	-	2.3	0.4
		SD	-	-	-	-
		Median	-	-	2	0
		Min	-	-	2	0
		Max	-	-	2	0

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Baseline	N	111		111	
		Mean	271.0		284.3	
		SD	70.0		94.0	
		Median	274		268	
		Min	104		140	
		Max	477		756	
	Cycle 2	N	110	109	103	103
		Mean	250.1	-24.1	207.3	-77.3
		SD	75.8	53.6	79.1	81.4
		Median	246	-20	193	-64
		Min	81	-198	82	-450
		Max	463	146	561	59
	Cycle 3	N	92	91	94	94
		Mean	238.1	-32.0	215.8	-65.8
		SD	73.9	55.1	76.5	91.8
		Median	237	-32	207	-60
		Min	47	-181	64	-415
		Max	558	217	445	173

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 4	N	79	78	87	87
		Mean	233.0	-35.0	219.9	-70.7
		SD	78.6	66.9	81.9	96.8
		Median	223	-36	196	-61
		Min	70	-208	79	-493
		Max	557	216	525	135
	Cycle 5	N	69	68	77	77
		Mean	235.2	-35.7	224.7	-54.1
		SD	83.6	69.6	80.8	81.6
		Median	224	-40	205	-59
		Min	82	-223	91	-295
		Max	661	320	508	216
	Cycle 6	N	62	61	73	73
		Mean	220.9	-50.5	208.8	-72.6
		SD	62.3	56.2	62.3	77.5
		Median	215	-54	197	-62
		Min	84	-214	107	-346
		Max	437	56	442	64

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 7	N	54	53	65	65
		Mean	242.4	-25.4	208.5	-71.5
		SD	94.0	85.1	67.8	89.5
		Median	229	-24	204	-61
		Min	86	-241	97	-370
		Max	704	363	537	78
	Cycle 8	N	45	44	61	61
		Mean	237.2	-32.1	210.8	-66.3
		SD	98.2	85.1	72.8	83.3
		Median	224	-29	204	-64
		Min	95	-242	97	-326
		Max	704	363	482	105
	Cycle 9	N	42	41	56	56
		Mean	227.9	-37.3	199.6	-75.3
		SD	102.0	87.3	58.3	80.9
		Median	209	-42	198	-64
		Min	96	-196	89	-344
		Max	733	392	354	53

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 10	N	36	36	49	49
		Mean	217.3	-47.4	200.5	-68.6
		SD	88.8	91.0	63.6	80.4
		Median	202	-55	195	-79
		Min	102	-220	82	-329
		Max	673	332	511	243
	Cycle 11	N	30	29	48	48
		Mean	204.9	-56.9	192.2	-76.3
		SD	58.8	59.9	64.5	77.9
		Median	201	-47	190	-67
		Min	96	-214	79	-392
		Max	402	59	469	40
	Cycle 12	N	25	25	39	39
		Mean	208.4	-48.7	185.8	-80.5
		SD	49.8	56.2	50.0	71.7
		Median	213	-47	192	-73
		Min	107	-161	75	-346
		Max	315	84	306	38

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 13	N	20	20	36	36
		Mean	204.2	-55.2	197.0	-67.6
		SD	50.2	51.3	77.9	93.3
		Median	207	-49	197	-69
		Min	103	-165	79	-327
		Max	297	9	562	294
	Cycle 14	N	16	16	35	35
		Mean	210.5	-56.8	177.4	-88.0
		SD	56.6	64.0	45.8	72.5
		Median	203	-32	184	-83
		Min	118	-172	66	-335
		Max	348	54	256	28
	Cycle 15	N	14	14	33	33
		Mean	207.8	-64.4	193.6	-72.6
		SD	55.1	51.0	53.4	76.2
		Median	207	-58	191	-63
		Min	114	-159	79	-347
		Max	311	28	290	56

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 16	N	7	7	30	30
		Mean	215.6	-78.0	212.7	-56.6
		SD	68.9	60.9	120.7	135.8
		Median	219	-68	199	-68
		Min	108	-187	83	-354
		Max	320	-16	793	525
	Cycle 17	N	7	7	25	25
		Mean	241.7	-51.9	195.4	-73.3
		SD	105.9	82.5	36.8	80.7
		Median	205	-31	208	-62
		Min	105	-211	96	-368
		Max	404	58	254	38
	Cycle 18	N	6	6	21	21
		Mean	235.5	-59.2	192.2	-80.8
		SD	90.6	69.8	35.8	85.5
		Median	222	-45	189	-61
		Min	106	-177	125	-362
		Max	366	12	257	33

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 19	N	4	4	19	19
		Mean	231.8	-77.8	207.4	-67.7
		SD	102.0	85.1	39.3	75.2
		Median	189	-45	216	-53
		Min	166	-203	131	-298
		Max	383	-19	272	54
	Cycle 20	N	3	3	18	18
		Mean	179.3	-86.3	206.3	-59.9
		SD	32.6	92.5	46.1	95.1
		Median	177	-47	206	-64
		Min	148	-192	135	-354
		Max	213	-20	302	73
	Cycle 21	N	3	3	15	15
		Mean	156.7	-109	200.1	-75.1
		SD	31.7	108.4	35.1	101.1
		Median	142	-53	196	-32
		Min	135	-234	134	-368
		Max	193	-40	253	27

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 22	N	2	2	14	14
		Mean	169.5	-44.5	192.4	-80.6
		SD	72.8	46.0	34.5	102.6
		Median	170	-45	188	-56
		Min	118	-77	141	-368
		Max	221	-12	256	46
	Cycle 23	N	2	2	13	13
		Mean	153.5	-60.5	213.8	-66.3
		SD	38.9	12.0	44.6	99.5
		Median	154	-61	212	-53
		Min	126	-69	148	-351
		Max	181	-52	325	40
	Cycle 24	N	1	1	11	11
		Mean	202.0	-31.0	195.5	-85.5
		SD	-	-	58.2	110.3
		Median	202	-31	184	-73
		Min	202	-31	124	-357
		Max	202	-31	340	55

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 25	N	1	1	10	10
		Mean	231.0	-2.0	180.4	-109
		SD	-	-	35.7	93.4
		Median	231	-2	174	-77
		Min	231	-2	118	-349
		Max	231	-2	231	-34
	Cycle 26	N	1	1	10	10
		Mean	204.0	-29.0	213.2	-76.6
		SD	-	-	50.3	106.8
		Median	204	-29	223	-53
		Min	204	-29	136	-348
		Max	204	-29	272	19
	Cycle 27	N	1	1	10	10
		Mean	229.0	-4.0	195.7	-94.1
		SD	-	-	38.0	97.2
		Median	229	-4	194	-63
		Min	229	-4	143	-337
		Max	229	-4	270	-9

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 28	N	0	0	9	9
		Mean	-	-	201.3	-98.7
		SD	-	-	37.6	105.4
		Median	-	-	195	-70
		Min	-	-	150	-355
		Max	-	-	265	-20
	Cycle 29	N	0	0	9	9
		Mean	-	-	201.0	-99.0
		SD	-	-	31.2	98.2
		Median	-	-	202	-72
		Min	-	-	155	-335
		Max	-	-	259	-26
	Cycle 30	N	0	0	7	7
		Mean	-	-	202.9	-65.3
		SD	-	-	44.5	22.9
		Median	-	-	202	-67
		Min	-	-	151	-103
		Max	-	-	285	-33

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 31	N	0	0	6	6
		Mean	-	-	176.5	-77.3
		SD	-	-	20.7	33.3
		Median	-	-	186	-73
		Min	-	-	140	-138
		Max	-	-	193	-36
	Cycle 32	N	0	0	5	5
		Mean	-	-	183.8	-73.2
		SD	-	-	27.8	43.0
		Median	-	-	176	-90
		Min	-	-	157	-121
		Max	-	-	218	-11
	Cycle 33	N	0	0	5	5
		Mean	-	-	197.8	-59.2
		SD	-	-	25.5	33.8
		Median	-	-	197	-61
		Min	-	-	168	-95
		Max	-	-	234	-10

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 34	N	0	0	4	4
		Mean	-	-	195.8	-68.3
		SD	-	-	33.3	20.6
		Median	-	-	195	-66
		Min	-	-	157	-92
		Max	-	-	237	-50
	Cycle 35	N	0	0	1	1
		Mean	-	-	250.0	-79.0
		SD	-	-	-	-
		Median	-	-	250	-79
		Min	-	-	250	-79
		Max	-	-	250	-79
	Cycle 36	N	0	0	1	1
		Mean	-	-	251.0	-78.0
		SD	-	-	-	-
		Median	-	-	251	-78
		Min	-	-	251	-78
		Max	-	-	251	-78

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Platelets (GIGA/L)	Cycle 37	N	0	0	1	1
		Mean	-	-	245.0	-84.0
		SD	-	-	-	-
		Median	-	-	245	-84
		Min	-	-	245	-84
		Max	-	-	245	-84
	Cycle 38	N	0	0	1	1
		Mean	-	-	332.0	3.0
		SD	-	-	-	-
		Median	-	-	332	3
		Min	-	-	332	3
		Max	-	-	332	3
	Cycle 39	N	0	0	1	1
		Mean	-	-	249.0	-80.0
		SD	-	-	-	-
		Median	-	-	249	-80
		Min	-	-	249	-80
		Max	-	-	249	-80

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
PT (s)	Baseline	N	100		104	
		Mean	12.8		12.5	
		SD	2.5		2.5	
		Median	12		12	
		Min	1		1	
		Max	26		21	
PTT (s)	Baseline	N	21		16	
		Mean	24.4		31.6	
		SD	10.9		12.7	
		Median	26		30	
		Min	1		17	
		Max	49		74	

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.1 Laboratory Data: Actual Value and Change From Baseline (Hematology)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
PT, INR (none)	Baseline	N	108		107	
		Mean	1.0		1.0	
		SD	0.1		0.1	
		Median	1		1	
		Min	1		1	
		Max	2		1	
aPTT (s)	Baseline	N	97		96	
		Mean	30.8		28.0	
		SD	15.7		8.9	
		Median	30		28	
		Min	1		1	
		Max	169		61	

Note: PTT and INR were measured at baseline only.
Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_01_LabH.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabH.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
Amylase (U/L)	Baseline	N	92		92	
		Mean	60.6		54.8	
		SD	31.0		29.3	
		Median	54		51	
		Min	1		1	
		Max	204		187	
	Cycle 2	N	84	79	77	72
		Mean	68.3	8.3	72.5	16.6
		SD	51.8	45.7	34.2	27.4
		Median	57	5	65	13
		Min	10	-148	1	-105
		Max	464	323	158	104
	Cycle 3	N	71	67	74	69
		Mean	61.7	1.7	58.8	5.6
		SD	29.8	28.4	28.0	30.0
		Median	54	4	60	7
		Min	1	-167	1	-135
		Max	166	89	152	83

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 4	N	63	59	64	60
		Mean	60.7	0.6	60.4	4.9
		SD	25.1	26.2	30.8	32.9
		Median	59	2	60	6
		Min	1	-156	16	-143
		Max	158	41	207	132
	Cycle 5	N	53	50	65	60
		Mean	60.9	-0.8	59.2	7.0
		SD	26.9	22.5	28.5	20.2
		Median	58	1	55	4
		Min	12	-114	1	-79
		Max	140	37	141	81
	Cycle 6	N	47	45	60	56
		Mean	61.7	-0.5	57.4	5.3
		SD	22.6	28.3	27.0	17.6
		Median	60	3	57	6
		Min	18	-144	2	-80
		Max	115	58	135	44

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 7	N	40	37	45	42
		Mean	62.2	-5.9	58.5	1.7
		SD	25.2	23.4	25.7	20.0
		Median	59	-2	62	5
		Min	18	-107	0	-85
		Max	134	31	149	43
	Cycle 8	N	32	29	46	42
		Mean	64.4	-5.1	57.2	1.8
		SD	31.0	32.7	29.1	23.4
		Median	59	-1	56	5
		Min	15	-134	0	-106
		Max	182	79	145	47
	Cycle 9	N	30	27	44	39
		Mean	66.5	-2.6	56.4	0.0
		SD	30.9	41.4	28.6	23.1
		Median	62	-3	52	1
		Min	14	-149	0	-89
		Max	159	131	132	48

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 10	N	25	23	38	34
		Mean	65.3	-5.3	61.5	5.6
		SD	28.1	31.3	37.1	32.3
		Median	60	0	56	4
		Min	16	-124	17	-91
		Max	144	41	226	142
	Cycle 11	N	19	17	36	33
		Mean	64.5	1.5	58.9	5.2
		SD	26.8	19.4	29.5	16.6
		Median	60	2	58	5
		Min	32	-41	2	-32
		Max	127	37	153	47
	Cycle 12	N	16	14	30	29
		Mean	67.4	2.7	63.1	4.4
		SD	20.8	23.5	25.4	16.3
		Median	63	7	61	1
		Min	34	-61	22	-31
		Max	107	32	114	45

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 13	N	13	11	29	27
		Mean	70.2	5.2	60.1	4.1
		SD	29.6	11.6	31.6	14.7
		Median	64	1	54	2
		Min	37	-14	2	-29
		Max	154	22	125	30
	Cycle 14	N	11	10	24	22
		Mean	77.0	9.0	58.7	1.7
		SD	45.8	38.1	30.6	13.9
		Median	60	-1	53	2
		Min	34	-19	1	-28
		Max	183	112	142	36
	Cycle 15	N	7	7	28	26
		Mean	78.1	3.3	64.0	7.0
		SD	34.4	19.8	31.6	22.7
		Median	73	3	63	2
		Min	39	-30	1	-41
		Max	138	38	133	83

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 16	N	6	5	24	23
		Mean	66.5	-11.2	62.6	1.7
		SD	39.6	9.6	30.8	16.8
		Median	57	-11	55	0
		Min	39	-23	2	-27
		Max	145	3	147	41
	Cycle 17	N	6	5	21	20
		Mean	64.5	-13.0	69.1	9.6
		SD	29.6	20.9	34.8	18.2
		Median	64	-4	73	5
		Min	37	-50	2	-12
		Max	118	1	140	57
	Cycle 18	N	5	4	18	17
		Mean	63.6	-16.3	63.8	3.0
		SD	33.5	25.1	26.4	13.1
		Median	55	-9	60	3
		Min	34	-52	28	-22
		Max	116	4	116	28

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 19	N	4	3	16	15
		Mean	63.0	-20.0	63.3	1.6
		SD	34.5	33.8	27.4	10.8
		Median	54	-1	58	5
		Min	36	-59	22	-25
		Max	109	0	114	16
	Cycle 20	N	3	3	15	14
		Mean	72.7	-19.0	69.5	10.0
		SD	39.2	30.3	34.6	21.1
		Median	68	-3	56	8
		Min	36	-54	24	-23
		Max	114	0	158	60
	Cycle 21	N	3	3	10	9
		Mean	76.7	-15.0	68.3	0.8
		SD	37.9	38.9	26.9	15.1
		Median	86	-1	75	-2
		Min	35	-59	29	-28
		Max	109	15	108	25

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 22	N	2	2	11	10
		Mean	43.5	-10.0	71.3	7.1
		SD	10.6	14.1	32.0	11.9
		Median	44	-10	75	9
		Min	36	-20	25	-14
		Max	51	0	120	21
	Cycle 23	N	2	2	10	9
		Mean	28.5	-25.0	69.2	4.4
		SD	7.8	32.5	40.5	28.9
		Median	29	-25	61	0
		Min	23	-48	29	-45
		Max	34	-2	163	65
	Cycle 24	N	1	1	7	6
		Mean	69.0	-2.0	67.4	-0.4
		SD	-	-	31.6	21.7
		Median	69	-2	70	1
		Min	69	-2	27	-37
		Max	69	-2	119	21

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 25	N	1	1	7	6
		Mean	73.0	2.0	66.7	-1.5
		SD	-	-	30.8	20.0
		Median	73	2	77	3
		Min	73	2	13	-26
		Max	73	2	104	28
	Cycle 26	N	1	1	7	6
		Mean	246.0	175.0	71.1	4.7
		SD	-	-	35.8	19.2
		Median	246	175	62	-1
		Min	246	175	26	-14
		Max	246	175	137	39
	Cycle 27	N	1	1	7	6
		Mean	206.0	135.0	80.7	14.5
		SD	-	-	30.6	12.1
		Median	206	135	73	15
		Min	206	135	39	-1
		Max	206	135	130	32

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 28	N	0	0	7	6
		Mean	-	-	70.7	3.5
		SD	-	-	24.4	4.0
		Median	-	-	72	4
		Min	-	-	38	-2
		Max	-	-	105	8
	Cycle 29	N	0	0	7	6
		Mean	-	-	76.8	13.3
		SD	-	-	30.2	11.3
		Median	-	-	71	15
		Min	-	-	34	-1
		Max	-	-	126	28
	Cycle 30	N	0	0	6	5
		Mean	-	-	71.4	13.9
		SD	-	-	38.0	25.7
		Median	-	-	68	3
		Min	-	-	37	-9
		Max	-	-	141	57

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 31	N	0	0	6	5
		Mean	-	-	74.2	16.2
		SD	-	-	25.5	9.8
		Median	-	-	70	15
		Min	-	-	39	4
		Max	-	-	115	31
	Cycle 32	N	0	0	5	4
		Mean	-	-	77.2	14.5
		SD	-	-	32.5	15.9
		Median	-	-	84	8
		Min	-	-	39	4
		Max	-	-	122	38
	Cycle 33	N	0	0	5	4
		Mean	-	-	66.0	4.3
		SD	-	-	24.2	5.5
		Median	-	-	73	3
		Min	-	-	34	-1
		Max	-	-	96	12

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 34	N	0	0	4	3
		Mean	-	-	62.3	-8.3
		SD	-	-	19.6	16.2
		Median	-	-	66	0
		Min	-	-	37	-27
		Max	-	-	81	2
	Cycle 35	N	0	0	1	0
		Mean	-	-	65.0	-
		SD	-	-	-	-
		Median	-	-	65	-
		Min	-	-	65	-
		Max	-	-	65	-
	Cycle 36	N	0	0	1	0
		Mean	-	-	71.0	-
		SD	-	-	-	-
		Median	-	-	71	-
		Min	-	-	71	-
		Max	-	-	71	-

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Amylase (U/L)	Cycle 37	N	0	0	1	0
		Mean	-	-	72.0	-
		SD	-	-	-	-
		Median	-	-	72	-
		Min	-	-	72	-
		Max	-	-	72	-
	Cycle 38	N	0	0	1	0
		Mean	-	-	79.0	-
		SD	-	-	-	-
		Median	-	-	79	-
		Min	-	-	79	-
		Max	-	-	79	-
	Cycle 39	N	0	0	1	0
		Mean	-	-	77.0	-
		SD	-	-	-	-
		Median	-	-	77	-
		Min	-	-	77	-
		Max	-	-	77	-

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Baseline	N	111		110	
		Mean	0.6		0.5	
		SD	0.3		0.3	
		Median	1		1	
		Min	0		0	
		Max	2		2	
	Cycle 2	N	107	106	100	99
		Mean	0.6	0.1	0.8	0.2
		SD	0.3	0.3	0.4	0.3
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	2	1	2	1
	Cycle 3	N	90	89	94	93
		Mean	0.8	0.2	0.8	0.3
		SD	0.4	0.4	0.4	0.3
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	2	2	2	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 4	N	79	78	86	85
		Mean	0.8	0.2	0.9	0.4
		SD	0.4	0.3	0.4	0.4
		Median	1	0	1	0
		Min	0	-1	0	0
		Max	2	1	2	1
	Cycle 5	N	67	66	75	74
		Mean	0.8	0.3	0.9	0.4
		SD	0.5	0.4	0.5	0.4
		Median	1	0	1	0
		Min	0	-1	0	0
		Max	2	1	3	2
	Cycle 6	N	63	62	72	71
		Mean	0.9	0.3	0.9	0.4
		SD	0.5	0.4	0.4	0.4
		Median	1	0	1	0
		Min	0	0	0	0
		Max	3	2	3	2

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 7	N	53	52	61	60
		Mean	0.8	0.3	0.8	0.3
		SD	0.4	0.4	0.5	0.4
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	1	3	2
	Cycle 8	N	44	43	60	59
		Mean	0.9	0.3	0.8	0.2
		SD	0.4	0.4	0.3	0.3
		Median	1	0	1	0
		Min	0	-1	0	0
		Max	2	1	2	1
	Cycle 9	N	41	41	53	52
		Mean	0.9	0.4	0.8	0.3
		SD	0.5	0.4	0.4	0.4
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	2	2	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 10	N	36	36	50	50
		Mean	1.0	0.4	0.8	0.3
		SD	0.7	0.6	0.4	0.4
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	3	2	2	1
	Cycle 11	N	28	28	47	47
		Mean	1.1	0.4	0.9	0.3
		SD	0.5	0.5	0.5	0.4
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	2	2	3	1
	Cycle 12	N	23	23	38	38
		Mean	1.0	0.4	0.8	0.3
		SD	0.5	0.5	0.4	0.3
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	2	2	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 13	N	19	19	36	36
		Mean	1.0	0.4	0.8	0.3
		SD	0.5	0.5	0.3	0.3
		Median	1	1	1	0
		Min	0	-1	0	0
		Max	2	1	2	1
	Cycle 14	N	16	16	34	34
		Mean	1.0	0.4	0.8	0.2
		SD	0.6	0.5	0.4	0.3
		Median	1	0	1	0
		Min	0	0	0	0
		Max	3	2	2	1
	Cycle 15	N	14	14	33	33
		Mean	1.0	0.4	0.7	0.2
		SD	0.4	0.4	0.3	0.3
		Median	1	0	1	0
		Min	0	-1	0	-1
		Max	2	1	1	1

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 16	N	7	7	29	29
		Mean	1.0	0.3	0.8	0.2
		SD	0.4	0.3	0.3	0.4
		Median	1	0	1	0
		Min	0	0	0	0
		Max	1	1	1	1
	Cycle 17	N	7	7	24	24
		Mean	1.0	0.3	0.7	0.2
		SD	0.5	0.4	0.3	0.4
		Median	1	1	1	0
		Min	0	0	0	-1
		Max	2	1	2	1
	Cycle 18	N	6	6	21	21
		Mean	0.9	0.2	0.8	0.3
		SD	0.5	0.2	0.4	0.3
		Median	1	0	1	0
		Min	0	0	0	-1
		Max	2	0	2	1

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 19	N	4	4	19	19
		Mean	0.8	0.2	0.8	0.3
		SD	0.5	0.5	0.4	0.3
		Median	1	0	1	0
		Min	0	0	0	0
		Max	1	1	2	1
	Cycle 20	N	3	3	18	18
		Mean	1.0	0.3	0.7	0.2
		SD	0.3	0.1	0.3	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	1
	Cycle 21	N	3	3	14	14
		Mean	0.7	-0.1	0.9	0.3
		SD	0.3	0.4	0.4	0.4
		Median	1	0	1	0
		Min	0	0	0	0
		Max	1	0	2	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 22	N	2	2	14	14
		Mean	0.8	-0.1	0.8	0.2
		SD	0.4	0.0	0.4	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	1
	Cycle 23	N	2	2	13	13
		Mean	1.1	0.2	0.9	0.3
		SD	0.9	0.5	0.4	0.2
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	1	2	1
	Cycle 24	N	1	1	10	10
		Mean	0.4	-0.2	0.8	0.2
		SD	-	-	0.3	0.2
		Median	0	0	1	0
		Min	0	0	0	0
		Max	0	0	1	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 25	N	1	1	10	10
		Mean	0.5	-0.1	0.7	0.2
		SD	-	-	0.4	0.3
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	1
	Cycle 26	N	1	1	10	10
		Mean	0.3	-0.3	0.9	0.4
		SD	-	-	0.5	0.3
		Median	0	0	1	0
		Min	0	0	0	0
		Max	0	0	2	1
	Cycle 27	N	1	1	10	10
		Mean	0.3	-0.3	0.8	0.3
		SD	-	-	0.3	0.3
		Median	0	0	1	0
		Min	0	0	0	0
		Max	0	0	1	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 28	N	0	0	9	9
		Mean	-	-	0.7	0.2
		SD	-	-	0.4	0.3
		Median	-	-	1	0
		Min	-	-	0	0
		Max	-	-	1	1
	Cycle 29	N	0	0	9	9
		Mean	-	-	0.9	0.3
		SD	-	-	0.4	0.3
		Median	-	-	1	0
		Min	-	-	0	0
		Max	-	-	1	1
	Cycle 30	N	0	0	7	7
		Mean	-	-	0.7	0.1
		SD	-	-	0.4	0.5
		Median	-	-	1	0
		Min	-	-	0	-1
		Max	-	-	1	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 31	N	0	0	6	6
		Mean	-	-	0.8	0.2
		SD	-	-	0.3	0.2
		Median	-	-	1	0
		Min	-	-	0	0
		Max	-	-	1	1
	Cycle 32	N	0	0	5	5
		Mean	-	-	0.7	0.1
		SD	-	-	0.3	0.3
		Median	-	-	1	0
		Min	-	-	0	0
		Max	-	-	1	0
	Cycle 33	N	0	0	5	5
		Mean	-	-	0.6	0.0
		SD	-	-	0.4	0.3
		Median	-	-	0	0
		Min	-	-	0	0
		Max	-	-	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 34	N	0	0	4	4
		Mean	-	-	0.9	0.3
		SD	-	-	0.4	0.2
		Median	-	-	1	0
		Min	-	-	0	0
		Max	-	-	1	0
	Cycle 35	N	0	0	1	1
		Mean	-	-	0.5	0.2
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 36	N	0	0	1	1
		Mean	-	-	0.5	0.2
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Bilirubin, total (mg/dL)	Cycle 37	N	0	0	1	1
		Mean	-	-	0.5	0.2
		SD	-	-	-	-
		Median	-	-	0	0
		Min	-	-	0	0
		Max	-	-	0	0
	Cycle 38	N	0	0	1	1
		Mean	-	-	0.5	0.2
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 39	N	0	0	1	1
		Mean	-	-	0.5	0.2
		SD	-	-	-	-
		Median	-	-	0	0
		Min	-	-	0	0
		Max	-	-	0	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Baseline	N	108		109	
		Mean	22.4		23.7	
		SD	10.3		11.7	
		Median	20		22	
		Min	7		5	
		Max	59		58	
	Cycle 2	N	105	101	101	100
		Mean	21.9	-0.7	23.8	-0.4
		SD	10.8	6.8	12.4	7.2
		Median	21	0	20	0
		Min	7	-22	5	-31
		Max	79	20	70	17
	Cycle 3	N	87	83	92	91
		Mean	23.1	0.2	21.5	-1.6
		SD	12.1	7.9	10.2	5.4
		Median	20	0	19	-1
		Min	7	-23	6	-17
		Max	75	39	47	10

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 4	N	78	75	84	83
		Mean	22.4	0.4	23.0	-0.3
		SD	10.7	6.7	11.3	6.5
		Median	20	0	20	-1
		Min	7	-20	4	-17
		Max	62	21	51	20
	Cycle 5	N	64	62	73	73
		Mean	23.0	0.2	23.6	-0.4
		SD	10.3	7.8	12.4	5.9
		Median	21	1	19	-1
		Min	7	-28	5	-13
		Max	45	18	56	14
	Cycle 6	N	59	57	71	70
		Mean	22.4	0.1	22.5	-1.4
		SD	11.6	7.0	13.7	8.2
		Median	20	0	18	-1
		Min	8	-24	5	-17
		Max	64	16	89	45

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 7	N	51	49	61	59
		Mean	20.2	-1.7	24.1	-0.3
		SD	9.6	8.6	13.3	8.8
		Median	17	-1	20	-1
		Min	7	-28	4	-16
		Max	43	20	60	29
	Cycle 8	N	44	42	60	58
		Mean	21.9	-0.1	22.9	-0.7
		SD	13.4	7.5	13.1	7.1
		Median	19	0	18	-1
		Min	7	-18	4	-23
		Max	85	26	58	25
	Cycle 9	N	41	39	56	54
		Mean	21.6	-0.7	22.1	-2.4
		SD	11.7	6.2	12.5	7.5
		Median	17	-2	18	-3
		Min	8	-13	5	-26
		Max	56	20	65	17

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 10	N	35	34	48	47
		Mean	24.0	0.6	22.4	-2.1
		SD	11.0	7.2	10.5	6.6
		Median	20	-1	19	-2
		Min	11	-20	5	-20
		Max	54	16	47	12
	Cycle 11	N	29	27	44	43
		Mean	21.6	-0.4	23.2	-1.8
		SD	9.6	8.9	12.3	7.5
		Median	20	0	19	-2
		Min	9	-21	7	-20
		Max	48	21	50	18
	Cycle 12	N	24	23	39	38
		Mean	24.6	0.6	21.4	-2.7
		SD	10.7	8.5	9.9	9.1
		Median	24	0	18	-3
		Min	10	-14	6	-19
		Max	50	23	45	27

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 13	N	18	18	36	35
		Mean	23.7	0.5	23.7	-0.6
		SD	10.7	7.6	11.2	6.9
		Median	23	-1	21	0
		Min	10	-13	6	-16
		Max	44	19	49	13
	Cycle 14	N	16	16	33	32
		Mean	23.7	0.1	23.3	-1.7
		SD	13.0	6.4	12.3	7.2
		Median	21	1	19	-2
		Min	11	-13	4	-15
		Max	63	9	47	11
	Cycle 15	N	14	14	31	30
		Mean	25.7	1.9	24.1	-1.0
		SD	9.6	8.2	12.4	7.9
		Median	23	3	24	-2
		Min	12	-11	4	-15
		Max	44	15	53	17

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 16	N	7	7	29	28
		Mean	24.5	2.8	24.8	-0.4
		SD	11.0	7.3	12.8	8.3
		Median	29	-1	21	-1
		Min	13	-3	3	-20
		Max	40	15	48	16
	Cycle 17	N	7	7	25	24
		Mean	24.8	3.2	23.7	-0.7
		SD	12.0	7.1	11.6	8.4
		Median	32	4	24	0
		Min	11	-5	6	-18
		Max	38	13	43	16
	Cycle 18	N	6	6	21	20
		Mean	25.8	3.4	23.8	-1.5
		SD	13.4	9.1	10.4	9.5
		Median	24	2	24	-1
		Min	13	-8	7	-22
		Max	43	16	47	15

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 19	N	4	4	19	18
		Mean	22.4	1.7	25.3	0.0
		SD	11.7	6.6	13.7	7.7
		Median	22	0	25	-1
		Min	10	-5	6	-15
		Max	36	11	64	15
	Cycle 20	N	3	3	18	18
		Mean	20.5	-1.8	27.8	1.4
		SD	10.9	9.5	14.2	8.1
		Median	16	-2	26	0
		Min	13	-11	8	-14
		Max	33	8	64	15
	Cycle 21	N	3	3	15	15
		Mean	27.8	5.5	25.4	0.1
		SD	12.1	5.8	13.6	7.8
		Median	31	6	22	4
		Min	15	-1	9	-19
		Max	38	11	57	10

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 22	N	2	2	14	14
		Mean	18.1	-2.9	28.2	2.2
		SD	9.8	1.3	15.1	6.3
		Median	18	-3	26	1
		Min	11	-4	11	-6
		Max	25	-2	65	16
	Cycle 23	N	2	2	13	13
		Mean	14.5	-6.5	28.2	1.6
		SD	0.7	7.8	15.7	11.7
		Median	15	-7	23	0
		Min	14	-12	11	-19
		Max	15	-1	64	32
	Cycle 24	N	1	1	11	11
		Mean	32.0	5.0	25.7	-3.3
		SD	-	-	11.3	7.0
		Median	32	5	26	-4
		Min	32	5	11	-15
		Max	32	5	47	8

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 25	N	1	1	10	10
		Mean	30.0	3.0	32.5	2.5
		SD	-	-	12.0	4.8
		Median	30	3	32	1
		Min	30	3	15	-3
		Max	30	3	55	10
	Cycle 26	N	1	1	10	10
		Mean	39.0	12.0	27.4	-2.6
		SD	-	-	14.0	8.1
		Median	39	12	26	-4
		Min	39	12	8	-12
		Max	39	12	52	12
	Cycle 27	N	1	1	10	10
		Mean	31.0	4.0	26.8	-3.2
		SD	-	-	13.4	8.9
		Median	31	4	23	-5
		Min	31	4	11	-18
		Max	31	4	48	13

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 28	N	0	0	9	9
		Mean	-	-	22.9	-4.8
		SD	-	-	9.1	10.2
		Median	-	-	23	-4
		Min	-	-	11	-24
		Max	-	-	43	11
	Cycle 29	N	0	0	9	9
		Mean	-	-	26.7	-1.0
		SD	-	-	11.3	11.0
		Median	-	-	25	0
		Min	-	-	13	-20
		Max	-	-	44	12
	Cycle 30	N	0	0	7	7
		Mean	-	-	22.7	-6.4
		SD	-	-	7.6	10.7
		Median	-	-	22	-3
		Min	-	-	14	-27
		Max	-	-	34	4

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 31	N	0	0	6	6
		Mean	-	-	21.0	-8.7
		SD	-	-	8.9	12.8
		Median	-	-	18	-9
		Min	-	-	13	-28
		Max	-	-	36	5
	Cycle 32	N	0	0	5	5
		Mean	-	-	27.6	-4.4
		SD	-	-	7.7	12.4
		Median	-	-	30	-3
		Min	-	-	19	-22
		Max	-	-	38	8
	Cycle 33	N	0	0	5	5
		Mean	-	-	23.0	-9.0
		SD	-	-	10.0	13.3
		Median	-	-	22	-11
		Min	-	-	15	-26
		Max	-	-	40	8

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 34	N	0	0	4	4
		Mean	-	-	18.5	-13.3
		SD	-	-	12.6	15.9
		Median	-	-	14	-13
		Min	-	-	9	-32
		Max	-	-	37	5
	Cycle 35	N	0	0	1	1
		Mean	-	-	33.0	1.0
		SD	-	-	-	-
		Median	-	-	33	1
		Min	-	-	33	1
		Max	-	-	33	1
	Cycle 36	N	0	0	1	1
		Mean	-	-	26.0	-6.0
		SD	-	-	-	-
		Median	-	-	26	-6
		Min	-	-	26	-6
		Max	-	-	26	-6

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
BUN (mg/dL)	Cycle 37	N	0	0	1	1
		Mean	-	-	28.0	-4.0
		SD	-	-	-	-
		Median	-	-	28	-4
		Min	-	-	28	-4
		Max	-	-	28	-4
	Cycle 38	N	0	0	1	1
		Mean	-	-	38.0	6.0
		SD	-	-	-	-
		Median	-	-	38	6
		Min	-	-	38	6
		Max	-	-	38	6
	Cycle 39	N	0	0	1	1
		Mean	-	-	36.0	4.0
		SD	-	-	-	-
		Median	-	-	36	4
		Min	-	-	36	4
		Max	-	-	36	4

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Baseline	N	111		111	
		Mean	0.8		0.8	
		SD	0.2		0.2	
		Median	1		1	
		Min	1		0	
		Max	2		2	
	Cycle 2	N	110	109	103	103
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.2	0.2	0.1
		Median	1	0	1	0
		Min	0	-1	0	0
		Max	1	1	1	1
	Cycle 3	N	91	90	95	95
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.2	0.2	0.1
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	1	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 4	N	79	78	87	87
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	2	0	1	0
	Cycle 5	N	68	67	77	77
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	1	1	0
	Cycle 6	N	62	61	73	73
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.1
		Median	1	0	1	0
		Min	1	0	0	0
		Max	2	1	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 7	N	54	53	62	62
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	0	0	-1
		Max	2	0	2	1
	Cycle 8	N	45	44	60	60
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	1
	Cycle 9	N	41	41	56	56
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	0	1	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 10	N	36	36	50	50
		Mean	0.8	0.0	0.8	0.0
		SD	0.3	0.2	0.2	0.2
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	1	1	0
	Cycle 11	N	29	28	47	47
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	0
		Min	1	0	0	-1
		Max	1	0	1	1
	Cycle 12	N	25	25	39	39
		Mean	0.8	0.1	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 13	N	19	19	36	36
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	1
	Cycle 14	N	16	16	35	35
		Mean	0.8	0.0	0.8	0.0
		SD	0.3	0.2	0.2	0.2
		Median	1	0	1	0
		Min	0	0	1	0
		Max	2	0	1	1
	Cycle 15	N	14	14	32	32
		Mean	0.8	0.0	0.8	0.0
		SD	0.3	0.2	0.2	0.2
		Median	1	0	1	0
		Min	0	0	0	0
		Max	2	0	1	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 16	N	7	7	30	30
		Mean	0.8	0.0	0.8	0.0
		SD	0.2	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	0
	Cycle 17	N	7	7	25	25
		Mean	0.8	0.0	0.7	0.0
		SD	0.1	0.0	0.2	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	0
	Cycle 18	N	6	6	21	21
		Mean	0.8	0.0	0.8	0.0
		SD	0.1	0.1	0.1	0.2
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 19	N	4	4	19	19
		Mean	0.7	0.0	0.8	0.0
		SD	0.1	0.1	0.2	0.2
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	0
	Cycle 20	N	3	3	18	18
		Mean	0.8	0.0	0.8	0.0
		SD	0.1	0.0	0.2	0.3
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	1
	Cycle 21	N	3	3	15	15
		Mean	0.7	-0.1	0.7	0.0
		SD	0.0	0.1	0.1	0.2
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 22	N	2	2	14	14
		Mean	0.7	0.0	0.7	0.0
		SD	0.1	0.0	0.1	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	0
	Cycle 23	N	2	2	13	13
		Mean	0.6	-0.1	0.7	0.0
		SD	0.2	0.2	0.2	0.2
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	0
	Cycle 24	N	1	1	11	11
		Mean	1.4	0.6	0.7	0.0
		SD	-	-	0.1	0.1
		Median	1	1	1	0
		Min	1	1	1	0
		Max	1	1	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 25	N	1	1	10	10
		Mean	0.9	0.1	0.7	0.0
		SD	-	-	0.2	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	0
	Cycle 26	N	1	1	10	10
		Mean	0.9	0.1	0.7	0.0
		SD	-	-	0.1	0.1
		Median	1	0	1	0
		Min	1	0	1	0
		Max	1	0	1	0
	Cycle 27	N	1	1	10	10
		Mean	0.7	-0.1	0.7	0.0
		SD	-	-	0.2	0.2
		Median	1	0	1	0
		Min	1	0	0	0
		Max	1	0	1	0

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 28	N	0	0	9	9
		Mean	-	-	0.7	0.0
		SD	-	-	0.1	0.1
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 29	N	0	0	9	9
		Mean	-	-	0.7	0.0
		SD	-	-	0.1	0.2
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 30	N	0	0	7	7
		Mean	-	-	0.7	0.0
		SD	-	-	0.1	0.1
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 31	N	0	0	6	6
		Mean	-	-	0.7	0.0
		SD	-	-	0.1	0.1
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 32	N	0	0	5	5
		Mean	-	-	0.6	-0.1
		SD	-	-	0.1	0.2
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 33	N	0	0	5	5
		Mean	-	-	0.7	-0.1
		SD	-	-	0.1	0.2
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 34	N	0	0	4	4
		Mean	-	-	0.6	-0.1
		SD	-	-	0.1	0.1
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 35	N	0	0	1	1
		Mean	-	-	0.7	0.0
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 36	N	0	0	1	1
		Mean	-	-	0.7	-0.1
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Creatinine (mg/dL)	Cycle 37	N	0	0	1	1
		Mean	-	-	0.7	-0.1
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 38	N	0	0	1	1
		Mean	-	-	0.7	0.0
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0
	Cycle 39	N	0	0	1	1
		Mean	-	-	0.7	0.0
		SD	-	-	-	-
		Median	-	-	1	0
		Min	-	-	1	0
		Max	-	-	1	0

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Baseline	N	35		40	
		Mean	88.3		82.0	
		SD	85.6		88.7	
		Median	55		40	
		Min	6		2	
		Max	282		326	
	Cycle 2	N	28	25	27	23
		Mean	105.2	-6.3	136.0	50.3
		SD	97.9	56.6	155.0	119.9
		Median	69	-1	74	36
		Min	3	-192	3	-288
		Max	409	127	692	409
	Cycle 3	N	23	20	28	20
		Mean	89.3	-13.9	97.7	35.7
		SD	83.5	56.7	108.2	94.1
		Median	48	1	50	18
		Min	6	-194	0	-217
		Max	281	32	385	294

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 4	N	26	22	22	18
		Mean	97.4	3.8	96.3	21.4
		SD	87.6	40.2	185.0	168.9
		Median	75	4	45	6
		Min	7	-143	0	-281
		Max	270	89	882	599
	Cycle 5	N	19	17	19	14
		Mean	103.9	12.6	78.1	16.7
		SD	97.2	34.6	95.0	36.9
		Median	71	5	41	12
		Min	8	-72	0	-53
		Max	295	94	355	83
	Cycle 6	N	20	17	17	14
		Mean	85.5	-8.9	78.9	13.4
		SD	82.0	39.5	107.5	56.1
		Median	38	2	37	3
		Min	2	-132	0	-106
		Max	264	25	399	120

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 7	N	20	15	16	12
		Mean	87.8	-4.2	80.8	-7.4
		SD	87.3	46.9	115.0	106.4
		Median	37	-4	37	1
		Min	9	-136	0	-281
		Max	315	64	416	133
	Cycle 8	N	14	10	17	14
		Mean	111.6	4.6	87.3	3.3
		SD	87.2	29.3	129.0	106.1
		Median	104	2	38	7
		Min	14	-60	0	-259
		Max	271	36	527	244
	Cycle 9	N	14	11	17	12
		Mean	100.7	5.9	63.0	-31.9
		SD	83.5	33.6	59.1	103.0
		Median	82	8	47	5
		Min	20	-84	0	-278
		Max	250	55	233	73

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 10	N	13	12	14	10
		Mean	87.4	-17.2	72.6	8.8
		SD	72.6	63.6	70.6	46.1
		Median	69	3	36	13
		Min	17	-177	16	-97
		Max	258	40	247	87
	Cycle 11	N	12	9	12	10
		Mean	99.9	-13.6	76.7	8.1
		SD	81.9	69.6	65.2	45.5
		Median	85	4	55	9
		Min	17	-179	20	-76
		Max	276	37	221	62
	Cycle 12	N	11	9	8	8
		Mean	118.8	0.1	75.0	2.5
		SD	81.0	41.1	67.3	45.6
		Median	112	0	51	10
		Min	13	-98	18	-96
		Max	241	53	182	66

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
Lipase (U/L)	Cycle 13	N	7	5	9	8
		Mean	128.9	0.8	84.3	14.2
		SD	83.4	29.5	93.3	36.1
		Median	142	3	39	4
		Min	17	-44	17	-32
		Max	211	39	252	92
	Cycle 14	N	6	5	9	7
		Mean	132.5	7.6	80.9	13.2
		SD	94.0	22.0	71.6	54.9
		Median	152	8	50	26
		Min	21	-25	23	-98
		Max	219	37	231	71
	Cycle 15	N	5	5	11	7
		Mean	161.0	16.2	67.6	8.1
		SD	99.6	51.8	56.4	73.1
		Median	188	26	46	16
		Min	12	-56	25	-141
		Max	257	87	205	96

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 16	N	1	1	10	9
		Mean	118.0	30.0	67.4	-0.5
		SD	-	-	55.9	49.9
		Median	118	30	46	11
		Min	118	30	27	-129
		Max	118	30	194	34
	Cycle 17	N	1	1	11	9
		Mean	109.0	21.0	74.0	12.4
		SD	-	-	76.3	46.4
		Median	109	21	54	16
		Min	109	21	13	-78
		Max	109	21	248	88
	Cycle 18	N	1	1	9	9
		Mean	117.0	29.0	73.3	7.0
		SD	-	-	81.6	65.4
		Median	117	29	44	8
		Min	117	29	14	-137
		Max	117	29	267	107

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 19	N	1	1	8	8
		Mean	32.0	-24.0	80.7	8.8
		SD	-	-	80.6	44.3
		Median	32	-24	51	11
		Min	32	-24	12	-81
		Max	32	-24	223	63
	Cycle 20	N	0	0	9	8
		Mean	-	-	85.4	17.9
		SD	-	-	95.6	62.5
		Median	-	-	50	8
		Min	-	-	18	-82
		Max	-	-	297	137
	Cycle 21	N	0	0	8	7
		Mean	-	-	78.1	7.8
		SD	-	-	78.8	63.2
		Median	-	-	42	10
		Min	-	-	13	-118
		Max	-	-	241	81

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 22	N	0	0	8	7
		Mean	-	-	75.0	0.5
		SD	-	-	81.7	76.9
		Median	-	-	51	12
		Min	-	-	15	-151
		Max	-	-	258	98
	Cycle 23	N	1	1	6	6
		Mean	38.0	-18.0	84.4	0.6
		SD	-	-	85.6	58.2
		Median	38	-18	42	6
		Min	38	-18	17	-108
		Max	38	-18	218	58
	Cycle 24	N	0	0	5	5
		Mean	-	-	102.2	4.2
		SD	-	-	103.5	87.1
		Median	-	-	46	10
		Min	-	-	14	-132
		Max	-	-	266	106

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 25	N	0	0	4	4
		Mean	-	-	163.0	44.9
		SD	-	-	122.7	41.2
		Median	-	-	161	41
		Min	-	-	44	8
		Max	-	-	286	90
	Cycle 26	N	0	0	4	4
		Mean	-	-	120.0	1.9
		SD	-	-	122.4	126.4
		Median	-	-	73	19
		Min	-	-	38	-167
		Max	-	-	297	137
	Cycle 27	N	0	0	4	4
		Mean	-	-	123.3	5.1
		SD	-	-	107.2	104.1
		Median	-	-	92	24
		Min	-	-	39	-138
		Max	-	-	270	110

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 28	N	0	0	4	4
		Mean	-	-	133.5	16.6
		SD	-	-	136.3	113.7
		Median	-	-	93	14
		Min	-	-	30	-119
		Max	-	-	318	158
	Cycle 29	N	0	0	4	4
		Mean	-	-	106.5	-10.4
		SD	-	-	110.5	131.8
		Median	-	-	60	23
		Min	-	-	36	-197
		Max	-	-	270	110
	Cycle 30	N	0	0	3	3
		Mean	-	-	59.3	-43.2
		SD	-	-	52.9	100.2
		Median	-	-	41	-13
		Min	-	-	18	-155
		Max	-	-	119	39

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Lipase (U/L)	Cycle 31	N	0	0	1	1
		Mean	-	-	50.0	47.5
		SD	-	-	-	-
		Median	-	-	50	48
		Min	-	-	50	48
		Max	-	-	50	48
	Cycle 33	N	0	0	1	1
		Mean	-	-	22.0	-9.0
		SD	-	-	-	-
		Median	-	-	22	-9
		Min	-	-	22	-9
		Max	-	-	22	-9

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Baseline	N	111		111	
		Mean	34.4		31.3	
		SD	27.4		21.7	
		Median	27		24	
		Min	14		12	
		Max	201		126	
	Cycle 2	N	108	107	101	101
		Mean	30.8	-3.1	33.1	2.3
		SD	20.0	13.7	16.2	16.4
		Median	25	-1	29	4
		Min	13	-69	13	-83
		Max	132	33	102	31
	Cycle 3	N	91	90	94	94
		Mean	27.5	-4.9	33.1	2.7
		SD	11.1	19.8	13.0	17.7
		Median	24	0	31	5
		Min	14	-120	15	-72
		Max	81	26	68	33

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 4	N	78	77	87	87
		Mean	27.8	-4.9	35.6	4.7
		SD	12.0	22.6	15.3	22.1
		Median	24	-2	32	5
		Min	14	-131	11	-75
		Max	70	30	96	70
	Cycle 5	N	68	67	76	76
		Mean	28.8	-4.6	36.5	6.0
		SD	21.6	19.8	16.8	24.8
		Median	24	-1	34	6
		Min	10	-116	12	-73
		Max	182	41	87	67
	Cycle 6	N	63	62	72	72
		Mean	26.6	-4.0	36.9	5.6
		SD	12.4	21.6	15.8	21.5
		Median	23	0	34	6
		Min	12	-117	14	-75
		Max	75	58	89	56

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

Laboratory Test	Visit	Statistics	Placebo (N = 112) Actual Value	Placebo (N = 112) Change From Baseline	Sorafenib (N = 112) Actual Value	Sorafenib (N = 112) Change From Baseline
SGOT/AST (U/L)	Cycle 7	N	54	53	61	61
		Mean	27.6	-2.9	38.0	7.4
		SD	11.5	21.1	28.7	30.9
		Median	25	0	31	5
		Min	12	-113	14	-75
		Max	69	49	216	190
	Cycle 8	N	44	43	60	60
		Mean	26.3	-5.4	36.6	5.1
		SD	9.0	21.5	17.6	24.8
		Median	24	0	34	5
		Min	14	-114	12	-81
		Max	55	26	92	57
	Cycle 9	N	42	41	56	56
		Mean	28.6	-2.0	37.9	7.0
		SD	12.7	23.1	19.9	26.5
		Median	25	1	35	5
		Min	14	-113	13	-83
		Max	79	62	108	66

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 10	N	36	36	50	50
		Mean	27.6	-3.5	35.9	4.9
		SD	11.4	23.4	16.1	24.8
		Median	25	0	35	6
		Min	15	-116	15	-88
		Max	68	43	102	74
	Cycle 11	N	28	27	47	47
		Mean	30.4	-1.6	34.6	3.2
		SD	17.8	27.3	12.0	22.1
		Median	26	1	34	6
		Min	15	-109	15	-92
		Max	108	43	67	39
	Cycle 12	N	25	25	38	38
		Mean	33.3	6.4	33.3	3.8
		SD	31.3	30.1	13.2	18.5
		Median	26	4	32	5
		Min	14	-44	12	-70
		Max	179	131	69	48

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 13	N	19	19	36	36
		Mean	28.4	1.2	34.4	6.9
		SD	11.7	17.0	14.8	14.6
		Median	26	3	32	3
		Min	15	-42	15	-21
		Max	60	35	63	48
	Cycle 14	N	16	16	34	34
		Mean	28.0	4.4	36.8	9.8
		SD	8.0	13.0	18.2	17.1
		Median	28	5	32	6
		Min	17	-34	14	-18
		Max	44	26	81	45
	Cycle 15	N	14	14	33	33
		Mean	28.0	4.7	35.1	8.7
		SD	6.7	12.0	16.0	15.0
		Median	29	7	29	4
		Min	18	-29	17	-16
		Max	42	22	79	48

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 16	N	7	7	30	30
		Mean	29.9	4.6	39.3	12.1
		SD	10.6	17.5	25.1	22.3
		Median	32	10	31	7
		Min	17	-30	14	-12
		Max	45	21	116	95
	Cycle 17	N	7	7	25	25
		Mean	29.4	4.1	43.6	15.9
		SD	10.2	18.4	31.8	30.8
		Median	28	12	37	5
		Min	18	-33	15	-13
		Max	42	19	150	127
	Cycle 18	N	6	6	21	21
		Mean	25.0	-0.3	32.9	5.6
		SD	7.5	17.7	12.4	11.0
		Median	23	3	33	6
		Min	18	-33	16	-20
		Max	38	21	60	28

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 19	N	4	4	19	19
		Mean	25.0	-2.8	34.6	7.3
		SD	7.0	20.1	13.2	11.7
		Median	23	4	31	7
		Min	19	-32	17	-27
		Max	35	13	66	28
	Cycle 20	N	3	3	18	18
		Mean	20.7	-9.3	29.9	3.7
		SD	3.1	21.0	10.1	11.4
		Median	20	-2	29	4
		Min	18	-33	17	-30
		Max	24	7	53	24
	Cycle 21	N	3	3	15	15
		Mean	25.0	-5.0	31.1	5.5
		SD	8.7	26.9	10.6	10.6
		Median	29	9	29	6
		Min	15	-36	16	-22
		Max	31	12	51	26

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 22	N	2	2	14	14
		Mean	23.0	-11.0	29.6	5.9
		SD	8.5	32.5	9.6	13.6
		Median	23	-11	30	4
		Min	17	-34	17	-28
		Max	29	12	46	31
	Cycle 23	N	2	2	13	13
		Mean	23.0	-11.0	34.5	10.1
		SD	17.0	41.0	15.2	19.4
		Median	23	-11	33	9
		Min	11	-40	16	-30
		Max	35	18	67	53
	Cycle 24	N	1	1	11	11
		Mean	20.0	-31.0	28.5	4.8
		SD	-	-	7.9	12.7
		Median	20	-31	29	5
		Min	20	-31	16	-29
		Max	20	-31	44	23

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 25	N	1	1	10	10
		Mean	22.0	-29.0	29.7	5.2
		SD	-	-	11.5	10.6
		Median	22	-29	29	5
		Min	22	-29	14	-19
		Max	22	-29	54	17
	Cycle 26	N	1	1	10	10
		Mean	15.0	-36.0	29.8	5.3
		SD	-	-	7.8	15.1
		Median	15	-36	29	8
		Min	15	-36	20	-33
		Max	15	-36	45	20
	Cycle 27	N	1	1	10	10
		Mean	20.0	-31.0	33.7	9.2
		SD	-	-	14.0	8.8
		Median	20	-31	31	12
		Min	20	-31	17	-8
		Max	20	-31	65	20

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 28	N	0	0	9	9
		Mean	-	-	29.1	4.7
		SD	-	-	10.8	10.4
		Median	-	-	28	7
		Min	-	-	19	-20
		Max	-	-	53	14
	Cycle 29	N	0	0	9	9
		Mean	-	-	29.1	4.7
		SD	-	-	14.9	6.6
		Median	-	-	25	5
		Min	-	-	17	-6
		Max	-	-	67	15
	Cycle 30	N	0	0	7	7
		Mean	-	-	32.3	7.1
		SD	-	-	20.0	18.0
		Median	-	-	21	3
		Min	-	-	17	-11
		Max	-	-	62	46

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 31	N	0	0	6	6
		Mean	-	-	24.8	7.7
		SD	-	-	4.6	4.0
		Median	-	-	25	8
		Min	-	-	17	3
		Max	-	-	31	13
	Cycle 32	N	0	0	5	5
		Mean	-	-	25.6	8.6
		SD	-	-	6.6	7.3
		Median	-	-	22	6
		Min	-	-	20	3
		Max	-	-	35	21
	Cycle 33	N	0	0	5	5
		Mean	-	-	30.8	13.8
		SD	-	-	16.1	11.1
		Median	-	-	25	12
		Min	-	-	16	2
		Max	-	-	58	31

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 34	N	0	0	4	4
		Mean	-	-	25.5	7.3
		SD	-	-	9.1	10.4
		Median	-	-	25	5
		Min	-	-	16	-2
		Max	-	-	36	22
	Cycle 35	N	0	0	1	1
		Mean	-	-	30.0	3.0
		SD	-	-	-	-
		Median	-	-	30	3
		Min	-	-	30	3
		Max	-	-	30	3
	Cycle 36	N	0	0	1	1
		Mean	-	-	29.0	2.0
		SD	-	-	-	-
		Median	-	-	29	2
		Min	-	-	29	2
		Max	-	-	29	2

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGOT/AST (U/L)	Cycle 37	N	0	0	1	1
		Mean	-	-	30.0	3.0
		SD	-	-	-	-
		Median	-	-	30	3
		Min	-	-	30	3
		Max	-	-	30	3
	Cycle 38	N	0	0	1	1
		Mean	-	-	26.0	-1.0
		SD	-	-	-	-
		Median	-	-	26	-1
		Min	-	-	26	-1
		Max	-	-	26	-1
	Cycle 39	N	0	0	1	1
		Mean	-	-	26.0	-1.0
		SD	-	-	-	-
		Median	-	-	26	-1
		Min	-	-	26	-1
		Max	-	-	26	-1

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Baseline	N	111		111	
		Mean	29.9		26.2	
		SD	21.3		17.2	
		Median	23		20	
		Min	9		5	
		Max	128		101	
	Cycle 2	N	110	109	101	101
		Mean	25.9	-3.7	29.0	3.1
		SD	16.2	14.3	15.7	17.1
		Median	21	-2	24	4
		Min	6	-77	8	-83
		Max	99	29	106	56
	Cycle 3	N	91	90	94	94
		Mean	26.0	-2.7	32.4	6.2
		SD	14.1	16.7	17.7	18.2
		Median	23	-1	27	7
		Min	7	-87	12	-48
		Max	90	41	121	88

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 4	N	79	78	87	87
		Mean	24.9	-3.9	34.8	8.4
		SD	11.6	17.3	20.6	22.5
		Median	22	-2	29	7
		Min	5	-88	12	-65
		Max	63	40	109	78
	Cycle 5	N	68	67	77	77
		Mean	25.6	-3.6	36.6	11.1
		SD	12.9	21.9	25.1	28.2
		Median	22	-1	28	7
		Min	10	-98	8	-50
		Max	71	56	133	121
	Cycle 6	N	63	62	73	73
		Mean	25.4	-4.2	36.1	10.3
		SD	16.5	24.2	21.8	21.1
		Median	21	-3	31	9
		Min	9	-100	10	-44
		Max	110	95	123	92

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 7	N	54	53	62	62
		Mean	27.1	-1.7	36.8	11.0
		SD	14.5	22.8	24.7	23.2
		Median	24	-1	29	7
		Min	7	-98	8	-48
		Max	82	67	143	118
	Cycle 8	N	44	43	60	60
		Mean	25.6	-4.2	34.3	8.6
		SD	13.9	21.6	19.8	22.7
		Median	21	-3	29	8
		Min	10	-99	10	-55
		Max	66	38	104	84
	Cycle 9	N	42	41	56	56
		Mean	26.9	-0.9	34.8	8.8
		SD	18.0	23.9	21.2	24.2
		Median	22	-2	30	9
		Min	8	-99	11	-59
		Max	93	78	111	91

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 10	N	36	36	50	50
		Mean	24.9	-2.3	33.4	7.0
		SD	14.2	22.3	18.1	21.2
		Median	22	-2	28	9
		Min	9	-94	8	-49
		Max	82	67	93	73
	Cycle 11	N	28	27	47	47
		Mean	27.0	0.0	33.2	6.5
		SD	17.2	26.5	15.5	19.7
		Median	23	-3	33	7
		Min	10	-92	10	-49
		Max	77	62	85	65
	Cycle 12	N	25	25	39	39
		Mean	27.9	3.5	30.1	5.6
		SD	16.6	16.8	15.3	15.9
		Median	20	0	26	7
		Min	9	-31	8	-42
		Max	70	55	84	54

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 13	N	19	19	36	36
		Mean	27.1	3.1	32.0	8.3
		SD	18.0	20.2	17.6	17.1
		Median	24	-1	29	6
		Min	8	-25	10	-21
		Max	85	69	95	75
	Cycle 14	N	16	16	34	34
		Mean	26.7	4.4	33.1	10.0
		SD	14.3	15.7	17.5	18.0
		Median	24	-1	27	8
		Min	9	-14	8	-34
		Max	67	51	88	68
	Cycle 15	N	14	14	33	33
		Mean	27.6	4.8	32.6	10.8
		SD	11.9	12.6	20.7	20.9
		Median	29	1	26	5
		Min	11	-13	8	-15
		Max	50	34	101	89

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 16	N	7	7	30	30
		Mean	27.1	6.7	33.4	10.6
		SD	17.9	21.2	19.2	19.7
		Median	24	-3	26	4
		Min	8	-15	15	-13
		Max	56	40	101	89
	Cycle 17	N	7	7	25	25
		Mean	24.3	3.9	34.6	11.1
		SD	12.7	16.5	19.1	18.0
		Median	22	0	31	6
		Min	11	-18	14	-17
		Max	46	30	93	60
	Cycle 18	N	6	6	21	21
		Mean	21.2	0.0	30.2	5.8
		SD	11.0	13.4	13.4	13.7
		Median	20	-1	26	6
		Min	7	-15	10	-17
		Max	40	25	60	40

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 19	N	4	4	19	19
		Mean	19.0	-3.3	35.7	11.5
		SD	7.6	9.2	18.3	19.4
		Median	22	-2	28	7
		Min	8	-15	14	-27
		Max	25	5	78	50
	Cycle 20	N	3	3	18	18
		Mean	17.0	-8.0	29.7	6.0
		SD	4.4	16.7	13.9	16.4
		Median	15	-5	27	3
		Min	14	-26	12	-30
		Max	22	7	64	44
	Cycle 21	N	3	3	15	15
		Mean	20.0	-5.0	29.0	6.1
		SD	5.6	16.0	14.0	15.7
		Median	19	-5	26	4
		Min	15	-21	12	-18
		Max	26	11	70	50

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 22	N	2	2	14	14
		Mean	21.5	-6.0	28.6	5.6
		SD	12.0	29.7	16.6	17.9
		Median	22	-6	25	4
		Min	13	-27	10	-24
		Max	30	15	77	57
	Cycle 23	N	2	2	13	13
		Mean	24.5	-3.0	34.2	10.8
		SD	16.3	33.9	16.5	22.2
		Median	25	-3	30	3
		Min	13	-27	17	-24
		Max	36	21	65	51
	Cycle 24	N	1	1	11	11
		Mean	14.0	-26.0	28.4	6.0
		SD	-	-	11.3	13.9
		Median	14	-26	28	5
		Min	14	-26	16	-21
		Max	14	-26	55	35

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 25	N	1	1	10	10
		Mean	18.0	-22.0	24.5	1.9
		SD	-	-	7.7	13.8
		Median	18	-22	23	3
		Min	18	-22	16	-33
		Max	18	-22	35	15
	Cycle 26	N	1	1	10	10
		Mean	24.0	-16.0	29.2	6.6
		SD	-	-	10.1	16.7
		Median	24	-16	28	8
		Min	24	-16	14	-32
		Max	24	-16	46	27
	Cycle 27	N	1	1	10	10
		Mean	21.0	-19.0	28.0	5.4
		SD	-	-	10.6	12.0
		Median	21	-19	26	8
		Min	21	-19	15	-23
		Max	21	-19	50	16

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 28	N	0	0	9	9
		Mean	-	-	25.6	2.7
		SD	-	-	9.4	11.8
		Median	-	-	25	6
		Min	-	-	13	-24
		Max	-	-	42	15
	Cycle 29	N	0	0	9	9
		Mean	-	-	24.0	1.1
		SD	-	-	8.2	9.6
		Median	-	-	21	4
		Min	-	-	15	-22
		Max	-	-	39	9
	Cycle 30	N	0	0	7	7
		Mean	-	-	22.1	2.3
		SD	-	-	7.7	14.3
		Median	-	-	20	3
		Min	-	-	13	-23
		Max	-	-	33	22

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 31	N	0	0	6	6
		Mean	-	-	23.8	9.7
		SD	-	-	7.9	10.3
		Median	-	-	23	9
		Min	-	-	14	-5
		Max	-	-	38	27
	Cycle 32	N	0	0	5	5
		Mean	-	-	23.2	9.0
		SD	-	-	2.9	5.8
		Median	-	-	24	9
		Min	-	-	19	0
		Max	-	-	27	15
	Cycle 33	N	0	0	5	5
		Mean	-	-	23.0	8.8
		SD	-	-	5.2	7.4
		Median	-	-	24	13
		Min	-	-	15	-4
		Max	-	-	28	13

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 34	N	0	0	4	4
		Mean	-	-	34.3	20.0
		SD	-	-	26.2	28.9
		Median	-	-	24	11
		Min	-	-	16	-3
		Max	-	-	73	62
	Cycle 35	N	0	0	1	1
		Mean	-	-	21.0	9.0
		SD	-	-	-	-
		Median	-	-	21	9
		Min	-	-	21	9
		Max	-	-	21	9
	Cycle 36	N	0	0	1	1
		Mean	-	-	20.0	8.0
		SD	-	-	-	-
		Median	-	-	20	8
		Min	-	-	20	8
		Max	-	-	20	8

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.2 Laboratory Data: Actual Value and Change From Baseline (Serum Chemistry)
(Safety Population)

			Placebo (N = 112)		Sorafenib (N = 112)	
Laboratory Test	Visit	Statistics	Actual Value	Change From Baseline	Actual Value	Change From Baseline
SGPT/ALT (U/L)	Cycle 37	N	0	0	1	1
		Mean	-	-	22.0	10.0
		SD	-	-	-	-
		Median	-	-	22	10
		Min	-	-	22	10
		Max	-	-	22	10
	Cycle 38	N	0	0	1	1
		Mean	-	-	21.0	9.0
		SD	-	-	-	-
		Median	-	-	21	9
		Min	-	-	21	9
		Max	-	-	21	9
	Cycle 39	N	0	0	1	1
		Mean	-	-	20.0	8.0
		SD	-	-	-	-
		Median	-	-	20	8
		Min	-	-	20	8
		Max	-	-	20	8

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_02_LabC.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabC.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.3 Incidence of Laboratory Values of CTCAE Toxicity Grade 3 and 4
(Safety Population)

	Placebo (N=112)		Sorafenib (N=112)	
Laboratory Test	Grade 3 n/N(%)	Grade 4 n/N(%)	Grade 3 n/N(%)	Grade 4 n/N(%)
Hemoglobin	0/110 (0%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Lymphocytes	9/108 (8.3%)	0/108 (0%)	4/103 (3.9%)	0/103 (0%)
Neutrophils	0/110 (0%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Platelets	1/110 (0.9%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
WBC	1/110 (0.9%)	0/110 (0%)	1/104 (1.0%)	0/104 (0%)
Amylase	3/91 (3.3%)	0/91 (0%)	0/90 (0%)	0/90 (0%)
Lipase	0/39 (0%)	0/39 (0%)	3/48 (6.3%)	1/48 (2.1%)
Bilirubin, total	1/109 (0.9%)	0/109 (0%)	0/104 (0%)	0/104 (0%)
Creatinine	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)
SGOT/AST	2/109 (1.8%)	0/109 (0%)	1/104 (1.0%)	0/104 (0%)
SGPT/ALT	0/110 (0%)	0/110 (0%)	0/104 (0%)	0/104 (0%)

Note: Grade in this table represents the worst post-baseline grade reported for the subject.
Note: n=number of subjects with the grade being the worst post baseline toxicity; N=total number of subjects with the laboratory measurement reported post baseline.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_03_LabGrd.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabGrd.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Amylase (U/L)	-2	0	1
	-1	3	1
	0	73	63
	1	7	13
	2	1	2
	3	2	0
	Unk	26	32
Bilirubin, total (mg/dL)	-1	3	1
	0	78	59
	1	19	33
	2	7	10
	3	1	0
	Unk	4	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabX.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Creatinine (mg/dL)	-1	1	2
	0	101	88
	1	5	13
	2	2	0
	Unk	3	9
Hemoglobin (g/dL)	-2	0	1
	-1	2	3
	0	77	70
	1	27	25
	2	3	3
	3	0	1
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabX.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Lipase (U/L)	-3	1	0
	-2	0	1
	0	27	20
	1	5	8
	2	0	2
	3	0	3
	Unk	79	78
Lymphocytes absolute ct (GIGA/L)	-3	0	1
	-2	0	1
	-1	0	5
	0	76	60
	1	19	24
	2	6	7
	3	3	3
	Unk	8	11

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabX.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
Neutrophils absolute ct (GIGA/L)	-1	2	2
	0	89	75
	1	16	18
	2	2	7
	3	0	1
	Unk	3	9
Platelets (GIGA/L)	0	99	70
	1	8	31
	2	2	2
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabX.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
SGOT/AST (U/L)	-2	0	1
	-1	7	4
	0	77	51
	1	22	42
	2	2	4
	3	0	1
	Unk	4	9
SGPT/ALT (U/L)	-1	7	4
	0	80	57
	1	21	34
	2	1	8
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabX.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.4 Change From Baseline in CTCAE Toxicity Grade of Laboratory Value
(Safety Population)

Laboratory Test	Change in CTCAE Grade	Placebo (N = 112)	Sorafenib (N = 112)
WBC (GIGA/L)	-1	1	1
	0	83	59
	1	19	35
	2	5	8
	3	1	0
	Unk	3	9

Note: Grade change in this table represents the worst grade change from baseline grade for the subject.
Note: The grades for PTT and INR were not captured in the study.
Note: Unk=Either baseline grade or worst post baseline grade is missing.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_04_LabX.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_LabX.sas (Run Date: 24SEP2010 9:52)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	110	79.4	10.2	60	123
	Cycle 2	106	78.8	10.4	52	108
	Cycle 3	92	78.1	10.1	57	110
	Cycle 4	78	79.2	10.4	54	105
	Cycle 5	68	77.9	12.3	50	120
	Cycle 6	63	77.3	12.1	56	130
	Cycle 7	55	78.0	9.3	60	96
	Cycle 8	46	78.7	10.7	60	100
	Cycle 9	42	81.7	10.0	60	110
	Cycle 10	37	78.5	12.0	51	110
	Cycle 11	30	76.4	9.5	60	90
	Cycle 12	25	78.9	9.4	60	100
	Cycle 13	20	80.8	9.3	69	101
	Cycle 14	18	78.4	7.0	65	90
	Cycle 15	14	80.5	6.8	67	90
	Cycle 16	7	81.0	8.6	70	90

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 17	7	76.4	7.8	65	88
	Cycle 18	6	81.5	8.4	70	96
	Cycle 19	4	77.3	4.9	70	80
	Cycle 20	3	69.3	10.1	60	80
	Cycle 21	3	82.3	4.0	80	87
	Cycle 22	2	78.5	12.0	70	87
	Cycle 23	2	82.0	2.8	80	84
	Cycle 24	1	70.0	-	70	70
	Cycle 25	1	80.0	-	80	80
	Cycle 26	1	80.0	-	80	80
	Cycle 27	1	70.0	-	70	70
	End of treatment	109	80.3	9.5	57	105
	Change from baseline: Cycle 2	104	-1.1	9.6	-22	22
	Change from baseline: Cycle 3	91	-1.2	10.5	-34	26
	Change from baseline: Cycle 4	77	-0.1	11.6	-43	30
	Change from baseline: Cycle 5	67	-1.3	12.4	-40	30
	Change from baseline: Cycle 6	63	-1.3	10.4	-30	30

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 7	55	0.0	10.6	-26	20
	Change from baseline: Cycle 8	46	0.3	10.7	-25	25
	Change from baseline: Cycle 9	42	2.3	10.5	-17	30
	Change from baseline: Cycle 10	37	-1.3	11.5	-30	20
	Change from baseline: Cycle 11	30	-4.0	12.0	-30	20
	Change from baseline: Cycle 12	25	-0.3	11.9	-30	20
	Change from baseline: Cycle 13	20	1.5	9.8	-20	16
	Change from baseline: Cycle 14	18	0.1	9.0	-20	10
	Change from baseline: Cycle 15	14	1.3	10.2	-20	13
	Change from baseline: Cycle 16	7	3.3	10.9	-20	10
	Change from baseline: Cycle 17	7	-1.3	8.2	-10	10
	Change from baseline: Cycle 18	6	2.5	9.1	-10	17
	Change from baseline: Cycle 19	4	-1.3	6.3	-10	5
	Change from baseline: Cycle 20	3	-10.3	10.0	-20	0
	Change from baseline: Cycle 21	3	2.7	4.6	0	8
	Change from baseline: Cycle 22	2	-1.0	12.7	-10	8
	Change from baseline: Cycle 23	2	2.5	3.5	0	5

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 24	1	-10.0	-	-10	-10
	Change from baseline: Cycle 25	1	0.0	-	0	0
	Change from baseline: Cycle 26	1	0.0	-	0	0
	Change from baseline: Cycle 27	1	-10.0	-	-10	-10
	Change from baseline: End of treatment	107	0.6	11.6	-32	35
Sorafenib	Baseline	112	77.9	10.5	50	103
	Cycle 2	100	81.9	12.3	45	110
	Cycle 3	95	82.1	11.1	60	120
	Cycle 4	87	82.1	10.0	60	120
	Cycle 5	77	81.0	8.6	54	105
	Cycle 6	76	81.1	10.8	59	110
	Cycle 7	66	81.9	11.5	60	133
	Cycle 8	61	79.4	11.3	57	103
	Cycle 9	56	81.2	8.1	65	100
	Cycle 10	50	81.9	8.1	68	100
	Cycle 11	48	82.1	8.1	60	97
	Cycle 12	40	81.7	10.5	66	111

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 13	36	82.0	9.0	60	100
	Cycle 14	35	79.4	10.1	60	97
	Cycle 15	33	80.0	9.2	60	100
	Cycle 16	30	81.2	10.4	60	100
	Cycle 17	25	80.9	11.6	60	100
	Cycle 18	22	81.0	11.0	60	100
	Cycle 19	19	78.5	11.2	60	100
	Cycle 20	18	77.7	14.3	40	101
	Cycle 21	15	82.5	13.3	60	110
	Cycle 22	14	84.8	15.3	60	110
	Cycle 23	13	77.8	9.6	60	90
	Cycle 24	11	80.3	9.9	60	90
	Cycle 25	10	76.4	12.0	50	90
	Cycle 26	10	75.7	10.2	60	90
	Cycle 27	10	74.3	7.3	60	83
	Cycle 28	9	76.0	9.2	60	90
	Cycle 29	9	75.6	8.8	60	90

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 30	7	82.3	14.9	60	106
	Cycle 31	6	83.3	10.3	70	100
	Cycle 32	5	80.8	11.1	70	94
	Cycle 33	5	83.6	10.7	70	98
	Cycle 34	4	84.3	11.8	70	97
	Cycle 35	1	94.0	-	94	94
	Cycle 36	1	81.0	-	81	81
	Cycle 37	1	95.0	-	95	95
	Cycle 38	1	85.0	-	85	85
	Cycle 39	1	90.0	-	90	90
	End of treatment	102	79.8	11.3	50	110
	Change from baseline: Cycle 2	100	3.7	11.9	-23	39
	Change from baseline: Cycle 3	95	3.7	11.1	-20	30
	Change from baseline: Cycle 4	87	3.4	11.5	-23	50
	Change from baseline: Cycle 5	77	2.1	11.8	-34	30
	Change from baseline: Cycle 6	76	2.3	13.0	-30	33
	Change from baseline: Cycle 7	66	2.5	11.6	-30	41

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 8	61	0.7	11.5	-40	21
	Change from baseline: Cycle 9	56	2.0	9.8	-20	20
	Change from baseline: Cycle 10	50	1.6	10.0	-20	21
	Change from baseline: Cycle 11	48	1.6	10.1	-20	40
	Change from baseline: Cycle 12	40	1.8	11.1	-20	30
	Change from baseline: Cycle 13	36	1.6	11.0	-20	30
	Change from baseline: Cycle 14	35	-0.7	11.5	-20	30
	Change from baseline: Cycle 15	33	0.2	9.6	-20	20
	Change from baseline: Cycle 16	30	1.5	8.3	-20	12
	Change from baseline: Cycle 17	25	1.6	11.8	-30	20
	Change from baseline: Cycle 18	22	1.5	13.3	-20	21
	Change from baseline: Cycle 19	19	0.6	12.5	-30	20
	Change from baseline: Cycle 20	18	-0.8	15.6	-40	25
	Change from baseline: Cycle 21	15	5.0	11.7	-12	26
	Change from baseline: Cycle 22	14	7.5	13.0	-20	21
	Change from baseline: Cycle 23	13	1.0	8.7	-10	20
	Change from baseline: Cycle 24	11	4.5	7.2	-5	20

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Diastolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 25	10	1.1	12.0	-20	20
	Change from baseline: Cycle 26	10	0.4	10.1	-10	20
	Change from baseline: Cycle 27	10	-1.0	12.9	-20	20
	Change from baseline: Cycle 28	9	2.3	10.9	-10	20
	Change from baseline: Cycle 29	9	1.9	16.3	-30	30
	Change from baseline: Cycle 30	7	4.7	12.1	-10	23
	Change from baseline: Cycle 31	6	7.8	6.6	0	17
	Change from baseline: Cycle 32	5	4.2	5.8	0	11
	Change from baseline: Cycle 33	5	7.0	6.7	0	15
	Change from baseline: Cycle 34	4	6.0	10.8	-10	14
	Change from baseline: Cycle 35	1	11.0	-	11	11
	Change from baseline: Cycle 36	1	-2.0	-	-2	-2
	Change from baseline: Cycle 37	1	12.0	-	12	12
	Change from baseline: Cycle 38	1	2.0	-	2	2
	Change from baseline: Cycle 39	1	7.0	-	7	7
	Change from baseline: End of treatment	102	1.6	11.2	-30	36

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	110	128.7	17.7	95	180

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 2	106	125.5	17.5	90	171
	Cycle 3	92	125.6	15.0	90	170
	Cycle 4	78	126.8	15.0	85	165
	Cycle 5	68	125.3	16.2	87	180
	Cycle 6	63	126.4	17.6	90	190
	Cycle 7	55	124.8	14.2	100	180
	Cycle 8	46	128.4	15.2	100	160
	Cycle 9	42	129.7	14.2	100	160
	Cycle 10	37	124.7	15.5	90	160
	Cycle 11	30	119.9	15.7	90	150
	Cycle 12	25	121.8	14.5	100	160
	Cycle 13	20	122.6	13.4	95	160
	Cycle 14	18	125.1	11.2	103	140
	Cycle 15	14	128.6	13.7	110	160
	Cycle 16	7	125.3	7.1	115	135
	Cycle 17	7	119.9	6.5	110	130
	Cycle 18	6	121.2	11.3	110	140

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 19	4	121.5	10.3	110	135
	Cycle 20	3	110.0	17.3	100	130
	Cycle 21	3	118.0	7.2	110	124
	Cycle 22	2	117.0	9.9	110	124
	Cycle 23	2	110.5	14.8	100	121
	Cycle 24	1	110.0	-	110	110
	Cycle 25	1	130.0	-	130	130
	Cycle 26	1	120.0	-	120	120
	Cycle 27	1	110.0	-	110	110
	End of treatment	109	127.7	17.7	100	190
	Change from baseline: Cycle 2	104	-2.7	13.9	-40	40
	Change from baseline: Cycle 3	91	-1.7	15.8	-40	40
	Change from baseline: Cycle 4	77	-1.0	17.6	-60	50
	Change from baseline: Cycle 5	67	-3.0	19.1	-60	33
	Change from baseline: Cycle 6	63	-1.0	17.8	-74	40
	Change from baseline: Cycle 7	55	-2.8	17.5	-70	40
	Change from baseline: Cycle 8	46	0.8	18.5	-60	30

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 9	42	0.4	15.5	-47	40
	Change from baseline: Cycle 10	37	-2.5	18.1	-51	36
	Change from baseline: Cycle 11	30	-7.8	17.9	-40	40
	Change from baseline: Cycle 12	25	-3.4	18.8	-40	30
	Change from baseline: Cycle 13	20	-3.1	19.0	-60	30
	Change from baseline: Cycle 14	18	0.3	15.0	-23	40
	Change from baseline: Cycle 15	14	3.9	14.7	-20	30
	Change from baseline: Cycle 16	7	5.6	12.3	-10	20
	Change from baseline: Cycle 17	7	0.1	11.3	-10	20
	Change from baseline: Cycle 18	6	2.3	16.4	-20	27
	Change from baseline: Cycle 19	4	0.8	12.7	-10	15
	Change from baseline: Cycle 20	3	-11.0	10.1	-20	0
	Change from baseline: Cycle 21	3	-3.0	15.7	-20	11
	Change from baseline: Cycle 22	2	0.5	14.8	-10	11
	Change from baseline: Cycle 23	2	-6.0	19.8	-20	8
	Change from baseline: Cycle 24	1	-10.0	-	-10	-10
	Change from baseline: Cycle 25	1	10.0	-	10	10

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 26	1	0.0	-	0	0
	Change from baseline: Cycle 27	1	-10.0	-	-10	-10
	Change from baseline: End of treatment	107	-0.6	18.2	-50	50
Sorafenib	Baseline	112	124.0	16.7	90	168
	Cycle 2	100	128.2	16.8	89	174
	Cycle 3	95	129.1	19.2	100	220
	Cycle 4	87	128.0	17.1	100	180
	Cycle 5	77	127.5	17.4	90	180
	Cycle 6	76	127.4	16.6	95	170
	Cycle 7	66	130.4	16.0	100	169
	Cycle 8	61	124.1	17.3	90	180
	Cycle 9	56	125.7	14.2	100	170
	Cycle 10	50	127.5	12.6	100	158
	Cycle 11	48	130.0	14.0	100	159
	Cycle 12	40	126.3	17.6	100	169
	Cycle 13	36	126.8	13.0	102	160
	Cycle 14	35	123.9	16.3	100	162

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 15	33	127.1	16.2	97	180
	Cycle 16	30	126.6	17.9	100	167
	Cycle 17	25	128.4	18.6	95	165
	Cycle 18	22	129.6	18.1	103	180
	Cycle 19	19	122.2	13.0	100	144
	Cycle 20	18	124.1	14.0	90	150
	Cycle 21	15	124.3	16.0	99	141
	Cycle 22	14	129.0	18.2	100	160
	Cycle 23	13	123.3	12.4	100	140
	Cycle 24	11	121.5	14.8	90	140
	Cycle 25	10	120.7	12.7	100	140
	Cycle 26	10	116.6	14.6	90	130
	Cycle 27	10	115.0	8.5	100	130
	Cycle 28	9	119.2	13.7	100	140
	Cycle 29	9	121.4	13.0	100	140
	Cycle 30	7	117.7	16.2	90	140
	Cycle 31	6	126.7	16.3	100	150

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 32	5	123.6	13.2	110	140
	Cycle 33	5	122.2	11.1	110	131
	Cycle 34	4	127.3	12.5	110	140
	Cycle 35	1	130.0	-	130	130
	Cycle 36	1	113.0	-	113	113
	Cycle 37	1	133.0	-	133	133
	Cycle 38	1	116.0	-	116	116
	Cycle 39	1	140.0	-	140	140
	End of treatment	102	123.4	15.9	80	170
	Change from baseline: Cycle 2	100	3.1	16.5	-45	40
	Change from baseline: Cycle 3	95	4.4	19.5	-35	80
	Change from baseline: Cycle 4	87	2.6	20.1	-39	53
	Change from baseline: Cycle 5	77	1.8	21.4	-53	60
	Change from baseline: Cycle 6	76	1.8	19.5	-48	50
	Change from baseline: Cycle 7	66	4.3	18.1	-30	50
	Change from baseline: Cycle 8	61	-1.6	17.8	-45	34
	Change from baseline: Cycle 9	56	-0.3	17.1	-43	31

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 10	50	1.8	16.7	-31	40
	Change from baseline: Cycle 11	48	4.1	16.5	-35	49
	Change from baseline: Cycle 12	40	0.7	17.9	-37	40
	Change from baseline: Cycle 13	36	1.6	16.3	-41	40
	Change from baseline: Cycle 14	35	-1.4	18.4	-40	36
	Change from baseline: Cycle 15	33	1.5	21.1	-52	44
	Change from baseline: Cycle 16	30	0.1	17.6	-30	30
	Change from baseline: Cycle 17	25	4.6	19.1	-30	31
	Change from baseline: Cycle 18	22	5.5	22.5	-41	40
	Change from baseline: Cycle 19	19	0.5	15.9	-30	30
	Change from baseline: Cycle 20	18	1.3	20.3	-21	40
	Change from baseline: Cycle 21	15	2.5	18.1	-24	31
	Change from baseline: Cycle 22	14	9.6	20.7	-21	40
	Change from baseline: Cycle 23	13	4.3	20.5	-30	40
	Change from baseline: Cycle 24	11	5.2	16.9	-10	30
	Change from baseline: Cycle 25	10	6.7	18.1	-20	30
	Change from baseline: Cycle 26	10	2.6	20.2	-20	30

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Systolic blood pressure (mmHg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 27	10	1.0	11.0	-20	20
	Change from baseline: Cycle 28	9	8.1	19.3	-20	30
	Change from baseline: Cycle 29	9	10.3	20.2	-40	23
	Change from baseline: Cycle 30	7	6.3	22.4	-30	30
	Change from baseline: Cycle 31	6	20.0	17.9	-10	40
	Change from baseline: Cycle 32	5	17.6	8.3	10	30
	Change from baseline: Cycle 33	5	16.2	5.7	10	21
	Change from baseline: Cycle 34	4	19.8	8.2	10	30
	Change from baseline: Cycle 35	1	20.0	-	20	20
	Change from baseline: Cycle 36	1	3.0	-	3	3
	Change from baseline: Cycle 37	1	23.0	-	23	23
	Change from baseline: Cycle 38	1	6.0	-	6	6
	Change from baseline: Cycle 39	1	30.0	-	30	30
	Change from baseline: End of treatment	102	-1.8	17.4	-70	45

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	112	67.3	12.6	37	116
	Cycle 2	109	67.1	12.8	38	114
	Cycle 3	93	67.3	12.5	38	110

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 4	79	66.4	11.6	37	109
	Cycle 5	69	66.6	11.3	45	107
	Cycle 6	63	67.4	11.3	50	107
	Cycle 7	55	67.6	12.2	50	111
	Cycle 8	46	68.5	12.5	52	111
	Cycle 9	42	69.4	12.5	53	110
	Cycle 10	37	69.1	13.4	52	110
	Cycle 11	30	70.2	14.1	52	111
	Cycle 12	25	69.4	13.6	51	111
	Cycle 13	20	69.2	10.9	51	90
	Cycle 14	18	68.6	10.0	50	84
	Cycle 15	14	67.8	10.1	51	84
	Cycle 16	7	71.2	8.0	62	81
	Cycle 17	7	71.5	7.8	63	82
	Cycle 18	6	69.3	8.0	61	82
	Cycle 19	4	65.4	3.1	63	70
	Cycle 20	3	66.2	3.3	63	70

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 21	3	66.4	3.4	63	70
	Cycle 22	2	63.9	3.0	62	66
	Cycle 23	2	64.0	2.8	62	66
	Cycle 24	1	62.0	-	62	62
	Cycle 25	1	61.0	-	61	61
	Cycle 26	1	62.2	-	62	62
	Cycle 27	1	62.0	-	62	62
	End of treatment	111	67.5	13.0	37	111
	Change from baseline: Cycle 2	109	-0.1	1.1	-4	4
	Change from baseline: Cycle 3	93	0.2	1.8	-7	5
	Change from baseline: Cycle 4	79	0.3	1.7	-3	4
	Change from baseline: Cycle 5	69	0.3	2.1	-5	6
	Change from baseline: Cycle 6	63	0.7	2.4	-6	7
	Change from baseline: Cycle 7	55	0.9	2.7	-6	7
	Change from baseline: Cycle 8	46	1.1	3.2	-7	11
	Change from baseline: Cycle 9	42	1.6	3.9	-9	16
	Change from baseline: Cycle 10	37	1.6	3.5	-11	9

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 11	30	1.4	3.8	-11	10
	Change from baseline: Cycle 12	25	1.7	4.2	-12	9
	Change from baseline: Cycle 13	20	1.9	4.5	-13	8
	Change from baseline: Cycle 14	18	1.6	5.1	-14	9
	Change from baseline: Cycle 15	14	2.3	3.1	-2	9
	Change from baseline: Cycle 16	7	3.6	2.9	0	9
	Change from baseline: Cycle 17	7	3.9	2.6	0	8
	Change from baseline: Cycle 18	6	2.4	2.6	-1	6
	Change from baseline: Cycle 19	4	3.0	3.1	0	7
	Change from baseline: Cycle 20	3	3.8	3.4	0	7
	Change from baseline: Cycle 21	3	4.0	3.6	0	7
	Change from baseline: Cycle 22	2	1.8	2.5	0	4
	Change from baseline: Cycle 23	2	1.9	2.6	0	4
	Change from baseline: Cycle 24	1	3.7	-	4	4
	Change from baseline: Cycle 25	1	2.7	-	3	3
	Change from baseline: Cycle 26	1	3.9	-	4	4
	Change from baseline: Cycle 27	1	3.7	-	4	4

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: End of treatment	111	0.3	3.4	-14	15
Sorafenib	Baseline	112	66.7	13.5	42	103
	Cycle 2	103	65.8	13.6	42	100
	Cycle 3	96	65.9	14.1	36	104
	Cycle 4	88	65.6	14.0	43	105
	Cycle 5	78	66.4	13.6	43	104
	Cycle 6	76	66.5	14.0	41	104
	Cycle 7	66	66.5	14.3	43	103
	Cycle 8	61	65.6	14.0	41	105
	Cycle 9	56	66.5	13.9	41	105
	Cycle 10	50	66.4	13.3	40	105
	Cycle 11	48	66.2	13.9	39	107
	Cycle 12	40	65.2	14.3	44	107
	Cycle 13	36	67.7	15.2	44	107
	Cycle 14	35	67.1	14.3	43	107
	Cycle 15	33	67.7	14.7	42	107
	Cycle 16	30	67.3	15.3	41	108

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 17	25	66.3	15.6	40	108
	Cycle 18	22	66.8	16.2	44	107
	Cycle 19	19	68.5	16.5	43	108
	Cycle 20	18	69.2	16.1	44	107
	Cycle 21	15	68.7	16.5	46	107
	Cycle 22	14	70.0	16.2	44	107
	Cycle 23	13	69.2	17.0	42	106
	Cycle 24	11	67.3	13.6	44	91
	Cycle 25	10	64.5	11.8	43	84
	Cycle 26	10	64.3	11.8	43	85
	Cycle 27	10	64.4	11.8	43	84
	Cycle 28	9	62.2	9.9	44	76
	Cycle 29	9	62.0	10.3	43	77
	Cycle 30	7	63.6	10.7	43	76
	Cycle 31	6	63.6	12.3	43	76
	Cycle 32	5	68.0	8.0	59	77
	Cycle 33	5	67.9	7.5	58	76

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 34	4	68.5	8.8	57	76
	Cycle 35	1	56.5	-	57	57
	Cycle 36	1	55.8	-	56	56
	Cycle 37	1	56.4	-	56	56
	Cycle 38	1	56.7	-	57	57
	Cycle 39	1	58.4	-	58	58
	End of treatment	102	63.0	13.6	36	105
	Change from baseline: Cycle 2	103	-1.4	2.0	-14	4
	Change from baseline: Cycle 3	96	-1.8	2.7	-14	3
	Change from baseline: Cycle 4	88	-2.7	6.1	-52	4
	Change from baseline: Cycle 5	78	-2.4	3.4	-16	4
	Change from baseline: Cycle 6	76	-2.5	3.9	-16	5
	Change from baseline: Cycle 7	66	-2.5	3.8	-15	6
	Change from baseline: Cycle 8	61	-2.9	4.3	-15	5
	Change from baseline: Cycle 9	56	-2.4	4.8	-15	10
	Change from baseline: Cycle 10	50	-3.0	5.1	-15	6
	Change from baseline: Cycle 11	48	-3.1	5.2	-16	7

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 12	40	-3.9	5.2	-16	7
	Change from baseline: Cycle 13	36	-2.9	7.1	-16	22
	Change from baseline: Cycle 14	35	-3.6	5.9	-18	8
	Change from baseline: Cycle 15	33	-3.1	6.1	-16	14
	Change from baseline: Cycle 16	30	-4.1	6.6	-16	8
	Change from baseline: Cycle 17	25	-3.5	7.0	-22	8
	Change from baseline: Cycle 18	22	-3.5	7.3	-23	7
	Change from baseline: Cycle 19	19	-2.9	7.0	-18	7
	Change from baseline: Cycle 20	18	-3.4	7.0	-16	10
	Change from baseline: Cycle 21	15	-3.3	7.6	-15	9
	Change from baseline: Cycle 22	14	-2.8	7.9	-16	9
	Change from baseline: Cycle 23	13	-4.0	8.1	-17	8
	Change from baseline: Cycle 24	11	-4.6	8.3	-16	10
	Change from baseline: Cycle 25	10	-5.1	8.1	-16	7
	Change from baseline: Cycle 26	10	-5.3	8.2	-17	7
	Change from baseline: Cycle 27	10	-5.2	8.0	-16	8
	Change from baseline: Cycle 28	9	-5.0	8.9	-17	9

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Weight (kg)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 29	9	-5.1	9.0	-17	9
	Change from baseline: Cycle 30	7	-3.6	9.2	-17	8
	Change from baseline: Cycle 31	6	-4.9	9.7	-17	10
	Change from baseline: Cycle 32	5	-4.1	10.7	-16	10
	Change from baseline: Cycle 33	5	-4.2	9.8	-15	9
	Change from baseline: Cycle 34	4	-2.6	10.5	-16	10
	Change from baseline: Cycle 35	1	-5.0	-	-5	-5
	Change from baseline: Cycle 36	1	-5.7	-	-6	-6
	Change from baseline: Cycle 37	1	-5.1	-	-5	-5
	Change from baseline: Cycle 38	1	-4.8	-	-5	-5
	Change from baseline: Cycle 39	1	-3.1	-	-3	-3
	Change from baseline: End of treatment	102	-3.4	5.0	-23	6

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Height (cm)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	112	158.4	7.1	140	176
Sorafenib	Baseline	112	158.5	6.7	144	187

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	111	1.7	0.1	1	2
	Cycle 2	109	1.7	0.2	1	2
	Cycle 3	93	1.7	0.2	1	2

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 4	79	1.7	0.1	1	2
	Cycle 5	69	1.7	0.1	1	2
	Cycle 6	63	1.7	0.1	1	2
	Cycle 7	55	1.7	0.1	1	2
	Cycle 8	46	1.7	0.1	1	2
	Cycle 9	42	1.7	0.1	1	2
	Cycle 10	37	1.7	0.2	1	2
	Cycle 11	30	1.7	0.2	1	2
	Cycle 12	25	1.7	0.2	1	2
	Cycle 13	20	1.7	0.1	1	2
	Cycle 14	18	1.7	0.1	1	2
	Cycle 15	14	1.7	0.2	1	2
	Cycle 16	7	1.7	0.1	2	2
	Cycle 17	7	1.7	0.1	2	2
	Cycle 18	6	1.7	0.1	2	2
	Cycle 19	4	1.7	0.1	2	2
	Cycle 20	3	1.7	0.1	2	2

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 21	3	1.7	0.1	2	2
	Cycle 22	2	1.6	0.0	2	2
	Cycle 23	2	1.6	0.0	2	2
	Cycle 24	1	1.6	-	2	2
	Cycle 25	1	1.6	-	2	2
	Cycle 26	1	1.6	-	2	2
	Cycle 27	1	1.6	-	2	2
	Change from baseline: Cycle 2	108	0.0	0.0	0	0
	Change from baseline: Cycle 3	93	0.0	0.0	0	0
	Change from baseline: Cycle 4	79	0.0	0.0	0	0
	Change from baseline: Cycle 5	69	0.0	0.0	0	0
	Change from baseline: Cycle 6	63	0.0	0.0	0	0
	Change from baseline: Cycle 7	55	0.0	0.0	0	0
	Change from baseline: Cycle 8	46	0.0	0.0	0	0
	Change from baseline: Cycle 9	42	0.0	0.0	0	0
	Change from baseline: Cycle 10	37	0.0	0.0	0	0
	Change from baseline: Cycle 11	30	0.0	0.0	0	0

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
Program: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\tblpgm\t_vital.sas (Run Date: 24SEP2010 9:54)

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 12	25	0.0	0.0	0	0
	Change from baseline: Cycle 13	20	0.0	0.0	0	0
	Change from baseline: Cycle 14	18	0.0	0.0	0	0
	Change from baseline: Cycle 15	14	0.0	0.0	0	0
	Change from baseline: Cycle 16	7	0.0	0.0	0	0
	Change from baseline: Cycle 17	7	0.0	0.0	0	0
	Change from baseline: Cycle 18	6	0.0	0.0	0	0
	Change from baseline: Cycle 19	4	0.0	0.0	0	0
	Change from baseline: Cycle 20	3	0.0	0.0	0	0
	Change from baseline: Cycle 21	3	0.0	0.0	0	0
	Change from baseline: Cycle 22	2	0.0	0.0	0	0
	Change from baseline: Cycle 23	2	0.0	0.0	0	0
	Change from baseline: Cycle 24	1	0.0	-	0	0
	Change from baseline: Cycle 25	1	0.0	-	0	0
	Change from baseline: Cycle 26	1	0.0	-	0	0
	Change from baseline: Cycle 27	1	0.0	-	0	0
Sorafenib	Baseline	112	1.7	0.2	1	2

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 2	103	1.7	0.2	1	2
	Cycle 3	96	1.7	0.2	1	2
	Cycle 4	88	1.7	0.2	1	2
	Cycle 5	78	1.7	0.2	1	2
	Cycle 6	76	1.7	0.2	1	2
	Cycle 7	66	1.7	0.2	1	2
	Cycle 8	61	1.7	0.2	1	2
	Cycle 9	56	1.7	0.2	1	2
	Cycle 10	50	1.7	0.2	1	2
	Cycle 11	48	1.7	0.2	1	2
	Cycle 12	40	1.7	0.2	1	2
	Cycle 13	36	1.7	0.2	1	2
	Cycle 14	35	1.7	0.2	1	2
	Cycle 15	33	1.7	0.2	1	2
	Cycle 16	30	1.7	0.2	1	2
	Cycle 17	25	1.7	0.2	1	2
	Cycle 18	22	1.7	0.2	1	2

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 19	19	1.7	0.2	1	2
	Cycle 20	18	1.7	0.2	1	2
	Cycle 21	15	1.7	0.2	1	2
	Cycle 22	14	1.7	0.2	1	2
	Cycle 23	13	1.7	0.2	1	2
	Cycle 24	11	1.7	0.2	1	2
	Cycle 25	10	1.6	0.1	1	2
	Cycle 26	10	1.6	0.1	1	2
	Cycle 27	10	1.6	0.1	1	2
	Cycle 28	9	1.6	0.1	1	2
	Cycle 29	9	1.6	0.1	1	2
	Cycle 30	7	1.7	0.1	1	2
	Cycle 31	6	1.7	0.2	1	2
	Cycle 32	5	1.7	0.1	2	2
	Cycle 33	5	1.7	0.1	2	2
	Cycle 34	4	1.7	0.1	2	2
	Cycle 35	1	1.6	-	2	2

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 36	1	1.6	-	2	2
	Cycle 37	1	1.6	-	2	2
	Cycle 38	1	1.6	-	2	2
	Cycle 39	1	1.6	-	2	2
	Change from baseline: Cycle 2	103	0.0	0.0	0	0
	Change from baseline: Cycle 3	96	0.0	0.0	0	0
	Change from baseline: Cycle 4	88	0.0	0.0	0	0
	Change from baseline: Cycle 5	78	0.0	0.0	0	0
	Change from baseline: Cycle 6	76	0.0	0.0	0	0
	Change from baseline: Cycle 7	66	0.0	0.0	0	0
	Change from baseline: Cycle 8	61	0.0	0.0	0	0
	Change from baseline: Cycle 9	56	0.0	0.1	0	0
	Change from baseline: Cycle 10	50	0.0	0.1	0	0
	Change from baseline: Cycle 11	48	0.0	0.1	0	0
	Change from baseline: Cycle 12	40	0.0	0.1	0	0
	Change from baseline: Cycle 13	36	0.0	0.1	0	0
	Change from baseline: Cycle 14	35	0.0	0.1	0	0

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 15	33	0.0	0.1	0	0
	Change from baseline: Cycle 16	30	0.0	0.1	0	0
	Change from baseline: Cycle 17	25	0.0	0.1	0	0
	Change from baseline: Cycle 18	22	0.0	0.1	0	0
	Change from baseline: Cycle 19	19	0.0	0.1	0	0
	Change from baseline: Cycle 20	18	0.0	0.1	0	0
	Change from baseline: Cycle 21	15	0.0	0.1	0	0
	Change from baseline: Cycle 22	14	0.0	0.1	0	0
	Change from baseline: Cycle 23	13	-0.1	0.1	0	0
	Change from baseline: Cycle 24	11	-0.1	0.1	0	0
	Change from baseline: Cycle 25	10	-0.1	0.1	0	0
	Change from baseline: Cycle 26	10	-0.1	0.1	0	0
	Change from baseline: Cycle 27	10	-0.1	0.1	0	0
	Change from baseline: Cycle 28	9	-0.1	0.1	0	0
	Change from baseline: Cycle 29	9	-0.1	0.1	0	0
	Change from baseline: Cycle 30	7	0.0	0.1	0	0
	Change from baseline: Cycle 31	6	-0.1	0.1	0	0

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Body surface area as recorded in CRF (m^2)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 32	5	0.0	0.1	0	0
	Change from baseline: Cycle 33	5	-0.1	0.1	0	0
	Change from baseline: Cycle 34	4	0.0	0.1	0	0
	Change from baseline: Cycle 35	1	-0.1	-	0	0
	Change from baseline: Cycle 36	1	-0.1	-	0	0
	Change from baseline: Cycle 37	1	-0.1	-	0	0
	Change from baseline: Cycle 38	1	-0.1	-	0	0
	Change from baseline: Cycle 39	1	0.0	-	0	0

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	109	80.7	12.7	54	126
	Cycle 2	106	81.7	11.8	53	118
	Cycle 3	92	79.9	11.2	52	108
	Cycle 4	78	80.4	12.1	58	112
	Cycle 5	68	78.8	10.7	44	112
	Cycle 6	63	78.0	12.7	43	116
	Cycle 7	55	80.0	12.0	54	112
	Cycle 8	46	77.3	11.6	55	106
	Cycle 9	42	78.7	12.5	50	104

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 10	37	77.5	11.5	51	104
	Cycle 11	30	76.9	12.3	55	106
	Cycle 12	25	77.6	11.0	63	110
	Cycle 13	20	76.0	11.8	60	108
	Cycle 14	18	75.4	7.1	60	91
	Cycle 15	14	76.2	11.1	60	102
	Cycle 16	7	81.6	12.5	68	102
	Cycle 17	7	77.0	9.8	64	91
	Cycle 18	6	77.0	10.1	67	95
	Cycle 19	4	81.8	6.7	75	90
	Cycle 20	3	83.7	6.7	76	88
	Cycle 21	3	81.0	8.2	72	88
	Cycle 22	2	73.5	13.4	64	83
	Cycle 23	2	79.0	1.4	78	80
	Cycle 24	1	78.0	-	78	78
	Cycle 25	1	76.0	-	76	76
	Cycle 26	1	88.0	-	88	88

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

Source: E:\Biometrics\Bay43-9006\Breast\OX12740\OS\Output\Tables\t_14_4_05_vital.rtf (Data Cutoff: 30JUN10, Download: 18AUG10)
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 27	1	86.0	-	86	86
	End of treatment	109	82.6	12.9	50	122
	Change from baseline: Cycle 2	103	0.2	11.7	-32	31
	Change from baseline: Cycle 3	90	-0.2	12.1	-30	34
	Change from baseline: Cycle 4	76	1.7	14.4	-38	34
	Change from baseline: Cycle 5	66	0.3	13.8	-40	28
	Change from baseline: Cycle 6	62	0.2	14.3	-41	34
	Change from baseline: Cycle 7	54	2.5	14.3	-30	28
	Change from baseline: Cycle 8	46	0.2	12.0	-28	32
	Change from baseline: Cycle 9	42	1.3	12.4	-30	30
	Change from baseline: Cycle 10	37	0.6	12.0	-28	30
	Change from baseline: Cycle 11	30	2.1	11.3	-21	25
	Change from baseline: Cycle 12	25	2.9	11.7	-24	24
	Change from baseline: Cycle 13	20	1.7	8.4	-16	14
	Change from baseline: Cycle 14	18	2.7	7.8	-16	11
	Change from baseline: Cycle 15	14	3.9	10.2	-11	28
	Change from baseline: Cycle 16	7	9.0	12.7	-10	28

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 17	7	4.4	11.3	-16	16
	Change from baseline: Cycle 18	6	4.0	8.6	-10	14
	Change from baseline: Cycle 19	4	8.3	7.9	3	20
	Change from baseline: Cycle 20	3	13.7	10.0	4	24
	Change from baseline: Cycle 21	3	11.0	12.1	0	24
	Change from baseline: Cycle 22	2	4.5	6.4	0	9
	Change from baseline: Cycle 23	2	10.0	8.5	4	16
	Change from baseline: Cycle 24	1	14.0	-	14	14
	Change from baseline: Cycle 25	1	12.0	-	12	12
	Change from baseline: Cycle 26	1	24.0	-	24	24
	Change from baseline: Cycle 27	1	22.0	-	22	22
	Change from baseline: End of treatment	106	1.6	12.2	-36	35
Sorafenib	Baseline	111	84.2	14.1	53	132
	Cycle 2	94	82.5	13.6	54	120
	Cycle 3	93	82.7	12.0	54	122
	Cycle 4	87	82.9	13.4	56	122
	Cycle 5	77	81.3	13.1	55	123

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 6	76	82.4	16.4	50	130
	Cycle 7	66	81.6	13.0	59	120
	Cycle 8	61	81.6	13.0	64	116
	Cycle 9	56	81.3	12.0	59	110
	Cycle 10	50	82.4	12.6	58	117
	Cycle 11	48	82.6	13.8	58	120
	Cycle 12	40	83.7	14.4	55	122
	Cycle 13	36	82.6	11.4	61	109
	Cycle 14	35	81.5	12.3	56	117
	Cycle 15	33	82.6	13.8	59	116
	Cycle 16	30	82.0	11.1	68	112
	Cycle 17	25	78.2	12.4	56	116
	Cycle 18	22	80.1	11.0	64	109
	Cycle 19	19	80.2	10.6	59	97
	Cycle 20	18	86.8	11.0	72	116
	Cycle 21	15	84.8	17.3	62	116
	Cycle 22	14	86.7	11.8	72	116

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 23	13	86.8	12.7	69	118
	Cycle 24	11	83.6	15.1	71	121
	Cycle 25	10	80.9	9.6	72	106
	Cycle 26	10	83.9	12.5	73	116
	Cycle 27	10	78.2	14.7	55	112
	Cycle 28	9	79.3	9.9	71	96
	Cycle 29	9	78.0	9.9	68	96
	Cycle 30	7	78.6	11.3	68	103
	Cycle 31	6	88.5	9.1	78	98
	Cycle 32	5	80.4	11.3	72	100
	Cycle 33	5	81.0	18.1	66	112
	Cycle 34	4	83.3	18.5	65	109
	Cycle 35	1	96.0	-	96	96
	Cycle 36	1	100.0	-	100	100
	Cycle 37	1	100.0	-	100	100
	Cycle 38	1	100.0	-	100	100
	Cycle 39	1	103.0	-	103	103

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	End of treatment	100	85.8	14.2	46	122
	Change from baseline: Cycle 2	94	-1.6	12.3	-37	32
	Change from baseline: Cycle 3	93	-1.0	13.2	-43	44
	Change from baseline: Cycle 4	86	-1.1	14.1	-45	36
	Change from baseline: Cycle 5	76	-1.5	11.2	-41	26
	Change from baseline: Cycle 6	75	0.1	13.4	-29	32
	Change from baseline: Cycle 7	65	-1.5	12.7	-32	31
	Change from baseline: Cycle 8	60	-0.4	10.9	-24	28
	Change from baseline: Cycle 9	55	-0.9	12.2	-28	30
	Change from baseline: Cycle 10	49	0.4	12.7	-28	28
	Change from baseline: Cycle 11	48	0.4	11.9	-28	29
	Change from baseline: Cycle 12	40	-0.4	10.3	-28	22
	Change from baseline: Cycle 13	36	-1.0	13.1	-36	26
	Change from baseline: Cycle 14	35	-2.1	10.4	-23	26
	Change from baseline: Cycle 15	33	-1.3	11.7	-24	31
	Change from baseline: Cycle 16	30	-2.3	11.9	-31	19
	Change from baseline: Cycle 17	25	-5.6	12.7	-32	16

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 18	22	-4.1	14.4	-28	18
	Change from baseline: Cycle 19	19	-5.4	13.9	-28	29
	Change from baseline: Cycle 20	18	0.3	13.1	-24	25
	Change from baseline: Cycle 21	15	0.2	18.0	-34	38
	Change from baseline: Cycle 22	14	3.4	15.5	-27	38
	Change from baseline: Cycle 23	13	4.4	6.6	-8	12
	Change from baseline: Cycle 24	11	4.8	10.4	-17	21
	Change from baseline: Cycle 25	10	2.0	10.4	-10	17
	Change from baseline: Cycle 26	10	5.0	10.5	-12	18
	Change from baseline: Cycle 27	10	-0.7	7.4	-10	12
	Change from baseline: Cycle 28	9	-0.8	11.5	-20	16
	Change from baseline: Cycle 29	9	-2.1	11.5	-17	16
	Change from baseline: Cycle 30	7	-2.3	9.5	-14	12
	Change from baseline: Cycle 31	6	7.5	9.0	-4	19
	Change from baseline: Cycle 32	5	-1.0	9.5	-15	8
	Change from baseline: Cycle 33	5	-0.4	14.4	-24	12
	Change from baseline: Cycle 34	4	1.5	18.0	-25	15

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Heart rate/pulse rate (/min)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 35	1	-4.0	-	-4	-4
	Change from baseline: Cycle 36	1	0.0	-	0	0
	Change from baseline: Cycle 37	1	0.0	-	0	0
	Change from baseline: Cycle 38	1	0.0	-	0	0
	Change from baseline: Cycle 39	1	3.0	-	3	3
	Change from baseline: End of treatment	99	1.3	15.0	-34	36

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Baseline	107	36.3	0.5	35	38
	Cycle 2	102	36.3	0.4	35	37
	Cycle 3	92	36.2	0.4	35	37
	Cycle 4	78	36.2	0.5	34	37
	Cycle 5	68	36.3	0.4	35	37
	Cycle 6	63	36.3	0.3	36	37
	Cycle 7	55	36.3	0.4	35	37
	Cycle 8	46	36.3	0.4	35	37
	Cycle 9	42	36.2	0.4	35	37
	Cycle 10	37	36.3	0.5	35	37
	Cycle 11	30	36.4	0.4	36	38

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Cycle 12	25	36.3	0.4	35	37
	Cycle 13	20	36.4	0.3	36	37
	Cycle 14	18	36.3	0.3	36	37
	Cycle 15	14	36.2	0.3	35	37
	Cycle 16	7	36.5	0.3	36	37
	Cycle 17	7	36.5	0.3	36	37
	Cycle 18	6	36.2	0.4	36	37
	Cycle 19	4	36.3	0.3	36	37
	Cycle 20	3	36.1	0.1	36	36
	Cycle 21	3	35.9	0.2	36	36
	Cycle 22	2	35.9	0.2	36	36
	Cycle 23	2	36.2	0.4	36	37
	Cycle 24	1	36.3	-	36	36
	Cycle 25	1	36.0	-	36	36
	Cycle 26	1	36.1	-	36	36
	Cycle 27	1	36.4	-	36	36
	End of treatment	108	36.3	0.4	35	37

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 2	97	0.0	0.4	-1	1
	Change from baseline: Cycle 3	89	0.0	0.5	-2	1
	Change from baseline: Cycle 4	75	-0.1	0.4	-2	1
	Change from baseline: Cycle 5	65	0.0	0.4	-1	1
	Change from baseline: Cycle 6	61	0.0	0.5	-1	2
	Change from baseline: Cycle 7	53	0.0	0.4	-1	1
	Change from baseline: Cycle 8	45	-0.1	0.4	-1	1
	Change from baseline: Cycle 9	41	-0.1	0.4	-1	1
	Change from baseline: Cycle 10	36	-0.1	0.4	-1	1
	Change from baseline: Cycle 11	29	0.1	0.3	-1	1
	Change from baseline: Cycle 12	25	0.0	0.4	-1	1
	Change from baseline: Cycle 13	20	0.1	0.4	-1	1
	Change from baseline: Cycle 14	18	0.0	0.3	-1	1
	Change from baseline: Cycle 15	14	0.0	0.3	-1	1
	Change from baseline: Cycle 16	7	0.2	0.2	0	1
	Change from baseline: Cycle 17	7	0.2	0.3	0	1
	Change from baseline: Cycle 18	6	-0.1	0.3	-1	0

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Placebo	Change from baseline: Cycle 19	4	-0.1	0.2	0	0
	Change from baseline: Cycle 20	3	-0.2	0.2	0	0
	Change from baseline: Cycle 21	3	-0.4	0.2	-1	0
	Change from baseline: Cycle 22	2	-0.4	0.1	-1	0
	Change from baseline: Cycle 23	2	-0.1	0.4	0	0
	Change from baseline: Cycle 24	1	0.1	-	0	0
	Change from baseline: Cycle 25	1	-0.2	-	0	0
	Change from baseline: Cycle 26	1	-0.1	-	0	0
	Change from baseline: Cycle 27	1	0.2	-	0	0
	Change from baseline: End of treatment	103	0.0	0.4	-1	2
Sorafenib	Baseline	110	36.4	0.5	35	38
	Cycle 2	93	36.3	0.4	35	38
	Cycle 3	94	36.3	0.4	35	37
	Cycle 4	87	36.4	0.5	35	38
	Cycle 5	77	36.3	0.4	36	37
	Cycle 6	76	36.4	0.3	35	37
	Cycle 7	66	36.3	0.4	36	38

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 8	61	36.3	0.4	35	37
	Cycle 9	56	36.3	0.5	35	37
	Cycle 10	50	36.2	0.5	34	37
	Cycle 11	48	36.3	0.4	36	37
	Cycle 12	40	36.3	0.5	36	37
	Cycle 13	36	36.3	0.5	36	38
	Cycle 14	35	36.2	0.5	35	37
	Cycle 15	33	36.3	0.5	35	37
	Cycle 16	30	36.3	0.4	35	37
	Cycle 17	25	36.2	0.4	35	37
	Cycle 18	22	36.4	0.5	35	37
	Cycle 19	19	36.3	0.3	36	37
	Cycle 20	18	36.3	0.3	36	37
	Cycle 21	15	36.2	0.5	35	37
	Cycle 22	14	36.2	0.6	35	38
	Cycle 23	13	36.2	0.5	35	37
	Cycle 24	11	36.2	0.4	36	37

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Cycle 25	10	36.2	0.4	36	37
	Cycle 26	10	36.2	0.2	36	37
	Cycle 27	10	36.2	0.3	36	37
	Cycle 28	9	36.1	0.3	36	37
	Cycle 29	9	36.3	0.4	36	37
	Cycle 30	7	35.9	0.4	35	37
	Cycle 31	6	36.0	0.1	36	36
	Cycle 32	5	36.0	0.0	36	36
	Cycle 33	5	36.0	0.2	36	36
	Cycle 34	4	36.2	0.4	36	37
	Cycle 35	1	35.5	-	36	36
	Cycle 36	1	36.0	-	36	36
	Cycle 37	1	36.0	-	36	36
	Cycle 38	1	36.0	-	36	36
	Cycle 39	1	36.0	-	36	36
	End of treatment	100	36.3	0.5	35	38
	Change from baseline: Cycle 2	92	-0.1	0.4	-1	1

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 3	92	-0.1	0.4	-2	1
	Change from baseline: Cycle 4	85	0.0	0.4	-1	1
	Change from baseline: Cycle 5	75	-0.1	0.4	-2	1
	Change from baseline: Cycle 6	74	0.0	0.5	-2	2
	Change from baseline: Cycle 7	64	-0.1	0.4	-1	1
	Change from baseline: Cycle 8	59	-0.1	0.4	-1	1
	Change from baseline: Cycle 9	55	-0.1	0.5	-2	1
	Change from baseline: Cycle 10	49	-0.2	0.6	-2	1
	Change from baseline: Cycle 11	48	0.0	0.4	-1	1
	Change from baseline: Cycle 12	40	-0.1	0.5	-1	2
	Change from baseline: Cycle 13	36	-0.1	0.5	-1	2
	Change from baseline: Cycle 14	35	-0.2	0.5	-1	1
	Change from baseline: Cycle 15	33	-0.1	0.5	-1	1
	Change from baseline: Cycle 16	30	-0.1	0.5	-1	1
	Change from baseline: Cycle 17	25	-0.2	0.5	-2	1
	Change from baseline: Cycle 18	22	-0.1	0.6	-1	1
	Change from baseline: Cycle 19	19	-0.2	0.3	-1	0

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 20	18	-0.2	0.4	-1	1
	Change from baseline: Cycle 21	15	-0.3	0.5	-1	1
	Change from baseline: Cycle 22	14	-0.2	0.6	-1	2
	Change from baseline: Cycle 23	13	-0.2	0.5	-1	1
	Change from baseline: Cycle 24	11	-0.1	0.4	-1	1
	Change from baseline: Cycle 25	10	-0.1	0.5	-1	1
	Change from baseline: Cycle 26	10	-0.1	0.3	-1	0
	Change from baseline: Cycle 27	10	-0.1	0.2	0	0
	Change from baseline: Cycle 28	9	-0.2	0.4	-1	1
	Change from baseline: Cycle 29	9	0.1	0.6	-1	1
	Change from baseline: Cycle 30	7	-0.3	0.6	-1	1
	Change from baseline: Cycle 31	6	-0.2	0.2	-1	0
	Change from baseline: Cycle 32	5	-0.2	0.2	-1	0
	Change from baseline: Cycle 33	5	-0.3	0.4	-1	0
	Change from baseline: Cycle 34	4	-0.2	0.5	-1	1
	Change from baseline: Cycle 35	1	-1.0	-	-1	-1
	Change from baseline: Cycle 36	1	-0.5	-	-1	-1

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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Table 14.4.5 Vital Sign
(Safety Population)

Variable=Temperature (^{o}C)

Treatment Group	CRF Cycle Number	N	Mean	SD	Min	Max
Sorafenib	Change from baseline: Cycle 37	1	-0.5	-	-1	-1
	Change from baseline: Cycle 38	1	-0.5	-	-1	-1
	Change from baseline: Cycle 39	1	-0.5	-	-1	-1
	Change from baseline: End of treatment	98	-0.2	0.6	-2	2

Note: Baseline is the last measurement prior to start of study treatment. Vital signs during treatment period are measured within 48 hours of cycle start.
The last measurement during treatment period is used as the end of treatment measurement when it is not available.

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14.5 Safety narratives: deaths, serious adverse events, and other significant adverse events

Study SOLTI 0701
Center 16-320
Subject 16-320-1004
65-year-old woman

SAE(s): Fever (related)

The patient was first diagnosed with stage IV breast cancer on 21-OCT-2004. She was diagnosed with metastatic breast cancer to the bone, liver, lymph nodes, and pleural effusion also on 21-OCT-2004.

No concomitant medications or medical history was reported. On 11-DEC-2007, the patient began therapy with sorafenib/placebo tablets 400 mg BID by mouth for metastatic breast cancer. On that same day she began therapy with capecitabine 1000 mg/m^2 or 3100 mg BID by mouth.

On 24-DEC-2007, while hospitalized to perform day 14 PK, a hematology report showed the patient to have leucopenia and neutropenia (not considered serious); neutrophils were 1.28 G/L (normal reference range 2.00 - 7.50). While hospitalized, the patient also experienced the event of FEVER (CTC GRADE 1) of 38.5ºC and general state deterioration, not considered a serious adverse event. The investigator decided to keep the patient hospitalized, and a follow-up hematology test was scheduled for 25-DEC-2007. Treatment rendered in response to the events was not provided. Capecitabine therapy was interrupted on 25-DEC-2007 and sorafenib/placebo therapy was interrupted on 26-DEC-2007 in response to the event, which resolved on 27-DEC-2007. Treatment with both study drugs was restarted on 03-JAN-2008.

The investigator considered the fever to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 16-320
Subject 16-320-1009
62-year-old woman

SAE(s): Cholestasis, Cytolisis, Icterus (unrelated)

The patient was diagnosed with breast cancer on 13-NOV-1997. In APR-2003, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, liver, lung, and adrenal gland. Primary therapy for non-metastatic disease included surgery, radiotherapy, and endocrine therapy. Prior metastatic treatment included radiotherapy, endocrine therapy, and 3 regimens of chemotherapy including anthracyclines (total dose of 50 mg/m^2). The final dose of the most recent metastatic treatment was administered on 31-OCT-2007.The final dose of the most recent radiotherapy was administered on 05-MAY-2003.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID PO and capecitabine 2000 mg/m^2 (3300 mg) PO on 23-JAN-2008. She discontinued treatment because of progressive disease on 11-JUN-2008, with the last dose of sorafenib/placebo having been administered on 11-JUN-2008 and the last dose of capecitabine having been administered on 04-JUN-2008.

On 18-JUN-2008, the patient was hospitalized for CYTOLISIS (CTC GRADE 3), CHOLESTASIS (CTC GRADE 3), and ICTERUS (CTC GRADE 2) resulting from dilatation of the biliary canals. The patient received surgery for biliary derivation on that same day. No action was taken with study drugs, as they had already been discontinued. Laboratory results on 20-JUN-2008 showed bilirubin at 76.2 µmol/L (normal lower limit of 17.1 µmol/L), SGOT at 259 UI (normal lower limit of 31 UI), and SGPT at 260 UI (normal lower limit of 34 UI). These levels improved by 23-JUN-2008 to bilirubin at 17.9 µmol/L, SGOT at 117 UI, and SGPT at 128 UI. During hospitalization, the patient received Perfalgan for pain and Exacyl for bleeding. The events of cytolisis and cholestasis were improved and the event of icterus resolved on 24-JUN-2008.

The investigator considered the events of cytolisis, cholestasis, and icterus to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease (hepatic progression) as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 16-320
Subject 16-320-1010
70-year-old woman

SAE(s): Cardiac arrest (related)

On 08-OCT-1999, the patient was diagnosed with stage II lobular invasive breast cancer. On 15-DEC-2006, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and liver. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, anthracyclines, and endocrine therapy. Primary metastatic therapy included endocrine therapy. The final dose of the most recent metastatic treatment was administered on 31-JAN-2008. The date of the final dose of the most recent radiotherapy was not reported.

No past medical history or concomitant medications were reported. The site confirmed that the patient did not have a cardiac history. On 05-FEB-2008, the patient began therapy with sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth for a total daily dose of 3300 mg.

On 15-FEB-2008, the patient was found by her doctor at home to be in a stable hemodynamic condition, she did not have a fever but was found to have mucositis and hand and foot syndrome since 06-FEB-2008. She also was found to have candidiasis that was being treated with Dactarin (dosage unknown). On an unknown date she had hematological labs performed which were considered normal. However, a chemistry lab report showed an increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), 2N and an increase in gamma-glutamyl transpeptidase (GGT) from 76 to 188. Action taken with sorafenib/placebo and capecitabine in response to the mucositis and hand and foot syndrome was drug interrupted. On 17-FEB-2008, the patient presented with a worsening general condition, anorexia and intravenous hydration was started, the patient was never hospitalized. On 18-FEB-2008, while in the presence of her private physician, the patient experienced a CARDIAC ARREST (CTC GRADE 5) and died at home. Action taken with sorafenib/placebo and capecitabine in response to the event of cardiac arrest was reported as none, the last dose of each having been administered on 15-FEB-2008.

On 21-FEB-2008, the patient was unblinded to PLACEBO.

According to the investigator, the event of cardiac arrest was RELATED to both study drugs.

Study SOLTI 0701
Center 16-320
Subject 16-320-1011
41-year-old woman

SAE(s): General status alteration, Pleural effusion (unrelated)

The patient was diagnosed with stage III lobular invasive breast cancer on 04-NOV-2004. On 01-OCT-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, lung, and pleural effusion (confirmed by cytology). Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant and neo-adjuvant chemotherapy, endocrine therapy, and anthracyclines (total dose of 600 mg/m^2). Her last dose of radiotherapy was administered on 25-MAY-2005. Prior metastatic treatment included chemotherapy and 1 regimen of taxane therapy on 27-DEC-2007.

No past medical history or concomitant medications were reported. On 07-FEB-2008, the patient began receiving therapy with sorafenib/placebo 400 mg BID by mouth. From 07-FEB-2008 to 11-APR-2008, she received therapy with capecitabine 1000 mg/m^2 (1650 mg) BID, for a total daily dose of 3300 mg by mouth. Dosage of capecitabine was reduced to 750 mg/m^2 (1267 mg) BID by mouth on 17-APR-2008.

On 10-JUN-2008, the patient was hospitalized for PLEURAL EFFUSION (CTC GRADE 3) with aggravated dyspnea. Treatment for the event included a right pleural evacuation puncture performed that same day; 800 cubic centimeters (cc) of liquid was removed. The event resolved on 10-JUN-2008. While no action was taken with study drugs in response to the event, sorafenib/placebo and capecitabine therapies were discontinued because of the non-serious dyspnea, with the last dose of sorafenib/placebo having been administered on 18-JUN-2008 and the last dose of capecitabine having been administered on 11-JUN-2008.

On 04-JUL-2008, the patient began experiencing GENERAL STATUS ALTERATION (CTC GRADE 5). Talc powder was introduced on 17-JUL-2008 to treat the patient's increased dyspnea. The patient's respiratory status worsened, and on 30-JUL-2008, the patient died from the general status alteration.

The investigator considered the events of pleural effusion and general status alteration to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 16-320
Subject 16-320-1012
52-year-old woman

SAE(s): Cognitive disturbance (unrelated)

In JAN-1996, the patient was diagnosed with stage II breast cancer. On 18-AUG-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, chest wall, and lung.

The patient has a history of pain, insomnia and asthenia. No history of depression or confusion was reported. The following concomitant medications were reported: Lexomil for the indication of insomnia, Lyrica, Oxycontin, and OxyNorm for the indication of pain. Start dates, dosages, and status of these medications were not reported. On 20-FEB-2008, the patient began therapy with sorafenib/placebo 400 mg BID by mouth and on 21-FEB-2008, she began therapy with capecitabine 2000 mg/m^2 (3650 mg) daily by mouth.

On 27-FEB-2008 at 15:00, the patient was hospitalized for confusion and a fall at home that morning; she also experienced the event of COGNITIVE DISTURBANCE (CTC GRADE 2). The patient was dehydrated without fever, nausea, and loss of appetite. Study drug treatment was stopped upon admission to the hospital. The patient refused intravenous hydration and laboratory tests. A magnetic resonance image of the brain done on 27-FEB-2008 showed no sign of secondary localization and meningitis. A computed tomography performed while the patient was hospitalized showed no cerebral metastasis. Treatment for the event included Haldol 20 drops at 19:30 and 21:00 on 27-FEB-2008 without effect. The patient was discharged on 28-FEB-2008 on Lexomil, the event having resolved. The patient withdrew consent and will no longer participate in the study. She received her last doses of sorafenib/placebo and capecitabine on 27-FEB-2008.

The investigator considered the event to be related to both study medications.

On 03-MAR-2008, the patient was unblinded to SORAFENIB.

On 20-JUN-2008, the investigator reassessed the relationship of sorafenib/placebo and capecitabine to the event of cognitive disturbance as UNRELATED, and provided the alternative explanation of concomitant drug, stating that the patient experienced dizziness and fall that could be explained by the toxicities of Lexomil, Lyrica, and recently prescribed morphinics.

Study SOLTI 0701
Center 16-320
Subject 16-320-1014
51-year-old woman

SAE(s): General status alteration (unrelated)

On 19-JUN-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, liver, lung, and pleural effusion. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy including anthracyclines (total dose of 300 mg/m^2), and endocrine therapy. Prior metastatic treatment included 1 regimen of chemotherapy including taxanes and anthracyclines (total dose of 450 mg/m^2) and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 22-FEB-2008.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 28-FEB-2008. On 25-NOV-2008, the patient discontinued treatment because of progressive disease. Her last dose of sorafenib/placebo was administered on 25-NOV-2008, and her last dose of capecitabine was administered on 18-NOV-2008.

The patient was hospitalized on 15-DEC-2008 for GENERAL STATUS ALTERATION (CTC GRADE 3) with symptoms of significant asthenia, leg pain, increase of diplopia, and stability disorders. A clinical exam revealed the existence of a urinary globule with abdominal pain, inferior right limb deficit, and hypoesthesia of inferior limbs. For pain, the patient received oral Propofan 400 mg from 15-DEC-2008 to 16-DEC-2008, oral Skenan 60 mg from 15-DEC-2008 to 19-DEC-2008, intravenous Perfalgan 3 g and oral Solu-Medrol 120 mg from 16-DEC-2008 to 19-DEC-2008, and oral Actiskenan 10 mg on 19-DEC-2008. No action was taken with study drugs, as they had already been discontinued. The patient was discharged on 19-DEC-2008, the event having resolved.

The investigator considered the event of general status alteration to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 16-320
Subject 16-320-1015
43-year-old woman

SAE(s): Pulmonary embolism, Cytolysis (related); Lumobo sacral pain, Meningeal carcinomatosis, Heparin-induced thrombocytopenia (unrelated)

The patient was diagnosed with stage I infiltrating ductal breast cancer on 12-JUL-2001. In SEP-2006, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, liver, lung, and lymph nodes. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, taxanes, anthracyclines (total dose of 600 mg/m^2), and endocrine therapy. Prior metastatic treatment included chemotherapy and 1 regimen of anthracyclines (total dose of 400 mg/m^2). The date of the final dose of the most recent metastatic treatment was not reported. Her last dose of radiotherapy was administered on 01-MAR-2002.

No past medical history was reported. Concomitant medications included Solumedrol, morphine, Topalgic, and myolastan. The patient began receiving therapy with sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1300 mg) BID by mouth on 03-APR-2008.

On 05-JUL-2008, the patient was hospitalized for LUMBO SACRAL PAIN (CTC GRADE 2) because of an "awkward move." No action was taken with study drugs as the patient was not hospitalized at the study site. X-rays showed no fracture, no pleural effusion, and no compression of the vertebrae, but chest X-ray did show moderate interstitial syndrome. The patient received oral Efferalgan (codeine, paracetamol) and oral Myolastan (tretazepam) 50 mg for pain, and she was discharged on 09-JUL-2008, the event having resolved. She remained on Myolastan after discharge.

The investigator considered the event of lumbo sacral pain to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

On 16-JUL-2008, the patient was hospitalized for PULMONARY EMBOLISM (CTC GRADE 5) and CYTOLYSIS (CTC GRADE 3). Blood gas test showed a pulmonary embolism, but an angioscan was negative. SGPT was 79 IU/L (normal 0 - 34) and SGOT was 417 IU/L (normal 0 - 31). Sorafenib/placebo and capecitabine were discontinued as a result of both events, with the last dose of sorafenib/placebo having been administered on 15-JUL-2008 and the last dose of capecitabine having been administered on 09-JUL-2008. The patient also experienced non-serious pain and dyspnea from 17-JUL-2008. She received intravenous heparin 250 mg daily to treat pulmonary embolism.

On 18-JUL-2008, the patient was unblinded; she had received PLACEBO.

On 22-JUL-2008, in response to headache and vomiting, a cerebral MRI was performed, which revealed MENINGEAL CARCINOMATOSIS (CTC GRADE 5). Study drugs were discontinued in response to the event.

On 23-JUL-2008, the patient experienced HEPARIN-INDUCED THROMBOCYTOPENIA (CTC GRADE 3) while hospitalized. Laboratory results showed platelets at 49 x 10^9/L (normal 150 x 10^9/L - 400 x 10^9/L).

No action was taken with study medications, as they had already been discontinued, but heparin treatment was stopped on 23-JUL-2008. She received intravenous Refludan 75 mg daily from 24-JUL-2008 to 26-JUL-2008 to treat the thrombocytopenia. On 27-JUL-2008, the patient experienced dyspnea, and her status was worsened. Platelet count on 28-JUL-2008 had fallen to 31 x 10^9/L. SGPT was 40 IU/L and SGOT was 423 IU/L. On 29-JUL-2008, the patient died; the outcomes of the meningeal carcinomatosis and pulmonary embolism were reported as death. The outcomes of the heparin-induced thrombocytopenia and cytolysis were reported as unchanged at the time of death.

The investigator considered the events of pulmonary embolism and cytolysis to be RELATED to sorafenib/placebo and UNRELATED to capecitabine. The investigator considered the event of meningeal carcinomatosis to be UNRELATED to sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation. The investigator considered the event of heparin-induced thrombocytopenia to be UNRELATED to sorafenib/placebo and capecitabine, citing intercurrent disease (heparin allergy) as an alternative explanation.

Study SOLTI 0701
Center 16-320
Subject 16-320-1017
72-year-old woman

SAE(s): Syncope vasovagal (unrelated)

The patient was diagnosed with breast cancer on 25-SEP-1985. On 26-APR-1994, she was diagnosed with stage IV metastatic breast cancer with metastases to the lung and lymph nodes. Primary therapy for non-metastatic disease included surgery, radiotherapy, chemotherapy, and endocrine therapy. Prior metastatic treatment included chemotherapy including anthracyclines (total dose of 400 mg/m^2) and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 13-MAR-2008. The final dose of the most recent radiotherapy was administered on 23-AUG-1994.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 10-APR-2008. On 15-OCT-2008, the patient discontinued from the study because of progressive disease. Her last dose of sorafenib/placebo was administered on 15-OCT-2008, and her last dose of capecitabine was administered on 08-OCT-2008.

On 12-NOV-2008, following administration of Taxol, the patient experienced SYNCOPE VASOVAGAL (CTC GRADE 3) with hot flushing, sweating, and a loss of consciousness. The episode resolved after 2 to 3 minutes, and she was hospitalized overnight for observation. Her troponin I level was 0.036 ng/mL (normal 0 - 0.034). No action was taken with study drugs, as they had already been discontinued. The event resolved on 13-NOV-2008.

The investigator considered the event of vasovagal episode to be UNRELATED to both sorafenib/placebo and capecitabine, citing loss of consciousness after Taxol injection as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 16-320
Subject 16-320-1020
72-year-old woman

SAE(s): Lumbar punction (unrelated)

On 01-OCT-2002, the patient was diagnosed with stage II infiltrating ductal breast cancer. On 05-JUL-2005, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and liver. Primary therapy for non-metastatic disease included surgery, radiotherapy and endocrine therapy. Primary metastatic therapy included one regimen of chemotherapy, anthracyclines (total dose 150 mg/m^2) and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 09-JUN-2008. The date of the final dose of the most recent radiotherapy was administered on 12-FEB-2003.

No past medical history or concomitant medications were reported. On 10-JUL-2008, the patient began therapy with sorafenib/placebo 400 mg BID orally. The patient also began therapy with capecitabine 1000 mg/m^2 (1450 mg) BID orally. On 18-SEP-2008, dosage of capecitabine was reduced to 750 mg/m^2 (1000 mg) BID in response to an adverse event. On 20-JAN-2009, a brain scan detected possible carcinomatous meningitis, and the patient discontinued treatment; her last dose of sorafenib/placebo was administered on 20-JAN-2009 and her last dose of capecitabine was administered on 13-JAN-2009.

On 05-FEB-2009, the patient was hospitalized to perform a LUMBAR PUNCTION (CTC GRADE 1) to confirm the diagnosis of carcinomatous meningitis. Cerebrospinal fluid analysis revealed "hyperproteinorachy" of 1.6 g/dL with a "normoglycorachy." The patient was not treated, and she was discharged on 06-FEB-2009, the event having resolved. She was scheduled to return for another lumbar punction. No action was taken with study drugs, as they had already been discontinued.

The investigator considered the event of lumbar punction to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 16-321
Subject 16-321-1001
58-year-old woman

SAE(s): Intestinal occlusion syndrome (unrelated)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 12-JUL-2000. On 30-JUN-2005, she was diagnosed with stage IV metastatic breast cancer with metastases to the bowel. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, endocrine therapy, and anthracyclines (total dose of 876 mg/m^2). Prior metastatic treatment included surgery and 1 regimen of chemotherapy (taxane and anthracycline 150 mg/m^2). The final dose of the most recent metastatic treatment was administered on 20-DEC-2005. The final dose of the most recent radiotherapy was administered on 19-APR-2001.

The patient's past medical history included occlusive syndrome from 01-JUL-2005 to 31-JUL-2005. No concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg twice a day orally and capecitabine 1000 mg/m^2 (1450 mg) twice a day orally on 04-FEB-2008.

On 22-MAR-2008, the patient was hospitalized for INTESTINAL OCCLUSION SYNDROME (CTC GRADE 3). Sorafenib/placebo therapy was discontinued because of progressive disease; no action was taken with capecitabine as the last dose had been administered on 21-MAR-2008. No action was taken with sorafenib/placebo as a result of this event. The patient was treated with Mopral (omeprazole) 20 mg orally and Spasfon (phloroglucinol) 24 mL intravenously from 22-MAR-2008 to 31-MAR-2008 for digestive pain. On 31-MAR-2008, a colonoscopy showed congestive colon and rigidity. The event of intestinal occlusion syndrome improved on 04-APR-2008.

The investigator considered the event of intestinal occlusion syndrome to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease of bowel metastases as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 16-322
Subject 16-322-1001
46-year-old woman

SAE(s): Hand and foot skin syndrome, Pruritus, Rash (related); Pleural effusion (unrelated)

On 05-NOV-1999, the patient was diagnosed with stage II breast cancer. Prior treatment for the non-metastatic disease was surgery, radiotherapy and chemotherapy with anthracyclines 800 mg (dates of therapy unknown). On 14-MAY-2002, she was diagnosed with metastatic breast cancer with metastases to the lymph nodes. Prior metastatic treatment consisted of surgery, radiotherapy and chemotherapy with anthracyclines; she received 1 regimen and the cumulative dose was 100 mg/m^2. She also received endocrine therapy; the final dose was received on 03-OCT-2007. The final dose of radiotherapy was 17-FEB-2003.

No concomitant medications or past medical history were reported. On 26-OCT-2007, the patient began treatment with sorafenib/placebo at 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth for the indication of metastatic breast cancer.

On 29-OCT-2007, the patient experienced non-serious hand and foot syndrome (CTC Grade 2), and on 04-NOV-2007, she experienced non-serious pruritus (CTC Grade 2) and rash (CTC Grade 2). On 06-NOV-2007, the patient experienced the important medical events of HAND AND FOOT SKIN SYNDROME (CTC GRADE 3), PRURITUS (CTC GRADE 3), and RASH (CTC GRADE 3), now considered serious due to persistent disability. Action taken with sorafenib/placebo and capecitabine in response to the events was reported as discontinued on 06-NOV-2007; the patient did not restart study drug therapy. The events improved to grade 2 non-serious adverse events on 27-NOV-2007.

The investigator considered hand and foot skin syndrome, pruritus, and rash related to both sorafenib/placebo and capecitabine treatment.

On 06-DEC-2007, the patient experienced PLEURAL EFFUSION (CTC GRADE 3). On 07-DEC-2007, a pleural punction was done, and the patient was started on treatment with intravenous Augmentin 3 g and Rovamycine 9 M UI for fever until 14-DEC-2007. On 17-DEC-2007, a pleural symphysis was done, and the event resolved that same day. No action was taken with sorafenib/placebo and capecitabine.

The investigator considered the event of pleural effusion to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 16-323
Subject 16-323-1001
63-year-old woman

SAE(s): Pleural effusion (unrelated)

On 06-JUL-1989, the patient was diagnosed with lobular invasive breast cancer. On 02-OCT-2007, the patient was diagnosed with stage IV metastatic breast cancer with metastastes to the bone, liver, and pleural effusion (cytology confirmed). Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant and neo-adjuvant chemotherapy including anthracyclines (total dose 640 mg/m^2), and endocrine therapy. Prior metastatic treatment included surgery, radiotherapy, chemotherapy, 1 regimen of taxane therapy, and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 13-OCT-2008. The final dose of the most recent radiotherapy was administered on 09-JAN-2008.

No past medical history or concomitant medications were reported. On 15-OCT-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth. On 09-JAN-2009, dosage of capecitabine was reduced to 750 mg/m^2 (1150 mg) BID in response to hand and foot syndrome.

On 20-FEB-2009, the patient was hospitalized for PLEURAL EFFUSION (CTC GRADE 2) with accompanying dyspnea. No action was taken with study drugs in response to the event, but study drugs were discontinued after a pleural punction on 23-FEB-2009 revealed malignant cells, signifying disease progression. The patient's last dose of sorafenib/placebo was administered on 19-FEB-2009 and her last dose of capecitabine was administered on 13-FEB-2009. The event of pleural effusion resolved on 23-FEB-2009.

The investigator considered the event of pleural effusion to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 24-300
Subject 24-300-1011
41-year-old woman

SAE(s): Thrombocytopenia (related); Mucositis, Septic Shock, Dyspnea, Neutropenia, Hypotension, Hyponatremia, Hypokalemia, Thrombocytopenia (unrelated)

On 05-JUL-2006, the patient was diagnosed with stage III infiltrating ductal breast cancer. On 23-JUL-2008, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the bone. Prior non-metastatic treatment included surgery, radiotherapy, adjuvant chemotherapy, anthracyclines (240 mg/m^2) and endocrine therapy. Primary therapy for metastatic disease included radiotherapy. The date of the final dose of the most recent radiotherapy was 27-AUG-2008.

No past medical history nor concomitant medications were reported. On 18-SEP-2008 the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg).

On 22-SEP-2008, the patient developed non-serious, grade 2 mucositis for which study drugs were interrupted. On 28-SEP-2008, the event worsened to MUCOSITIS (CTC GRADE 4), now considered an important medical event. The patient was hospitalized on 29-SEP-2008 with a diagnosis of SEPTIC SHOCK (CTC GRADE 4), considered life-threatening. She also presented with DYSPNEA (CTC GRADE 4), NEUTROPENIA (CTC GRADE 4), and HYPOTENSION (CTC GRADE 3). Computed tomography of the thorax on 30-SEP-2008 revealed bilateral basal infiltrates. On 30-SEP-2008, the patient was admitted to the intensive care unit (ICU) where she then developed hemodynamic instability. Non-serious thrombocytopenia from 29-SEP-2008 worsened to THROMBOCYTOPENIA (CTC GRADE 4) and improved that same day. Non-serious thrombocytopenia continued. Both study drugs were discontinued as a result of mucositis and septic shock; the patient's last doses of sorafenib/placebo and capecitabine were administered on 22-SEP-2008. No action was taken with study drugs for thrombocytopenia and neutropenia. The patient also experienced HYPONATREMIA (CTC GRADE 4) on 30-SEP-2008 that resolved that same day. In addition, non-serious hypokalemia from 30-SEP-2008 worsened to HYPOKALEMIA (CTC GRADE 4) on 01-OCT-2008 that resolved on 02-OCT-2008. The event of hypotension resolved on 03-OCT-2008. All of these conditions were considered important medical events.

Treatment included mycostain and lidocaine for mucositis, GCSF (granulocyte colony-stimulating factor) and antibiotics for neutropenia, platelet transfusion for thrombocytopenia, oxygenotherapy and corticosteroids for dyspnea, and noradrenaline and furosemide for hypotension. Norepinephrine treatment was withdrawn on 03-OCT-2008. Treatment with oxygen was reduced to 4L/min, and the patient's oxygen saturation was 97% and arterial gas was 95 mm Hg. Radiological results and physical examination showed that the patient's condition was improving. The patient continued to experience grade 4 leukopenia and thrombocytopenia despite therapy with granulocyte colony-stimulating factor (G-CSF), packed red blood cells, and platelets. The patient's mucositis improved and she was able to tolerate oral liquids and she was continued on antibiotics and mouth washes. The event of septic shock resolved on 04-OCT-2008.

On 05-OCT-2008, the patient was discharged from the ICU and admitted to the Oncology Hospitalization Area. The patient was reported as stable and was taking tramadol for pain management. On 08-OCT-2008, the patient's condition worsened, and she was somnolent. The patient's dyspnea, initially a grade 3 event, worsened to become a grade 4 event. Treatment with tramadol was withdrawn, and the patient was given naloxone. On 09-OCT-2008, a blood gas revealed hypercaphic respiratory insufficiency (pCO2 = 75). The patient was readmitted to the ICU that day with an oxygen saturation of 96% and an FiO2 of 0.35. The patient was reported as having abundant respiratory secretions and respiratory insufficiency. At this time, non-serious leukopenia (WBC at 0.1 x 10E9/L) and non-serious thrombocytopenia (platelets at 29 x 10E9/L) were ongoing. While in the ICU, the patient was intubated and started on mechanical ventilation. Respiratory cultures revealed Stenotrophomona maltophilia; the patient was started on ceftazidine. On 10-OCT-2008, the patient was extubated, and on 12-OCT-2008, she required non-invasive mechanical ventilation and had to be re-intubated on 13-OCT-2008 because of respiratory clinical worsening. Also on 12-OCT-2008, the patient's thrombocytopenia worsened to THROMBOCYTOPENIA (CTC GRADE 4), considered serious once again. The patient was reported as stable in a serious status context. She continued treatment with G-CSF and received blood transfusions. On 15-OCT-2008, she had a fever with temperature up to 38ºC. On 17-OCT-2008, a tracheotomy was done in order to maintain mechanical ventilation. On an unknown date, antibiotic treatment was ended, the patient having shown an improvement of the signs of respiratory infection. On 28-OCT-2008, because of the persistence of pancytopenia, the patient had a bone marrow biopsy that showed aplasia with a presence of regenerative signs. Mucositis and dyspnea resolved on 01-NOV-2008.

On 02-NOV-2008, the patient experienced an acute decrease in the level of consciousness akin to a coma. Treatment with Flumacenil and Naloxone was started. Computed tomography of the CNS showed normal results. Further tests similarly revealed no malignant activity or metastases, despite the patient's clinical worsening and continuing unconsciousness. Treatment-refractory hepatomegaly and splenomegaly were detected, along with pleural effusion. Neutropenia and thrombocytopenia resolved on 17-NOV-2008 with white blood cells at 2800 (units NOS) and platelets at 124,000 (units NOS). The patient died on 20-NOV-2008. No action was taken with study drugs as a result of dyspnea, hypotension, hyponatremia, hypokalemia, and thrombocytopenia (12-OCT-2008), as they had already been discontinued. During hospitalization, the patient had also received Acyclovir, vancomycin, Amikacine, Neupogen, Tazocel, pantoprazole, Primperan, glucosaline serum, seroalbumin, potassium chloride, vitamin K, calcic gluconate, and insulin.

The first event of thrombocytopenia was considered to be RELATED to both sorafenib/placebo and capecitabine. The events of mucositis and neutropenia and the second event of thrombocytopenia were considered to be UNRELATED to sorafenib/placebo and RELATED to capecitabine. The events of septic shock, dyspnea, hypotension, hypokalemia, and hyponatremia were considered to be UNRELATED to both study drugs by the investigator, citing intercurrent disease as an alternative explanation for septic shock and dyspnea and citing "Other - Unknown cause" as an alternative explanation for hypotension, hyponatremia,and hypokalemia.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-300
Subject 24-300-1016
59-year-old woman

SAE(s): Femoral nail replacement surgery (unrelated)

On 28-FEB-2000, the patient was diagnosed with stage III infiltrating ductal breast cancer. On 23-APR-2006, the patient was diagnosed with stage IV metastatic breast cancer with metastastes to the liver, lung, and pleural effusion. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy including taxanes and anthracyclines (total dose 60 mg/m^2) , and endocrine therapy. Prior metastatic treatment included surgery, chemotherapy (no taxanes or anthracyclines), and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 07-OCT-2007. The final dose of the most recent radiotherapy was administered on 09-FEB-2002.

No past medical history or concomitant medications were reported. On 12-DEC-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth.

On 23-JAN-2009, the patient was hospitalized for FEMORAL NAIL REPLACEMENT SURGERY (CTC GRADE 3) planned for 27-JAN-2009. No action was taken with study drugs as a result of the surgery, and the patient was discharged on 27-FEB-2009, the event having resolved.

The investigator considered the event of femoral nail replacement surgery to be UNRELATED to sorafenib/placebo and capecitabine, citing concomitant disease (bone nail fracture) as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-301
Subject 24-301-1008
39-year-old woman

SAE(s): Metastasis breast cancer (unrelated)

On 20-MAR-2006, the patient was diagnosed with stage I infiltrating ductal breast cancer. On 07-MAY-2008, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the bone. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy including anthracyclines (total dose 300 mg/m^2), and endocrine therapy. Prior metastatic treatment included surgery and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 05-JUN-2008. The final dose of the most recent radiotherapy was administered on 08-NOV-2006.

No past medical history or concomitant medications were reported. On 23-JUN-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth. On 03-NOV-2008, sorafenib/placebo treatment was discontinued because of progressive disease. On 05-AUG-2008, dosage of capecitabine was reduced to 750 mg/m2 (1300 mg) BID in response to an adverse event, and on 29-DEC-2008, dosage of capecitabine was further reduced to 500 mg/m^2 (950 mg) BID in response to an adverse event.

On 27-FEB-2009, an adnexal tumor mass, a lump in tissue near the uterus, was detected, and capecitabine was held. The patient's last dose of capecitabine was administered on 22-FEB-2009. On 25-MAR-2009, the patient was hospitalized for METASTASIS BREAST CANCER (CTC GRADE 3). No action was taken with sorafenib/placebo, as it had already been discontinued. No action was taken with capecitabine, as it had already been interrupted. The patient underwent a hysterectomy, double adnexectomy, and double ooforectomy on 27-MAR-2009. Biopsy revealed bilateral ovarian metastases. The patient received iron to treat anemia. The event of metastasis breast cancer resolved on 01-APR-2009. On 15-APR-2009, the patient discontinued from the study because of progressive disease.

The investigator considered the event of metastasis breast cancer to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-302
Subject 24-302-1003
61-year-old woman

SAE(s): Brain metastases (disease progression), Hypercalcemia, Hypopotassemia, Increased ASAT transferases, Thrombocytopenia (unrelated)

On 09-SEP-2006, the patient was initially diagnosed with stage II infiltrating ductal breast cancer. She was diagnosed with stage IV metastatic breast cancer on 30-SEP-2008 with metastases to the bone, liver, and lymph nodes. She received no therapy for non-metastatic disease. Prior therapy for metastatic disease included radiotherapy and endocrine therapy. The final dose of her most recent treatment with endocrine therapy was administered on 23-JAN-2008, and the final dose of her most recent radiotherapy was administered on 14-OCT-2004.

No relevant medical history or concomitant medications were provided. The patient received sorafenib/placebo at a total daily dose of 400 mg BID by mouth for metastatic breast cancer, starting on 18-FEB-2008. The patient received her first dose of capecitabine by mouth 1000 mg/m^2 BID for a total daily dose of 3500 mg on 18-FEB-2008. The patient discontinued from treatment on 18-MAR-2008 because of progressive disease.

Also on 18-MAR-2008, the patient was hospitalized for HYPERCALCEMIA (CTC GRADE 3) and HYPOPOTASSEMIA (CTC GRADE 1). Laboratory results on that day showed calcium at 12.70 mg/dL (normal range 8.40 - 10.20) and potassium at 3.3 mEq/L (normal range 3.5 - 5.0). No action was taken with study drugs, as they had already been discontinued. Both events improved on 20-MAR-2008, and laboratory results showed calcium at 9.80 mg/dL and potassium at 2.8 mEq/L on 22-MAR-2008.

The investigator considered both events to be UNRELATED to sorafenib/placebo and capecitabine, citing an alternative explanation of disease progression to the brain.

The patient remained in the hospital following the improvement of hypercalcemia and hypopotassemia because of an increase in AST to 107 IU/L (normal range 5 - 45), reported as INCREASED ASAT TRANSFERASES (CTC GRADE 3). On 25-MAR-2008, laboratory tests showed THROMBOCYTOPENIA (CTC GRADE 3) with platelets at 70 x 10E9/L (normal range 125 - 338). On 26-MAR-2008, the patient displayed neurological symptoms; as a result, a CT scan was performed on 27-MAR-2008 and followed by an MRI on 31-MAR-2008 that confirmed a diagnosis of leptomeningeal carcinomatosis. The patient died on 04-APR-2008 of BRAIN METASTASES (DISEASE PROGRESSION) (CTC GRADE 5). The events of increased ASAT transferases and thrombocytopenia were ongoing at the time of death. No action was taken with study drugs, as they had been discontinued.

The investigator considered the events of increased ASAT transferases, thrombocytopenia, and brain metastases(disease progression) to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as the alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-302
Subject 24-302-1011
61-year-old woman

SAE(s): Fever, Maxillofacial pain (unrelated)

The patient was initially diagnosed with stage III neuroendocrine breast cancer on 09-OCT-1991. On 02-JAN-1994, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy including anthracyclines (total dose of 75 mg/m^2), and endocrine therapy. Prior therapy for metastatic disease included radiotherapy. The final dose of the most recent treatment was administered on 04-SEP-2008, and the final dose of the most recent radiotherapy was administered on 10-MAY-2002.

No relevant medical history or concomitant medications were provided. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth on 05-SEP-2008.

On 18-NOV-2008, the patient came to the emergency room with worsened FEVER (CTC GRADE 1) and MAXILLOFACIAL PAIN (CTC GRADE 3). Her temperature was 38.5°C. A mandibular CT scan was performed but provided no clinically significant results. Both sorafenib/placebo and capecitabine therapies were interrupted on 18-NOV-2008 in response to these events. Fever resolved on 19-NOV-2008, and maxillofacial pain resolved on 20-NOV-2008. The patient received clindamycin 300 mg three times daily and levofloxacin 500 mg once a day for ten days from 19-NOV-2008. Study drugs were restarted on 21-NOV-2008.

The investigator considered the events of fever and maxillofacial pain to be UNRELATED to both sorafenib/placebo and capecitabine,citing intercurrent disease as an alternative explanation for fever and underlying disease as an alternative explanation for maxillofacial pain.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-302
Subject 24-302-1014
61-year-old woman

SAE(s): Septic shock, Acute renal failure, Metabolic acidosis, Leucocytosis (unrelated)

On 07-JUN-2005, the patient was diagnosed with stage III infiltrating lobular invasive breast cancer. Primary therapy included surgery, radiotherapy, adjuvant chemotherapy including taxanes and anthracyclines (total dose of 75 mg/m^2), and endocrine therapy. The final dose of the most recent radiotherapy was on 29-DEC-2005. On 23-JUN-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the "peri-renal." Prior metastatic treatment included endocrine therapy with the final dose administered on 21-AUG-2008.

Past medical history included hypertension which was ongoing at the time of this report. Concomitant medications were reported as enalapril for hypertension and Zaldiar (37.5 mg tramadol and 325 mg paracetamol) and Myolastan (Tetrazepam) for pain control (start dates not reported). On 11-SEP-2008, the patient began therapy with sorafenib/placebo 400 mg BID orally and capecitabine 1000 mg/m^2 (1500 mg) BID orally for 14 days, with a seven-day rest period. On 05-MAR-2009, the sorafenib/placebo dose was reduced to 400 mg once daily in response to an adverse event (AE). On 08-OCT-2008, the capecitabine dose was reduced to 750 mg/m2 (1075 mg) in response to an AE. On 04-JUN-2009, the capecitabine dose was decreased again to 500 mg/m^2 in response to an AE.

On 17-JUN-2009, the patient was admitted to the hospital for SEPTIC SHOCK (CTC GRADE 5), ACUTE RENAL FAILURE (CTC GRADE 4), METABOLIC ACIDOSIS (CTC GRADE 4), and LEUCOCYTOSIS (CTC GRADE 4). The patient was also reported to be experiencing severe cervical and muscle pain and general deterioration on the date of admission. Both sorafenib/placebo and capecitabine therapies were discontinued in response to these events. She was treated with broad spectrum intravenous (IV) antibiotics, IV hydration and oxygen therapy. On 17-JUN-2009, the patient had a chest X-ray which indicated a possible infiltration on the left inferior lobe with pleural effusion. She also had a renal echography and an electrocardiogram (ECG) on 17-JUN-2009; no results were reported. On 17-JUN-2009, laboratory investigations revealed leucocytes 17.61 x 1000/uL (normal 3.40-10.10), hemoglobin 11.2 g/dL (11.5-14.7), hematocrit 35.2 % (normal 33.7-45.4), platelet count 272.9 x1000/uL (normal 125-338), neutrophil count 88.0 % (normal 40.7-74.4), creatinine 7.0 mg/dL (normal 0.5-0.9), Lactate dehydrogenase (LDH) 694 U/L (normal 240-480), glutamic-pyruvic transaminase (GPT) 328 U/L (normal 5-35), glutamic-oxaloacetic transaminase (GOT) 371 U/L (normal 5-31), procalcitonin (PCT) 1.26 mg/ml (normal 0-0.05), international normalized ratio (INR)1.36, potassium 6.5 mEq/L (normal 3.5-5.0), prothrombin60.67 % (normal 75-125) and pH 7.141 (normal 7.350-7.450). On 18-JUN-2009, laboratory investigations revealed leucocytes 21.34 x 1000/uL, hemoglobin 10.3 g/dL, hematocrit 31.8 %, platelet count 102.1 x1000/uL, neutrophil count 91.3 %, creatinine 4.5 mg/dL, LDH 619 u/L, GPT 213 u/L, GOT 328 u/L, urea 103 mg/dL (normal 20-48), lactate 11.1 mmol/L (normal 0.5-2.2), C-reactive protein 8.35 mg/dL (normal 0-0.5), procalcitonin (PCT) 1.27 mg/mL, and pH 7.292. On 18-JUN-2009, her blood pressure was 80/50 mmHg. On 18-

JUN-2009, the patient died from septic shock. Acute renal failure, metabolic acidosis, and leukocytosis were all unchanged at the time of death.

The investigator considered the events of septic shock, acute renal failure, metabolic acidosis, and leukocytosis to be UNRELATED to both sorafenib/placebo and capecitabine, citing concomitant disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 24-302
Subject 24-302-1017
65-year-old woman

SAE(s): Diarrhea, Hand-foot syndrome, Emesis (related)

On 02-JUL-1998, the patient was initially diagnosed with stage I infiltrating ductal breast cancer. She was diagnosed with stage IV metastatic breast cancer on 21-JUN-2004 with metastases to the breast and lymph nodes. Primary therapy for non-metastatic disease included surgery, radiotherapy, and adjuvant chemotherapy (no taxanes or anthracyclines). Prior therapy for metastatic disease included surgery and radiotherapy. The final dose of the most recent treatment was administered on 09-OCT-2008, and the final dose of the most recent radiotherapy was administered on 13-MAR-2008.

No relevant medical history or concomitant medications were provided. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 10-OCT-2008.

On 17-NOV-2008, the patient came to the emergency room with DIARRHEA (CTC GRADE 3), HAND-FOOT SYNDROME (CTC GRADE 3), and EMESIS (CTC GRADE 2) (start date reported as 15-NOV-2008). Study drugs were interrupted in response to emesis and discontinued in response to diarrhea and hand-foot syndrome. The patient's last dose of sorafenib/placebo was administered on 16-NOV-2008, and her last dose of capecitabine was administered on 14-NOV-2008. On 17-NOV-2008, laboratory results showed leukocytes at 7.44E3/µL (normal 3.40 - 10.10), hemoglobin at 13.4 g/dL (normal 11.5 - 14.7), and hematocrit of 38.7% (normal 33.7% - 45.4%). In addition, the patient's glucose level was 190 mg/dL (normal 60 - 110), creatinine level was 1.7 mg/dL (normal 0.5 - 0.9), and amylase level was 143 U/L (normal 28 - 100). The patient received oral ciprofloxacin 1500 mg and metronidazole 1500 mg for diarrhea from 18-NOV-2008 to 24-NOV-2008, and she was discharged on 27-NOV-2008. From 27-NOV-2008, she received oral dexamethasone 2 mg and metoclopramide 30 mg for emesis and omeprazole 40 mg for gastric protection. Laboratory results at discharge showed leukocytes at 16.20E3/µL, hemoglobin at 10.1 g/dL, and hematocrit of 29.0%. Emesis and diarrhea resolved on 27-NOV-2008. Hand-foot syndrome resolved on 02-DEC-2008.

The investigator considered the events of diarrhea, hand-foot syndrome, and emesis to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-302
Subject 24-302-1023
81-year-old woman

SAE(s): Radius fracture (unrelated)

On 10-FEB-2006 the patient was diagnosed with stage III lobular invasive breast cancer. Primary therapy included surgery, radiotherapy, adjuvant chemotherapy including taxanes and anthracyclines (total dose of 364 mg/m^2), and endocrine therapy. The final dose of the most recent radiotherapy was on 17-JAN-2007. On 02-JUN-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, chest wall, liver and lymph nodes. Prior metastatic treatment was not reported with the final dose administered on 13-NOV-2008.

No past medical history nor concomitant medications were reported. On 03-DEC-2008, the patient began therapy with sorafenib/placebo 400 mg BID orally and capecitabine 1000 mg/m^2 (1500 mg) BID orally. On 26-MAR-2009, the sorafenib/placebo dose was reduced to 400 mg once daily. On 05-MAR-2009, the capecitabine dose was reduced to 750 mg/m^2 (1075 mg) and again reduced on 04-JUN-2009 to 500 mg/m^2 (750 mg).

On 12-JUN-2009, the patient experienced an accidental fall and fractured her right radius. She was admitted to the hospital with a RADIUS FRACTURE (CTC GRADE 3) on the same date. She was splinted. On 16-JUN-2009, she underwent an operation to repair the fracture, a cast was placed, and she was discharged to home, the event having improved. No action was taken with study drugs in response to this event.

The investigator assessed the event as UNRELATED to both study medications, citing the accidental fall as an alternative explanation for the event.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-305
Subject 24-305-1001
57-year-old woman

SAE(s): Dyspnea (related)

On 20-JAN-2006, she was diagnosed with metastatic breast cancer with metastases to liver and lymph nodes. Treatment received prior to entry in the study was chemotherapy with taxanes and endocrine therapy. She received her final dose of chemotherapy on 06-SEP-2007.

No past medical history was reported. Concomitant medications included Enalapril for non-serious event of hypertension. On 09-OCT-2007, the patient began receiving sorafenib/placebo 400 mg BID orally and capecitabine 1000 mg/m^2 (1650 mg) BID orally. On 23-OCT-2007, the dosage of sorafenib/placebo was reduced to 400 mg daily in response to an adverse event. On 07-NOV-2007, the dosage of capecitabine was reduced to 750 mg/m^2 (1500 mg) BID in response to an adverse event.

The patient was hospitalized for DYSPNEA (CTC GRADE 3) on 16-NOV-2007. Radiology and physical exam showed pleural effusion. Vital signs included blood pressure of 135/85, heart rate of 93 rpm, temperature of 36.3°C, and oxygen saturation of 88%. She received morphine chloride 200 mg orally and dexamethasone 4 mg orally since 16-NOV-2007. On 19-NOV-2007, an echocardiogram (ECG) was performed, showing indirect symptoms of pulmonary hypertension. Both sorafenib/placebo and capecitabine therapies were discontinued in response to the event. The patient received her last doses of sorafenib/placebo and capecitabine on 16-NOV-2007. On 26-NOV-2007, a Swan-Ganz catheterization was performed; no pulmonary hypertension was observed. An ECG on 29-NOV-2007 also showed no pulmonary hypertension. The dyspnea resolved on 29-NOV-2007.

The investigator considered the event of dyspnea to be RELATED to sorafenib and RELATED to capecitabine.

On 29-NOV-2007, the patient was unblinded by the site and found to have received SORAFENIB.

Study SOLTI 0701
Center 24-305
Subject 24-305-1002
75-year-old woman

SAE(s): Asthenia, Mucositis, General status worsening (unrelated)

On 05-SEP-2006, the patient was initially diagnosed with stage II infiltrating ductal breast cancer. She was diagnosed with stage IV metastatic breast cancer on 01-OCT-2007 with metastatses to bone, lymph, and liver.

No relevant medical history or concomitant medications were provided. The patient began receiving sorafenib/placebo 400 mg BID orally and capecitabine 1000 mg/m^2 (1500 mg) BID orally on 17-OCT-2007.

On 26-OCT-2007, the patient telephoned the investigator because of grade 2 asthenia. The patient continued on study medication until she arrived at the emergency room on 30-OCT-2007, when she was hospitalized for ASTHENIA (CTC GRADE 3) and MUCOSITIS (CTC GRADE 3). Both sorafenib/placebo and capecitabine therapies were interrupted in response to asthenia, but no action was taken in response to mucositis. Asthenia improved on 06-NOV-2007, but the patient remained hospitalized. She had an average general state with nausea, headache, and dizziness due to morphic treatment. Morphic treatment was interrupted. Treatment for the events included Enantyum (dexketoprofen). Mucositis resolved on 08-NOV-2007.

The investigator considered the events of asthenia and mucositis to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 22-NOV-2007, the patient had an oncology visit where it was noted that she was experiencing uncontrollable pain and a general worsening status; her ECOG was 3. On 23-NOV-2007, the investigator decided to hospitalize the patient for GENERAL STATUS WORSENING (CTC GRADE 3). Both study drugs were discontinued in response to this event. The patient received her last doses of sorafenib/placebo and capecitabine on 29-OCT-2007. On 29-NOV-2007, she was discharged from the hospital, the event having resolved.

The investigator considered the event of general status worsening to be UNRELATED to both sorafenib/placebo and capecitabine, citing concomitant disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-305
Subject 24-305-1003
74-year-old woman

SAE(s): Diarrhea, Vomiting (related)

On 09-MAR-1999, the patient was diagnosed with stage III infiltrating ductal breast cancer. On 14-JAN-2007, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the bone and liver.

No relevant medical history or concomitant medications were provided. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 17-OCT-2007.

On 26-OCT-2007, the patient telephoned the investigator because of grade 2 diarrhea. The investigator decided to stop treatment for 3 days in order to improve diarrhea. On 30-OCT-2007, however, the patient arrived at the urgency room and was hospitalized for DIARRHEA (CTC GRADE 3). On 31-OCT-2007, she also experienced VOMITING (CTC GRADE 3). The patient received physiological saline. Both sorafenib/placebo and capecitabine therapies were discontinued in response to diarrhea, but no action was taken in response to vomiting. The patient received her last doses of sorafenib/placebo and capecitabine on 25-OCT-2007. Stool culture on 03-NOV-2007 showed infection by Campylobacter jejuni, and the patient received intravenous ciprofloxacin until 06-NOV-2007. Diarrhea resolved on 06-NOV-2007, but the patient remained hospitalized until 13-NOV-2007, when she was discharged asymptomatic, the vomiting also having resolved.

The investigator considered the events of diarrhea and vomiting to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-305
Subject 24-305-1004
50-year-old woman

SAE(s): Siringometaplasia escamosa ecrina (related)

On 23-OCT-1992, the patient was diagnosed with stage II infiltrating ductal breast cancer. On 27-NOV-2007, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the skin.

No past medical history or concomitant medications were reported. On 19-DEC-2007, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 BID by mouth, for a total daily dose of 3500 mg.

On 03-JAN-2008, the patient presented to the oncologist with grade 2 skin toxicity, and the dermatologist considered the non-serious event possibly related to study medication. On 06-JAN-2008, treatment with sorafenib/placebo was interrupted in response to the event, and on 08-JAN-2008, treatment with capecitabine was also interrupted in response to the event, although at the time of the event, the patient was in the resting phase of capecitabine administration.

On 10-JAN-08, the event worsened to grade 3, and the physician considered the possibility that the patient suffered from Lyell Syndrome; however, results of a skin biopsy on 10-JAN-2008 confirmed the diagnosis of ECCRINE SQUAMOUS SYRINGOMETAPLASIA (CTC GRADE 3), now considered to be an important medical event. Based on the skin biopsy results, the pathologist ruled out Lyell syndrome. Laboratory work included leukocytes 2.80 109/L (normal reference range: 4.8 to 10.8), neutrophils: 2.06 109/L (normal reference range: 1.4 to 6.5), hemoglobin: 15.9 g/dL (normal reference range: 12-16), platlelets: 108 109/L (normal reference range: 140-450). On 21-JAN-2008, the investigator considered the event of eccrine squamous syringometaplasia to no longer be serious, as the patient's condition improved to a grade 1 non-serious adverse event. The event was considered to have resolved.

The patient's dermatologist advised against the reintroduction of either sorafenib/placebo or capecitabine because of the extent of the event, and the patient decided to no longer continue sorafenib/placebo or capecitabine treatment even though the investigator wanted to reintroduce study drugs at a lower dose. Both sorafenib/placebo and capecitabine therapies were discontinued in response to the event. The patient's last doses of sorafenib/placebo and capecitabine prior to the event were administered on 06-JAN-2008 and 01-JAN-2008, respectively.

The investigator considered the event of eccrine squamous syringometaplasia to be RELATED to both sorafenib/placebo and capecitabine. According to the investigator, eccrine squamous syringometaplasia is a relatively common cutaneous toxicity reported in many cytotoxic drugs but intensely with 5-FU and the derivatives.

On 22-JAN-2008, the patient was unblinded and found to have received SORAFENIB.

Study SOLTI 0701
Center 24-305
Subject 24-305-1008
57-year-old woman

SAE(s): Ascites, Ascites, Ascites, Progressive disease (unrelated)

On 06-MAY-2002, the patient was diagnosed with stage II infiltrating lobular breast cancer. On 14-FEB-2005, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the bone, CNS (brain), and liver. Primary therapy for non-metastatic disease included surgery, adjuvant chemotherapy including anthracyclines (total dose 420 mg/m^2), and endocrine therapy. Prior metastatic treatment included radiotherapy and 1 regimen of taxanes. The final dose of the most recent metastatic treatment was administered on 18-JUN-2008. The final dose of the most recent radiotherapy was administered on 01-JUL-2008.

No past medical history or concomitant medications were reported. On 03-SEP-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth.

On 15-SEP-2008, the patient was hospitalized for ASCITES (CTC GRADE 2) with abdominal pain. Laboratory results showed normal leukocyte count, hemoglobin, creatinine, and GPT but increased GOT (34 UI/L, normal 5 - 32). An abdominal paracentesis was performed, extracting 7.5 L of ascitic fluid. Both sorafenib/placebo and capecitabine therapies were interrupted as a result of this event. From 15-SEP-2008 to 16-SEP-2008, the patient received intravenous Seguril (furosemide) 60 mg for ascites, and from 15-SEP-2008 to 20-SEP-2008, she received oral Seguril 50 mg for ascites prophylaxis. The event improved on 19-SEP-2008. Study medications were reintroduced on 25-SEP-2008, with dosage of sorafenib/placebo reduced to 400 mg once daily and dosage of capecitabine reduced to 750 mg/m^2 (1450 mg) BID. Dosage of sorafenib/placebo was re-escalated to 400 mg BID on 01-OCT-2008.

The investigator considered the event of ascites to be UNRELATED to sorafenib/placebo and capecitabine, citing concomitant disease as an alternative explanation.

On 20-OCT-2008, the patient experienced a non-serious event of grade 2 ascites. Laboratory results showed normal hemoglobin and creatinine, decreased leukocyte count (4.30 x 10^9/L, normal 4.8 - 10.8), and increased GOT (35 UI/L) and bilirubin (1.45 mg/dL, normal 0.1 - 1.1). An abdominal paracentesis was performed, extracting 6 L of ascitic fluid. The patient began receiving oral Seguril on 20-OCT-2008 for ascites. No action was taken with study drugs as a result of this event and the event “improved” on the same day.

On 13-NOV-2008, the patient was again hospitalized for ASCITES (CTC GRADE 2). Laboratory results on 10-NOV-2008 showed normal leukocyte count, hemoglobin, and creatinine but increased GGT (84 UI/L, normal 7 - 32) and bilirubin (1.45 mg/dL). On 14-NOV-2008, an abdominal paracentesis was performed, extracting 8 L of ascitic fluid. No action was taken with study drugs as a result of this event, which improved on on 15-NOV-2008.

On 24-NOV-2008, the patient was once again hospitalized for ASCITES (CTC GRADE 2). Laboratory results on 27-NOV-2008 showed normal leukocyte count, hemoglobin,

creatinine, and bilirubin (0.93 mg/dL) but increased GGT (93 UI/L). On 27-NOV-2008, an abdominal paracentesis was performed, extracting 8 L of ascitic fluid. No action was taken with study drugs as a result of this event, which improved on 28-NOV-2008.

The investigator considered these two events of ascites to be UNRELATED to sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

On 15-DEC-2008, the patient discontinued treatment because of worsening of her general status. Her last dose of sorafenib/placebo was administered on 15-DEC-2008, and her last dose of capecitabine was administered on 23-NOV-2008.

On 07-JAN-2009, the patient died of PROGRESSIVE DISEASE (CTC GRADE 5). No action was taken with study drugs, as they had already been discontinued.

The investigator considered the event of progressive disease to be UNRELATED to sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 24-307
Subject 24-307-1002
60-year-old woman

SAE(s): Acute pancreatitis (related)

On 20-MAY-2008, the patient was diagnosed with stage IV infiltrating ductal breast cancer and stage IV metastatic breast cancer with metastases to the lymph nodes. Primary therapy for metastatic disease included surgery, radiotherapy, taxanes, chemotherapy, anthracyclines, and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 20-MAY-2008. The final dose of the most recent radiotherapy was administered on 26-AUG-2005.

No past medical history or concomitant medications were reported. On 11-JUN-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth.

On 18-NOV-2008, the patient came to the emergency room with lumbo-abdominal pain. On 19-NOV-2008 laboratory data showed bilirubin at 94 µmol/L (normal 0 - 18), and a hemoccult and urine test were both normal. Computed tomography on 19-NOV-2008 showed acute pancreatitis, and on 20-NOV-2008, the patient was hospitalized for ACUTE PANCREATITIS (CTC GRADE 3). Sorafenib/placebo therapy was interrupted on 20-NOV-2008 as a result of this event; no action was immediately taken with capecitabine because she was between cycles. Bilirubin fell to 69 µmol/L on 21-NOV-2008. The patient recovered and was discharged on 25-NOV-2008, the event having resolved. Bilirubin was at 28 µmol/L on 28-NOV-2008. Sorafenib/placebo therapy was restarted on 05-DEC-2008. Dosage of capecitabine was reduced to 750 mg/m^2 (1150 mg) BID on 05-DEC-2008.

The investigator considered the event of acute pancreatitis to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 24-308
Subject 24-308-1002
59-year-old woman

SAE(s): Femur fracture (unrelated)

On 25-NOV-2005, the patient was diagnosed with stage IV infiltrating ductal breast cancer and stage IV metastatic breast cancer with metastases to the bone and chest wall. No prior non-metastatic treatment was reported. Primary therapy for metastatic disease included surgery, radiotherapy, taxane chemotherapy, and anthracyclines. The date of the final dose of most recent metastatic treatment was 12-JUN-2008.

No past medical history or concomitant medications were reported. On 19-JUN-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth. Study drug therapy for capecitabine was not reported.

On 23-SEP-2008, patient was hospitalized for a BONE FRACTURE (FEMUR) (CTC GRADE 3). No action was taken with sorafenib/placebo and capecitabine as a result of this event, which resolved on 09-OCT-2008.

The investigator considered the event of bone fracture (femur) to be UNRELATED to sorafenib/placebo and capecitabine, citing an accidental fall as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-330
Subject 50-330-1002
65-year-old woman

SAE(s): Cardiac decompensation, Left upper limb pain (unrelated)

On 12-JUN-2003, the patient was diagnosed with stage III infiltrating ductal breast cancer. She was treated with surgery, neo-adjuvant chemotherapy, and anthracyclines (total dose of 240 mg/m^2). On 11-NOV-2003, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, lung, lymph nodes, and skin. She was treated with radiotherapy (last dose on 14-MAY-2004), anthracyclines (cumulative dose of 390 mg/m^2), and endocrine therapy. On 19-FEB-2008, she received her final dose of chemotherapy and endocrine treatment for metastatic disease.

No past medical history was reported. Concurrent medical history included headache, left upper limb pain, thoracic pain and insomnia. Concomitant medications included Tramadol, omeprazole and dipirone. On 28-FEB-2008, the patient began receiving sorafenib/placebo 400 mg BID orally and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth (Days 1 through 14 of a 21-day cycle). On 22-DEC-2008, the sorafenib/placebo dose was reduced to 400 mg once a day in response to an adverse event (AE). On 06-MAY-2008, the capecitabine dose was reduced to 750 mg/m^2 in response to an AE. On 02-DEC-2008, the capecitabine dose was again reduced to 500 mg/m^2 in response to an AE.

On 09-JAN-2009, the patient developed grade 3 dyspnea and grade 2 thoracic pain, which were assessed as secondary to possible pneumonia. The patient decided to stop taking sorafenib/placebo at this time. On 10-JAN-2009, the dyspnea worsened and the patient was admitted to the hospital. On 15-JAN-2009, an echocardiogram revealed left ventricular ejection fraction at 47 percent. A chest X-ray (date not reported) indicated CARDIAC DECOMPENSATION (CTC GRADE 3). The event of pneumonia was ruled out. Treatment medications included furosemide (intravenous and oral), digoxin, ceftriaxone, midazolam, morphine, and oxygen therapy. No action was taken with sorafenib/placebo, but capecitabine therapy was interrupted in response to the event. On 16-JAN-2009, the event resolved, and the patient was discharged from the hospital.

The investigator considered the event of cardiac decompensation to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

On 13-FEB-2009, the patient developed left upper limb pain, considered non-serious until she was hospitalized for LEFT UPPER LIMB PAIN (CTC GRADE 3) on 18-FEB-2009. On 18-FEB-2009, the patient began receiving intravenous morphine 30 mg and oral gabapentin 900 mg to treat left upper limb pain. She also received ondansetron and haloperidol for nausea. No action was taken with study drugs as a result of this event. The event resolved on 22-FEB-2009, and the patient was discharged.

On 23-FEB-2009, the patient was unblinded because no causality assessment was initially reported; she received SORAFENIB.

On 25-FEB-2009, the patient discontinued treatment because of progressive disease; her last dose of sorafenib/placebo was administered on 25-FEB-2009 and her last dose of capecitabine was administered on 24-FEB-2009.

The investigator considered the event of left upper limb pain to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

Study SOLTI 0701
Center 50-330
Subject 50-330-1003
61-year-old woman

SAE(s): Multi-organ failure (unrelated)

The patient was diagnosed with stage I infiltrating ductal breast cancer on 27-APR-2000. On 20-AUG-2003, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, and endocrine therapy. Prior metastatic treatment included surgery, endocrine therapy, and 1 regimen of anthracyclines (cumulative dose of 500 mg/m^2). The final dose of the most recent metastatic treatment was administered on 11-MAR-2008. The final dose of the most recent radiotherapy was administered on 15-MAR-2004.

The patient's past medical history included cough and pain in left ribs. She had the concomitant conditions of menopause, depression, hypothyroidism, anxiety, hypercholesterolemia, diabetes, left shoulder pain, cough, and hypertension. Concomitant medications included Natrilix, Sotacor, metformina, sinvastatin, Pondera, and Pasalix. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth on 31-MAR-2008.

Since 29-JUL-2008, the patient had been experiencing non-serious left lower and upper limb grade 3 paresthesia, grade 2 diplopia, and grade 1 confusion. These non-serious events were considered to be possibly related to disease progression and all symptoms of CNS metastasis. Computed tomography of the brain on 25-AUG-2008 revealed calcifications. The patient was hospitalized on 29-AUG-2008 for evaluation. The patient received Diprospan 1 vial intravenously on 29-AUG-2008 as treatment. No action was taken with study drugs. The patient worsened, and her condition was diagnosed as MULTI-ORGAN FAILURE (CTC GRADE 5). Over 6 days beginning 02-SEP-2008, she received the following medications as treatment for disease progression: dexamethasone, phenytoin, ipratropium, fenoterol, oxygen, levofloxacin, furosemide, haloperidol, promethazine, ceftriaxone, phenoterol, hydrocortisone, clindamycin, phenobarbital, and acyclovir. Her hemoglobin level fell to 9.4 g/dL on 02-SEP-2008 and 8.4 g/dL on 04-SEP-2008 (normal 11.5-16). She received a blood transfusion. The patient died of multi-organ failure on 07-SEP-2008.

The investigator considered the event of multi-organ failure to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-330
Subject 50-330-1010
38-year-old woman

SAE(s): CNS metastasis, Multi-organ failure (unrelated)

On 31-DEC-2006, the patient was diagnosed with stage III infiltrating ductal breast cancer. On 25-MAR-2008, she was diagnosed with stage IIIb or IIIc metastatic breast cancer with metastases to the bone and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, taxanes, and anthracyclines (total dose of 380 mg/m^2). Prior metastatic treatment included 1 regimen of anthracyclines (total dose of 240 mg/m^2). The final dose of the most recent metastatic treatment was administered on 30-MAY-2008. The final dose of the most recent radiotherapy was administered on 10-AUG-2007.

No past medical history was reported. Concomitant medications included morphine, omeprazole, and ciprofloxacin. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 24-JUL-2008. On 12-APR-2008, dosage of capecitabine was reduced to 750 mg/m^2 (1000 mg) BID by mouth.

On 09-SEP-2008, the patient developed confusion, considered to be possibly related to CNS metastasis or morphine intoxication. The non-serious event, initially a grade 3 event, became a grade 4 event on 11-SEP-2008, and the patient was hospitalized on 16-SEP-2008 to diagnose. Computed tomography of the central nervous system revealed multiple nodules, representative of CNS METASTASIS (CTC GRADE 5). No action was taken with study drugs, as they had been discontinued because of progressive disease. The last dose of sorafenib/placebo had been received on 09-SEP-2008, and the last dose of capecitabine had been received on 26-AUG-2008. During hospitalization, the patient also experienced general pain, inappetence, thoracic pain, upper limb edema, lower limb edema, and cough, none of which were considered serious adverse events. Treatment medications for CNS metastasis included dexamethasone, promethazine, haloperidol, diazepan, phenytoin, and midazolam. The patient died on 06-OCT-2008. Causes of death were reported as MULTI-ORGAN FAILURE (CTC GRADE 5) and metastatic breast cancer. No action was taken with study drugs as a result of the event of multi-organ failure.

The investigator considered the events of CNS metastasis and multi-organ failure to be UNRELATED to sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation for both events.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-330
Subject 50-330-1018
55-year-old woman

SAE(s): Dyspnea, Left breast pain, Respiratory failure (unrelated)

On 27-MAY-2008 the patient was diagnosed with stage IV metastatic infiltrating ductal breast cancer with metastasis to the lung. She received 2 regimens of taxanes and anthracyclines (cumulative dose of 200 mg/m²). Her last dose of treatment was on 11-NOV-2008.

No past medical history was reported. Concomitant medications included omeprazole for gastric prophylaxis.

On 09-DEC-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m² (1650 mg) BID by mouth (Days 1 through 14 of 21-day cycle).

On 06-JAN-2009, the patient began experiencing non-serious, grade 3 breast pain, considered to be related to breast cancer. On 10-JAN-2009, she began experiencing non-serious, grade 3 dyspnea, considered to be possibly related to morphine administration for breast pain. On 12-JAN-2009, the patient was hospitalized for DYSPNEA (CTC GRADE 3) and LEFT BREAST PAIN (CTC GRADE 3), now considered serious. Treatment medications included tramadol (IV and oral), dipyrone, hydrocortisone, fenoterol and ipratropium inhalers, ondansetron, lorazepam, oxygen, and IV hydration. On 13-JAN-2009, both events improved to grade 2. On 15-JAN-2009, the patient was discharged.

On 16-JAN-2009, the events of dyspnea and breast pain worsened to grade 3 and the patient was again hospitalized. Treatment medications included tramadol (IV), dipyrone, morphine, hydrocortisone, midazolam, promethazine, haloperidol, insulin, glycerine solution, oxygen and IV hydration. On 19-JAN-2009, the subject became anemic (hemoglobin of 7.4 mg/dL) and was transfused with red blood cells. Her clinical condition deteriorated and the dyspnea worsened. On 23-JAN-2009, the patient died from RESPIRATORY FAILURE (CTC GRADE 5).

The investigator considered the events of dyspnea, left breast pain, and respiratory failure to be UNRELATED to sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-331
Subject 50-331-1006
50-year-old woman

SAE(s): Pleural effusion (unrelated)

The patient was diagnosed with stage III infiltrating ductal breast cancer in MAY-2006. On 27-SEP-2006, she was diagnosed with stage IIIb or IIIc metastatic breast cancer with metastases to the bone and liver. Primary therapy for non-metastatic disease included surgery, adjuvant chemotherapy, and taxanes. Prior metastatic treatment included surgery and 3 regimens of chemotherapy including taxanes. The final dose of the most recent metastatic treatment was administered on 29-OCT-2007.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID PO and capecitabine 1000 mg/m^2 (3200 mg) daily by mouth on 27-FEB-2008. Sorafenib/placebo and capecitabine were discontinued on 02-APR-2008 and 15-MAR-2008, respectively, because of hematological toxicity.

On 29-APR-2008, the patient presented in the outpatient setting with severe dyspnea, dehydration, and somnolence. Oxygen saturation of hemoglobin was 93%. The patient was referred to the emergency care unit, where she presented with confusion, mood alteration (agitation), and disorientation. Oxygen saturation of hemoglobin was now 78%. Laboratory tests on 29-APR-2008 showed a red blood cell count of 3.26 x 10^3/mm3 (normal 4.0 - 5.4), hemoglobin at 8.2 g/dL (normal 12 - 16), total bilirubin at 3.53 mg/dL (normal 0.2 - 1.0), and AST at 394 U/L (upper limit of 31). The patient was diagnosed with PLEURAL EFFUSION (CTC GRADE 4 on admission). She received non-invasive respiratory ventilation (continuous positive airway pressure [CPAP]), morphine 2 mg Q8H IV, dypirone PRN, metoclopramide PRN, and IV solution containing 5% glucose solution (1000 mL), NaCl 10% (40 mL), KCl 19.6% (10 mL) Q12H. No action was taken with study drugs, as they had already been discontinued. Laboratory data on 30-APR-2008 showed serum glutamic pyruvic transaminase at 134 U/L (upper limit of 31). On 30-APR-2008, the patient was referred to an intensive care unit. On 03-MAY-2008, the patient died, and the severity of the event was upgraded to grade 5.

The investigator considered the event of pleural effusion to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-331
Subject 50-331-1013
47-year-old woman

SAE(s): Hepatic obstruction syndrome, Sepsis, Pneumonia (unrelated)

The patient was diagnosed with stage III ductal invasive breast cancer on 07-DEC-2006. On 19-MAY-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the liver and lung. Primary therapy included surgery, radiotherapy, neo-adjuvant chemotherapy, taxanes, and anthracyclines (total dose of 240 mg/m^2). Prior metastatic treatment included 1 regimen of chemotherapy (no taxanes or anthracyclines). The final dose of the most recent metastatic treatment was administered on 03-SEP-2008. The final dose of the most recent radiotherapy was administered on 16-MAR-2008.

No past medical history or concomitant medications were reported. On 24-SEP-2008, the patient began therapy with sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth. Dosage of sorafenib/placebo was reduced to 400 mg once daily on 25-NOV-2008 because of an adverse event. Dosage of capecitabine was reduced to 750 mg/m^2 (1300 mg) BID on 05-NOV-2008 because of hand and foot syndrome and reduced to 500 mg/m2 (950 mg) BID on 16-DEC-2008 because of an adverse event.

On 06-FEB-2009, the patient presented with jaundice and hyperbilirubinemia (total bilirubin of 14.19 mg/dL). Computed tomography revealed life-threatening HEPATIC OBSTRUCTION SYNDROME (CTC GRADE 4) caused by liver metastases. The patient discontinued treatment because of progressive disease; her last doses of each study drug were received on 06-FEB-2009. The patient was hospitalized for several weeks. On 03-MAR-2009, the patient underwent a biliary drainage. On 04-MAR-2009, the patient had a fever, the first symptom of SEPSIS (CTC GRADE 5). On 06-MAR-2009, she also began experiencing PNEUMONIA (CTC GRADE 5). Both sepsis and pneumonia led to the patient's death on 07-MAR-2009.

The investigator considered the events of hepatic obstruction syndrome, sepsis, and pneumonia to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation for hepatic obstruction syndrome and intercurrent disease as an alternative explanation for sepsis and pneumonia.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-331
Subject 50-331-1014
47-year-old woman

SAE(s): Hand and foot syndrome (related)

The patient was diagnosed with stage III ductal invasive breast cancer on 29-JAN-2007. On 01-JUN-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and ovary. Primary therapy included surgery, radiotherapy, neo-adjuvant chemotherapy, taxanes, anthracyclines (total dose of 240 mg/m^2), and endocrine therapy. Prior metastatic treatment included surgery. The final dose of the most recent radiotherapy was administered on 29-FEB-2008.

No past medical history or concomitant medications were reported. On 26-SEP-2008, the patient began therapy with sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth.

On 04-NOV-2008, the patient began experiencing HAND AND FOOT SYNDROME (CTC GRADE 3), considered serious because of persistent or significant disability. The patient reported severe desquamation, erythema, dysesthesia (usually with a tingling sensation), and burning pain in the palms of her hands and soles of her feet that interfered with function. She was not able to perform daily activities because of the pain and loss of an epidermal layer. Both sorafenib/placebo and capecitabine therapies were interrupted on 06-NOV-2008 as a result of this event, which improved on 08-NOV-2008. The event improved further to a grade 1 event on 15-NOV-2008; the patient presented with only erythema and moderate desquamation without pain on 18-NOV-2008. Study drugs were reintroduced on 18-NOV-2008. Capecitabine dosage was reduced to 750 mg/m^2 (1650 mg) BID, and sorafenib/placebo was continued at the same dosage.

The investigator considered the event of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-332
Subject 50-332-1002
55-year-old woman

SAE(s): Hand and foot syndrome, Oral mucositis (related); Diarrhea, Neutropenia (unrelated)

On 06-DEC-2000, the patient was diagnosed with stage II breast cancer. On 13-NOV-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, liver, and lung.

No past medical history or concomitant medications were reported. On 24-JAN-2008, the patient began therapy with sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth.

On 30-JAN-2008, after about a week on therapy she presented with grade 1 hand foot syndrome, considered a non-serious adverse event. On 04-FEB-2008, the patient began experiencing an important medical event of DIARRHEA (CTC GRADE 3) with over 10 episodes per day. On 05-FEB-2008, the patient was advised to discontinue capecitabine and begin using Imosec. She was instructed by the site to go to the hospital, where she received intravenous (IV) hydration. On the same day, the hand and foot syndrome worsened to an important medical event of HAND AND FOOT SYNDROME (CTC GRADE 3) with hand desquamation, paronychia observed in all nails as well as nail detachment from the nail bed, and inability to open the hand. In addition, the patient had lesions on her feet with internal pus, and she could not walk. The patient did not report this condition to the site until her visit on 09-FEB-2008. On 05-FEB-2008, the patient also experienced an important medical event of ORAL MUCOSITIS (CTC GRADE 3). On 06-FEB-2009 and 07-FEB-2008, the diarrhea continued, and the patient visited the emergency room on each day to receive additional IV hydration. On 07-FEB-2008, she reported an improvement of the diarrhea, with six episodes per day; the event was considered a grade 2.

On 09-FEB-2008, the patient had a site visit, and she was hospitalized for diarrhea, hand and foot syndrome, oral mucositis, and NEUTROPENIA (CTC GRADE 2). That same day, laboratory tests showed leukocytes at 2.300/mm3 (normal range 3.500 - 10.000) and neutrophils at 1.380/mm^3 (normal range 1.755 - 8.800). Treatment for diarrhea included oral Imosec (loperamide) (unknown dosage from 04-FEB-2008 to 06-FEB-2008 and 6 mg QD from 09-FEB-2008 to 10-FEB-2008) and intravenous saline solution (unknown dosage from 05-FEB-2008 to 06-FEB-2008 and 2000 mL from 09-FEB-2008 to 11-FEB-2008). Treatment for hand and foot syndrome included Rocefin (ceftriaxone) 2 g IV from 09-FEB-2008 to 10-FEB-2008, Diflucan (flucanazole) 200 mg IV from 09-FEB-2008 to 10-FEB-2008, and Dersani 45 mL topically on 10-FEB-2008. Treatment for oral mucositis included B complex 15 mL PO, Nistatin (mycostatin) 15 mL PO, Xylocaine(lidocaine) 3 mL PO, bicarbonate 3 mL PO, and camomile 30 mL PO from 09-FEB-2008 to 10-FEB-2008. Diarrhea resolved and oral mucositis improved on 11-FEB-2008, and the patient was discharged. Hand and foot syndrome and neutropenia resolved on 15-FEB-2008. Sorafenib/placebo and capecitabine therapies were discontinued in response to hand and foot syndrome and diarrhea, as the patient decided to no longer participate in the study because of the adverse events. She received her last dose of

sorafenib/placebo on 08-FEB-2008 and her last dose of capecitabine on 05-FEB-2008. No action was taken with study drugs in response to oral mucositis and neutropenia.

The investigator considered the events of hand and foot syndrome and oral mucositis to be RELATED to both sorafenib/placebo and capecitabine. The investigator considered the events of diarrhea and neutropenia to be UNRELATED to sorafenib/placebo but RELATED to capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-332
Subject 50-332-1006
76-year-old woman

SAE(s): Deep vein thrombosis (unrelated)

The patient was diagnosed with breast cancer on 07-DEC-1993. On 01-FEB-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the liver and mediastinum. Primary therapy for non-metastatic disease included surgery, adjuvant chemotherapy, and anthracyclines (total dose of 300 mg/m^2). No prior metastatic treatment was reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (2000 mg) BID by mouth on 21-MAY-2008. Dosage of capecitabine was reduced to 750 mg/m^2 (1300 mg) BID on 18-JUN-2008 and 500 mg/m2 (1000 mg) BID on 13-AUG-2008. Dosage of sorafenib/placebo was reduced to 400 mg once a day on 22-JUL-2008 as a result of hand-foot skin reaction and reduced to 400 mg every other day on 10-SEP-2008.

On 05-JAN-2009, the patient was hospitalized for DEEP VEIN THROMBOSIS (CTC GRADE 2). Left lower limb venous Doppler scan on 05-JAN-2008 showed consistent signals of deep venous thrombosis involving the popliteal segment. Sorafenib/placebo therapy was interrupted on 05-JAN-2009 because of the risk of bleeding. No action was taken with capecitabine. The event improved on 08-JAN-2009, and the patient was discharged. On 08-JAN-2008, the patient's prothrombin time (PT) was 19.0 s (normal 13 s)and her INR was 1.63. Her activated partial thromboplastin time (aPTT) was 147 s (normal 25 - 40 s) and her reptilase time (RT) was 4.59 (normal up to 1.25). Sorafenib/placebo was restarted on 08-JAN-2009.

The investigator considered the event of deep vein thrombosis to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

The patient was unblinded by the sponsor for safety reporting reasons; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-332
Subject 50-332-1012
59-year-old woman

SAE(s): Jaundice, Jaundice (unrelated)

The patient was diagnosed with stage III lobular invasive breast cancer on 10-DEC-2002. On 01-NOV-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, liver and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, anthracyclines (total dose of 450 mg/m^2), and endocrine therapy. Prior metastatic treatment included radiotherapy, 2 regimens of taxane chemotherapy, and endocrine therapy. The date of the final dose of the most recent radiotherapy was reported as 01-DEC-2007, and the date of the final dose of chemotherapy, taxanes, and endocrine therapy was reported as 21-JUL-2008.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (2000 mg) BID by mouth on 13-AUG-2008. Dosage of capecitabine reduced by 25% on 03-SEP-2008 in response to hand-foot skin syndrome and reduced by 25% once again on 12-NOV-2008 in response to an adverse event. Dosage of sorafenib/placebo was reduced to 400 mg once daily on 24-SEP-2008 in response to an adverse event. On 18-FEB-2009, the patient discontinued treatment because of progressive disease; her last doses of sorafenib/placebo and capecitabine were received that same day.

On 06-MAR-2009, the patient was hospitalized for JAUNDICE (CTC GRADE 3). No action was taken with sorafenib/placebo or capecitabine as a result of this event. The patient received chemotherapy. Jaundice resolved on 08-MAR-2009, and the patient was discharged.

On 17-MAR-2009, the patient was once again hospitalized for JAUNDICE (CTC GRADE 2). No action was taken with study drugs as a result of this event, but she received medication. The event resolved on 20-MAR-2009, and the patient was discharged with her bilirubin level at 17 mg/dL.

The investigator considered both events of jaundice to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease (liver metastases) as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-332
Subject 50-332-1013
47-year-old woman

SAE(s): Infection on tumor site, Hypotension (unrelated)

On 08-NOV-2005, the patient was diagnosed with stage II infiltrating ductal breast cancer. On 12-JUN-2006, she was diagnosed with stage IIIb or IIIc metastatic breast cancer with metastases to the lymph nodes. Primary therapy for non-metastatic disease included surgery and radiotherapy. Prior metastatic treatment included surgery, radiotherapy, and 2 regimens of chemotherapy including taxanes and anthracyclines (total dose of 240 mg/m^2). The final dose of the most recent metastatic treatment was administered on 29-AUG-2007. The final dose of the most recent radiotherapy was administered on 01-MAY-2007.

The patient's medical history included a tumor on the right axilla. No concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 27-AUG-2008.

On 23-OCT-2008 the patient was hospitalized for a life-threatening INFECTION ON TUMOR SITE (CTC GRADE 4). Sorafenib/placebo therapy was interrupted on 23-OCT-2008 as a result of this event, but no action was taken with capecitabine. From 23-OCT-2008 to 26-OCT-2008, the patient was treated with intravenous Zinacef (cefuroxime) 1500 mg daily for infection. From 27-OCT-2008 to 15-NOV-2008, the patient was treated with intravenous ceftriaxone 2 g and teicoplanin 400 mg daily for infection. On 27-OCT-2008, the patient experienced life-threatening HYPOTENSION (CTC GRADE 3) and was admitted to intensive care. The hypotension was caused by the tumor site infection, initially reported as grade 2 but now upgraded to grade 4. No action was taken with study drugs as a result of hypotension, and the event resolved on 29-OCT-2008. A computed tomography (CT) scan showed disease progression, and the patient received second-line chemotherapy before being discharged on 15-NOV-2008, the infection having improved.

The investigator considered both the event of infection on tumor site and the event of hypotension to be UNRELATED to sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation for both events.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-332
Subject 50-332-1015
73-year-old woman

SAE(s): Hypertension, Diarrhea (related)

On 09-NOV-1992, the patient was diagnosed with stage II infiltrating ductal breast cancer. On 13-MAY-2004, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, and endocrine therapy. Prior metastatic treatment included radiotherapy and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 01-SEP-2008. The final dose of the most recent radiotherapy was administered on 01-JUL-2004.

The patient's medical history included hypertension since 1998. Concomitant medications included losartan and furosemide for hypertension. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 30-SEP-2008.

At study entry, the patient's baseline blood pressure was 160/80 mm Hg. On 05-OCT-2008, the patient's blood pressure was 170/110 mm Hg, and on 07-OCT-2008, it had dropped to 150/100 mm Hg. The patient's heart rate was 120 bpm, up from her baseline heart rate of 82 bpm. The diagnosis was HYPERTENSION (CTC GRADE 3), considered an important medical event. The patient also presented with non-serious dyspnea, fatigue, mucositis, and acne. She received intravenous Flebocortid (hydrocortisone hydrogen succinate) 300 mg as treatment for the dyspnea. Blood work was normal. A thoracic X-ray showed no pleural effusion, and electrocardiogram showed only sinus tachycardia. Beginning on 07-OCT-2008, she received oral amiodarone 200 mg for hypertension and tachycardia and oral Atensina (clonidine) 200 mg for hypertension. The patient was sent home with a Holter monitor, and an echocardiogram was scheduled for the next week. Sorafenib/placebo therapy was interrupted on 07-OCT-2008 as a result of this event, but no action was taken with capecitabine; however, capecitabine therapy was interrupted on 07-OCT-2008 in response to non-serious, grade 2 mucositis. The event of hypertension improved to a grade 2 event on 09-OCT-2008. On 14-OCT-2008, sorafenib/placebo was restarted at a reduced dosage of 400 mg once daily by mouth. On 22-OCT-2008, capecitabine was restarted at a reduced dosage of 750 mg/m^2 (1150 mg) BID.

The investigator considered the event to be RELATED to sorafenib/placebo and UNRELATED to capecitabine. The investigator believed that sorafenib/placebo exacerbated the primary hypertension.

On 11-NOV-2008, capecitabine therapy was interrupted because of non-serious, grade 2 diarrhea. On 15-NOV-2008, the patient was hospitalized for DIARRHEA (CTC GRADE 3). No action was taken with sorafenib/placebo because the drug had been interrupted since 04-NOV-2008 because of rash acneiform on face and throat. No action was taken with capecitabine because the drug was already interrupted. The patient was discharged on 17-NOV-2008, the event having improved. Study drugs were restarted on 25-NOV-2008. Dosage of sorafenib/placebo was reduced to 400 mg every other day; dosage of capecitabine was not changed.

The investigator considered the event of diarrhea to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-332
Subject 50-332-1016
62-year-old woman

SAE(s): Left breast mastitis, Surgery scar infection, Left breast wound dehiscence, Left breast wound dehiscence, Infection on wound dehiscence (unrelated)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 29-MAR-1999. On 05-SEP-2006, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and liver. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, and endocrine therapy. Prior metastatic treatment included radiotherapy and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 05-OCT-2008. The final dose of the most recent radiotherapy was administered on 01-MAY-1999.

No past medical history or concomitant medications were reported. On 09-OCT-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth. Dosage of sorafenib/placebo was reduced to 400 mg once daily on 12-NOV-2008 in response to an adverse event. Dosage of capecitabine was reduced to 750 mg/m^2 (1150 mg) BID on 29-OCT-2008 in response to hand-foot syndrome and reduced further to 500 mg/m^2 (800 mg) BID on 17-DEC-2008 in response to an adverse event.

On 10-MAR-2009, the patient experienced LEFT BREAST MASTITIS (CTC GRADE 2), which was determined to be an important medical event. On 11-MAR-2009, she began treatment with oral levofloxacin, ketoprofen, and dipirone/caffeine. On 26-MAR-2009, the patient underwent same-day surgery for abscess drainage and mammary prosthesis removal. On 30-MAR-2009, the patient experienced left breast wound dehiscence, considered a non-serious event. Both sorafenib/placebo and capecitabine therapies were interrupted in response to the event of left breast mastitis, which resolved on 17-APR-2009.

The investigator considered the event of left breast mastitis to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

On 12-MAY-2009, both sorafenib/placebo and capecitabine therapies were interrupted in response to non-serious herpes zoster on thorax.

On 04-JUN-2009, the patient was hospitalized for SURGERY SCAR INFECTION (CTC GRADE 2), presenting with an infection on the scar lesion from her previous surgery. No action was taken with study drugs, as they had already been interrupted. A surgical cleansing was performed, and the event resolved on 11-JUN-2009, at which time the patient was discharged.

The investigator considered the event of surgery scar infection to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation

On 15-JUN-2009, sorafenib/placebo and capecitabine therapies were restarted.

On 10-OCT-2009, the patient was hospitalized for an elective surgical correction of LEFT BREAST WOUND DEHISCENCE (CTC GRADE 3). The patient presented with an 8- x 10-centimeter ulceration in the left chest with costo-pleural exposure. The ulceration was believed to be secondary to cutaneous closing after removal of a prosthesis (date not reported). She received mechanical water jet cleaning and chemical debridants. Because of intense pain, a closing with surrounding fascio-cutaneous thoracic-abdominal flaps was proposed, supposing a "well succeeded drying of devitalized costal arc." Some were removed under intercostals anesthesia, although new devitalizations were observed under the cutaneous edges. The flap was not completed because of the inability to remove all the devitalized tissues. There was no relapse of tumor in the bed and the costal metastasis was not near the site of ulceration. No action was taken with study drugs in response to the event, which improved the same day. The patient was discharged from the hospital.

On 23-OCT-2009, the patient was due to receive Cycle 17, but she did not report to the site for treatment per patient choice. On 23-OCT-2009, the capecitabine was reported as dose interrupted because of investigator/patient decision, and was not restarted.

On 26-OCT-2009, the patient was hospitalized for ANEMIA (CTC GRADE 3) and worsening LEFT BREAST WOUND DEHISCENCE (CTC GRADE 3). She was initially hospitalized for anemia but was reported to have ongoing wound dehiscence after surgery on 23-OCT-2009. She was treated with hyperbaric oxygen therapy for wound dehiscence, and the hospitalization was prolonged so the patient could receive this treatment. No action as taken with study drugs in response to these events. On 07-NOV-2009, the anemia resolved and wound dehiscence improved, and the patient was discharged from the hospital.

On 10-NOV-2009, the patient was again admitted to the hospital with INFECTION ON WOUND DEHISCENCE (CTC GRADE 3). She also had a fever (value not specified). She was treated with intravenous antibiotics (Rocefin), and the surgical wound infection resolved on 12-NOV-2009. No action was taken with study drugs in response to the event. The patient did discontinue treatment because of these events, however. She received her last dose of capecitabine on 15-OCT-2009 (Cycle 16) and her last dose of sorafenib/placebo on 27-NOV-2009.

The investigator considered the events of left breast wound dehiscence, anemia, left breast wound dehiscence, and infection on wound dehiscence to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation for all events.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-332
Subject 50-332-1020
43-year-old woman

SAE(s): Dyspnea, Pleural effusion (unrelated)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 29-OCT-2004. On 01-JUL-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, lymph nodes, and pleural effusion (cytology confirmed). Primary therapy included surgery, radiotherapy, adjuvant chemotherapy including taxanes and anthracyclines (total dose of 300 mg/m^2), and endocrine therapy. Prior metastatic treatment included endocrine therapy. The final dose of the most recent metastatic treatment was administered on 01-OCT-2008. The final dose of the most recent radiotherapy was administered on 01-MAY-2005.

No past medical history or concomitant medications were reported. On 22-DEC-2008, the patient began therapy with sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth. On 10-FEB-2009, dosage of capecitabine was reduced to 750 mg/m^2 (1150) mg BID in response to hand and foot syndrome.

Tumor assessment on 29-JAN-2009 showed chest wall/lung lesions and loculated pleural effusion in the right hemithorax. On 16-MAR-2009, the patient was hospitalized for DYSPNEA (CTC GRADE 2). No action was taken with study drugs as a result of this event. The patient received antibiotics and corticoids, and she was discharged on 23-MAR-2009, the event having resolved.

On 30-MAR-2009, the patient was hospitalized again with dyspnea. No CT scan or X-ray was available because the patient was not hospitalized at the study site, but the investigator suspected progressive disease and PLEURAL EFFUSION (CTC GRADE 5). The patient's mother reported that the patient had lung metastases, and the patient died on 09-APR-2009. Causes of death were reported as respiratory insufficiency, extensive bilateral pleural effusion, and metastatic breast cancer. No action was taken with study drugs as a result of this event. Her last doses of sorafenib/placebo and capecitabine were administered on 16-MAR-2009.

The investigator considered the events of dyspnea and pleural effusion to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1003
44-year-old woman

SAE(s): Hand and foot syndrome (related)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 14-OCT-2004. On 04-OCT-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, and endocrine therapy. No prior metastatic treatment was reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 15-JAN-2008.

On 26-JAN-2008, the patient presented with HAND AND FOOT SYNDROME (CTC GRADE 3), considered serious because of persistent or significant disability. She had shown no skin changes on 14-JAN-2008; now, however, the patient was unable to walk. On 28-JAN-2008, both sorafenib/placebo and capecitabine therapies were interrupted, and the event improved to grade 1 on 29-JAN-2008. Study drugs were restarted on 08-FEB-2008 with capecitabine dosage reduced by 25%.

The investigator considered the event of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1004
58-year-old woman

SAE(s): Colon metastase (unrelated)

The patient was diagnosed with stage III lobular invasive cancer on 14-MAY-2004. On 18-SEP-2006, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy included taxanes and anthracyclines (total dose of 591 mg/m^2), and endocrine therapy. Prior metastatic treatment included radiotherapy and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 18-DEC-2007. The final dose of the most recent radiotherapy was administered on 18-DEC-2006.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1950 mg) BID by mouth on 11-JAN-2008. The dosage of capecitabine was reduced to 750 mg/m^2 (1500 mg) BID on 26-FEB-2008 as a result of an adverse event. Both study drugs were interrupted on 05-MAY-2008 in preparation for surgery.

On 16-MAY-2008, the patient had a laparoscopic hemicolectomy for the partial resection of a metastatic lesion on the colon (COLON METASTASE [CTC GRADE 2]). The patient had no complications during this elective surgery, and the patient was discharged on 17-MAY-2008. Action taken with both study drugs was reported as none. Study drugs were reintroduced on 27-MAY-2008.

The investigator considered the event of colon metastase to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-334
Subject 50-334-1005
53-year-old woman

SAE(s): Hand-foot skin reaction, Hand-foot skin syndrome (related)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 14-FEB-2002. On 10-NOV-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the chest wall. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, and anthracyclines (total dose of 576 mg/m^2). No prior metastatic treatment was reported.

The patient had the concomitant conditions of hypothyroidism and carpal tunnel syndrome. Concomitant medications included synthyroid, dipyrone, paracetamol, ginkgo biloba, and vitamin C. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth on 25-JAN-2008.

On 06-MAR-2008, the patient began experiencing grade 1 hand-foot skin reaction that worsened to HAND-FOOT SKIN REACTION (CTC GRADE 3) on 18-MAR-2008. Sorafenib/placebo therapy was interrupted on 18-MAR-2008 and capecitabine therapy was interrupted on 27-MAR-2008 as a result of this event. The patient received dexamethasone cream from 27-MAR-2008 to 01-APR-2008 and moisturizer since 27-MAR-2008. On 01-APR-2008, the event of hand-foot skin reaction improved to grade 1. Sorafenib/placebo was reintroduced with no dosage reduction on 09-APR-2008. Capecitabine was reintroduced at a 25% dosage reduction on 11-APR-2008.

The investigator considered the event of hand-foot skin reaction to be RELATED to both sorafenib/placebo and capecitabine.

On 22-MAY-2008, the ongoing grade 1 hand-foot skin reaction worsened to HAND-FOOT SKIN SYNDROME (CTC GRADE 3), now considered serious because of significant disability. Sorafenib/placebo and capecitabine therapies were interrupted on 11-JUN-2008 as a result of this event, which improved to a grade 2 event on 18-JUN-2008. On 02-JUL-2008, both study medications were restarted. Because of the non-serious event of hand-foot skin syndrome, sorafenib/placebo dosage was reduced by 50% (400 mg once daily). There was no change to capecitabine dosage.

The investigator considered the event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received PLACEBO.

Study SOLTI 0701
Center 50-334
Subject 50-334-1009
63-year-old woman

SAE(s): Infection site tumor (unrelated)

On 19-OCT-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, breast, chest wall, and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, taxanes, and anthracyclines. Prior metastatic treatment included radiotherapy. The final dose of the most recent radiotherapy was administered on 02-JAN-2008.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 19-FEB-2008. She was removed from the study because of progressive disease on 11-MAR-2008, with the last dose of sorafenib/placebo having been administered that same day and the last dose of capecitabine having been administered on 04-MAR-2008.

On 18-MAR-2008, the patient was hospitalized for an INFECTION SITE TUMOR (CTC GRADE 3). She received intravenous ceftriaxone 2 g and intravenous clindamycin 1200 mg from 18-MAR-2008 to 19-MAR-2008. Additionally, she received intravenous hydrocortisone 500 mg and oral hydroxyzine 75 mg for pruritis and rash. She was also treated with subcutaneous clexane 40 mg for DVT prophylaxis. No action was taken with study drugs, as they had already been discontinued. The patient was discharged on 20-MAR-2008 with oral antibiotics, and the event was considered resolved on that day.

The investigator considered the event of infection site tumor to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternate explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1011
52-year-old woman

SAE(s): Dyspnea (unrelated)

On 19-JUN-2000, the patient was diagnosed with stage II infiltrating ductal breast cancer. On 17-JAN-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the breast, lung, and lymph nodes. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, and anthracyclines. No prior metastatic treatment was reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine1000 mg/m^2 (1800 mg) BID by mouth on 15-FEB-2008.

On 23-MAR-2008, she was hospitalized for DYSPNEA (CTC GRADE 3) and received treatment with oxygen. The patient's clinical condition worsened with bronchospasm, and on 26-MAR-2008, the patient began receiving paclitaxel plus cisplatin intravenously in addition to mechanical ventilation. On 27-MAR-2008, a thoracic computed tomography (CT) scan confirmed disease progression, and study drugs were discontinued. The patient's last dose of sorafenib/placebo was administered on 27-MAR-2008, and her last dose of capecitabine had been administered on 21-MAR-2008. No action was taken with study drugs as a result of the event of dyspnea, as they were discontinued because of disease progression. On 30-MAR-2008, she had a fever and received intravenous cefepime. The patient remained under mechanical ventilation and clinical support until the event of dyspnea resolved on 02-APR-2008 and she was discharged.

The investigator considered the event of dyspnea to be UNRELATED to sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-334
Subject 50-334-1013
56-year-old woman

SAE(s): Febrile neutropenia, Diarrhea (related)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 28-SEP-2005. In DEC-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the breast, lymph nodes, and stomach. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, and anthracyclines. No prior metastatic treatment was reported. The date of the final dose of most recent metastatic treatment was not reported.

No past medical history or concomitant medications were reported. The patient received sorafenib/placebo 400 mg BID by mouth from 19-MAR-2008 to 24-JUL-2008 and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth from 19-MAR-2008 to 21-JUL-2008. The patient discontinued treatment because of progressive disease, and she began chemotherapy treatment with carboplatin and docetaxel on 04-AUG-2008.

On 07-AUG-2008, the patient began experiencing diarrhea. On 11-AUG-2008, the patient was hospitalized for FEBRILE NEUTROPENIA (CTC GRADE 3) and DIARRHEA (CTC GRADE 2). From 11-AUG-2008 to 18-AUG-2008, she received intravenous ceftriaxone sodium 2 mg daily and oral metronidazole 1500 mg daily for febrile neutropenia, and from 11-AUG-2008, she received subcutaneous granulokine for febrile neutropenia. No action was taken with study drugs as a result of these events, which resolved on 18-AUG-2008.

The investigator considered the events of febrile neutropenia and diarrhea to be UNRELATED to both sorafenib/placebo and capecitabine, citing concomitant drug (chemotherapy) as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-334
Subject 50-334-1016
55-year-old woman

SAE(s): Urinary tract infection, Pnemothorax, Pleural effusion, Pleural empyema, Respiratory insufficiency (unrelated)

On 04-OCT-2006, the patient was diagnosed with stage III infiltrating ductal breast cancer. On 29-OCT-2007, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the bone. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, taxanes, and anthracyclines. Prior metastatic treatment included radiotherapy. The final dose of the most recent metastatic treatment was administered on 10-APR-2008. The final dose of the most recent radiotherapy was administered on 18-JAN-2008.

No past medical history or concomitant medications were reported. The patient was in the screening phase and had not received sorafenib/placebo or capecitabine.

On 19-APR-2008, the patient began experiencing grade 1 fever and urinary pain. On 20-APR-2008, the patient was hospitalized for a URINARY TRACT INFECTION (CTC GRADE 3). Both uroculture and hemoculture were positive for Escherichia coli. The patient received ceftriaxe 2g/day for 10 days, and she was discharged on 01-MAY-2008 with complete resolution of events.

The investigator considered the event of urinary tract infection to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

The patient was randomized on 20-MAY-2008. She received sorafenib/placebo 400 mg BID by mouth from 20-MAY-2008 to 01-JUL-2008, when she discontinued because of progressive disease diagnosed on 25-JUN-2008. She also received capecitabine 1000 mg/m^2 (1950 mg) BID by mouth from 20-MAY-2008 to 24-JUN-2008.

On 12-JUL-2008, the patient experienced non-serious, unrelated grade 3 dyspnea, which was treated with thoracocentesis on 15-JUL-2008. After the procedure, however, she had complications including PNEMOTHORAX (CTC GRADE 2) and was hospitalized. No action was taken with study drugs, as they had already been discontinued. The patient was discharged on 17-JUL-2008, the event having resolved.

The investigator considered the event of pneumothorax to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

On 22-JUL-2008, the patient was hospitalized for dyspnea, a symptom of PLEURAL EFFUSION (CTC GRADE 3). On that same day, the patient underwent a thoracentesis as treatment for the event of pleural effusion. On 24-JUL-2008, the patient also developed PLEURAL EMPYEMA (CTC GRADE 3) while hospitalized. No action was taken with study drugs as as result of these events. On 06-AUG-2008, the patient died of RESPIRATORY INSUFFICIENCY (CTC GRADE 5). Pleural effusion and pleural empyema were unchanged at the time of death.

The investigator considered the events of respiratory insufficiency, pleural effusion, and pleural empyema to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation for the pleural effusion and respiratory insufficiency and intercurrent disease for the pleural empyema.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-334
Subject 50-334-1019
65-year-old woman

SAE(s): Hand-foot skin syndrome (related)

The patient was diagnosed with stage III lobular invasive breast cancer on 13-APR-2005. On 09-JUN-2006, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and skin. Primary therapy for non-metastatic disease was reported as surgery, radiotherapy, endocrine therapy, and adjuvant and neo-adjuvant chemotherapy, including taxanes and anthracyclines (total dose of 75 mg/m^2). Prior metastatic treatment included endocrine therapy. The date of the final dose of the most recent metastatic treatment was not reported. The final dose of the most recent radiotherapy was administered on 30-MAY-2006.

No past medical history or concomitant medications were reported. On 30-MAY-2008, the patient began therapy with sorafenib/placebo 400 mg BID by mouth. On that same day she began therapy with capecitabine 1000 mg/m^2 (1450 mg) BID by mouth; this dosage was reduced to 750 mg/m^2 (1150 mg) on 25-JUN-2008 in response to an adverse event.

On 07-JUL-2008, the patient experienced HAND-FOOT SKIN SYNDROME (CTC GRADE 3), considered to result in significant disability for the patient. Her symptoms included pain, erythema, and peeling on her hands. Both study drugs were interrupted on 08-JUL-2008 as a result of this event, and the event improved on 10-JUL-2008. Study drugs were not restarted for Cycle 3 because of continuing grade 2 hand-foot skin reaction. On 29-JUL-2008, the patient discontinued from the study because of decreased performance status due to her breast cancer. The patient's last doses of sorafenib/placebo and capecitabine were administered on 07-JUL-2008.

The investigator considered the event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1020
48-year-old woman

SAE(s): Hand-foot skin syndrome, Hand-foot skin syndrome, Hand-foot skin syndrome, Hand and foot syndrome (related)

On 11-AUG-1997, the patient was diagnosed with stage I infiltrating ductal breast cancer. Primary treatment for the Breast Cancer was reported as surgery and adjuvant and neo-adjuvant chemotherapy. On 10-APR-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, lung, and skin. Prior metastatic treatment was not reported.

No past medical history or concomitant medications were reported. On 10-JUN-2008, the patient began therapy with sorafenib/placebo 400 mg by mouth BID. On that same day she began therapy with capecitabine 1000 mg/m^2 (1650 mg) by mouth BID.

On 23-JUN-2008, the patient came to the site after experiencing the symptoms of pain and edema related to the event of HAND-FOOT SKIN SYNDROME (CTC GRADE 3) that began on 18-JUN-2008. The investigator considered the hand-foot skin syndrome to be a persistent or significant disability. Sorafenib/placebo and capecitabine therapies were interrupted on 23-JUN-2008 in response to the event. On 30-JUN-2008, the patient returned to the site and reported that the hand and foot syndrome had resolved on 26-JUN-2008. The event was then considered a grade 1 non-serious adverse event. On 30-JUN-2008, the dosage of capecitabine was reduced by 25%. The dosage of sorafenib/placebo was not changed. Both study drugs were restarted on 02-JUL-2008.

The investigator considered the event of hand-foot skin syndrome to be related to both sorafenib/placebo and capecitabine.

On 07-JUL-2008, the patient again experienced HAND-FOOT SKIN SYNDROME(CTC GRADE3), considered a persistent or significant disability. The patient had pain in her feet and bullas on her hands. Both study drugs were interrupted as a result of this event, and the event resolved on 10-JUL-2008. On 11-JUL-2008, the patient reported peeling skin on her hand (with grade 2 severity) that stopped on 13-JUL-2008. Study drugs were restarted on 14-JUL-2008. The patient continues to experience grade 1 hand-foot skin syndrome, and the dosage of sorafenib/placebo was reduced.

The investigator considered the event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 10-AUG-2008, the patient once again experienced HAND-FOOT SKIN SYNDROME (CTC GRADE 3) with pain in and erythema on her hands and feet. Sorafenib/placebo therapy was interrupted on 13-AUG-2008 as a result of the event. The event resolved on 15-AUG-2008. Sorafenib/placebo was restarted on 18-AUG-2008 with no dosage change. Capecitabine dosage was reduced by 25% once again as of 20-AUG-2008.

The investigator considered the event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 02-SEP-2008, the patient yet again experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain that made it difficult for her to walk. Sorafenib/placebo was

interrupted on 02-SEP-2008 as a result of this event, which resolved on 06-SEP-2008. Sorafenib/placebo was restarted on 10-SEP-2008 at a reduced dosage of 400 mg every other day. There was no action taken with capecitabine.

The investigator considered the event of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1021
56-year-old woman

SAE(s): Hand-Foot Skin Syndrome, Hand-Foot Skin Syndrome, Hand Foot Syndrome, Hand and Foot Skin Syndrome (related)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 11-OCT-2002. On 13-MAY-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the liver, lung, and lymph nodes. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, anthracyclines (total dose of 300 mg/m^2), and endocrine therapy. No prior metastatic treatment was reported. The date of the final dose of the most recent radiotherapy was not reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 19-JUN-2008.

On 26-JUN-2008, the patient experienced HAND-FOOT SKIN SYNDROME (CTC GRADE 3), considered an important medical event. She presented to the clinic on 10-JUL-2008 with pain in her feet that made it difficult to walk. Sorafenib/placebo therapy was interrupted on 10-JUL-2008 as a result of this event and was reintroduced at the same dose on 17-JUL-2008. The capecitabine dosing was interrupted on 10-JUL-2008 and was restarted on 17-JUL-2008 at a reduced dose of 750 mg/m^2 (1150 mg). The event resolved on 13-JUL-2008.

The investigator considered the event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 20-JUL-2008, the patient again experienced HAND-FOOT SKIN SYNDROME (CTC GRADE 3) with pain in her feet that made it difficult to walk. Both sorafenib/placebo and capecitabine therapies were interrupted on 22-JUL-2008 as a result of this event. The event improved to a grade 1 event on 25-JUL-2008. On 28-JUL-2008, treatment with capecitabine was restarted with no dosage modifications. On 29-JUL-2008, treatment with sorafenib/placebo was restarted at a reduced dosage of 400 mg once daily by mouth.

The investigator considered the event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 06-AUG-2008, the patient once again experienced HAND FOOT SYNDROME (CTC GRADE 3) that compromised her normal activities. Both sorafenib/placebo and capecitabine therapies were interrupted on 07-AUG-2008 as a result of this event, which improved to a grade 1 event on 09-AUG-2008. Study drugs were restarted on 12-AUG-2008 with capecitabine at a reduced dosage of 500 mg/m^2 (750 mg) BID. No change was made to the dosage of sorafenib/placebo.

The investigator considered the event of hand foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 25-AUG-2008, the patient yet again experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain in her feet. Sorafenib/placebo therapy was interrupted on 27-

AUG-2008 and capecitabine therapy was interrupted on 28-AUG-2008 as a result of this event, which improved to a grade 1 event on 01-SEP-2008. Sorafenib/placebo was restarted at a reduced dosage of 400 mg once every other day and capecitabine was restarted with no dose reduction on 04-SEP-2008.

The investigator considered the event of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1023
56-year-old woman

SAE(s): Hand-foot skin syndrome, Hand-foot skin syndrome, Hand and foot syndrome (related)

The patient was diagnosed with stage I infiltrating ductal breast cancer on 13-SEP-2007. On 25-APR-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the breast and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, taxanes, and endocrine therapy. Prior metastatic treatment included surgery and 8 regimens of chemotherapy (no taxanes or anthracyclines). The dates of the final dose of most recent metastatic treatment and radiotherapy were not reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 17-JUN-2008.

On 14-JUL-2008, the patient experienced HAND-FOOT SKIN SYNDROME (CTC GRADE 3), considered to result in significant disability for the patient. She presented to the clinic on 16-JUL-2008 with pain in her feet that made it difficult to walk and dysesthesia in her hands. Both sorafenib/placebo and capecitabine therapies were interrupted on 16-JUL-2008 as a result of this event, which resolved on 20-JUL-2008. The patient presented with grade 1 hand-foot skin syndrome on 27-JUL-2008. Study drugs were restarted on 30-JUL-2008 with capecitabine at a reduced dosage of 750 mg/m^2 (1300 mg) BID.

The investigator considered the event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 03-AUG-2008, the patient once again experienced HAND-FOOT SKIN SYNDROME (CTC GRADE 3). She presented to the clinic with pain in her feet that made it difficult to walk on 06-AUG-2008, and both sorafenib/placebo and capecitabine therapies were interrupted on 06-AUG-2008 as a result of this event, which improved on 15-AUG-2008. Study drugs were restarted with sorafenib/placebo at a reduced dosage of 400 mg QD and capecitabine with no dosage reduction.

The investigator considered this event of hand-foot skin syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 03-SEP-2008, the patient yet again experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain in her feet. Sorafenib/placebo therapy was interrupted on 03-SEP-2008 as a result of this event. No action was taken with capecitabine, as the patient was between cycles, but Cycle 5 therapy was delayed. The event improved on 05-SEP-2008 to a grade 2 event that improved to a grade 1 event on 09-SEP-2008. Study drugs were reintroduced on 17-SEP-2008 with capecitabine at a reduced dosage of 500 mg/m^2 (950 mg) BID and sorafenib/placebo with no dosage reduction.

The investigator considered this event of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1024
56-year-old woman

SAE(s): Uterine polyps (unrelated)

On 01-JUN-1990, the patient was diagnosed with stage III infiltrating ductal breast cancer. Primary therapy for non-metastatic disease included surgery, radiotherapy, and adjuvant chemotherapy. Final dose of radiotherapy was reported as 16-JAN-1991. On 13-MAY-2004, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and skin. Prior therapy for metastatic disease included endocrine therapy. The final dose of the most recent metastatic treatment was administered on 09-JUN-2008.

Relevant past medical history included diagnosis with uterine polyps in DEC-2008. No concomitant medications were reported. On 11-JUL-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1800 mg) BID by mouth. On 21-AUG-2008, sorafenib/placebo dosage was reduced to 400 mg once daily on in response to an adverse event. On 05-MAR-2009, sorafenib/placebo dosage was again reduced to 400 mg every other day. On 13-AUG-2009, capecitabine dosage was reduced to 750 mg/m^2 (1450mg) BID in response to an adverse event and reduced further to 500 mg/m2 (950 mg) BID on 23-OCT-2009. On 06-AUG-2009, sorafenib/placebo therapy was interrupted in response to uterine polyps. On 11-AUG-2009, capecitabine therapy was interrupted in response to of uterine polyps.

On 12-AUG-2009, the patient was hospitalized for UTERINE POLYPS (CTC GRADE 2) and underwent a polipectomy by video-hysteroscopy. The patient was treated with intravenous (IV) Cepralotin for infection prophylaxis, and IV Tilatil and oral paracetamol for pain prophylaxis. No action was taken with sorafenib/placebo and capecitabine in response to this event, as study drugs had already been interrupted. On 13-AUG-2009, the event resolved, and the patient was discharged from the hospital. On 21-AUG-2009, the patient resumed treatment with both study drugs.

The investigator considered the event of uterine polyps to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1025
74-year-old woman

SAE(s): Hand-foot skin syndrome, Hand-foot skin syndrome, Hand and foot syndrome, Renal insufficiency, Hand and foot syndrome (related)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 14-FEB-2007. On 12-JUL-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the lung. Primary therapy for non-metastatic disease included surgery. Prior metastatic treatment included 6 cycles of chemotherapy including taxanes. The final dose of the most recent metastatic treatment was administered on 13-JUN-2008.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo400 mg BID by mouth and capecitabine 1000 mg/m^2 (1450 mg) BID by mouth on 20-FEB-2008.

On 12-AUG-2008, the patient began experiencing grade 1 hand and foot syndrome that worsened to grade 2 on 15-AUG-2008 and then HAND-FOOT SKIN SYNDROME (CTC GRADE 3) on 19-AUG-2008. Sorafenib/placebo therapy was interrupted on 20-AUG-2008 as a result of this event. The event resolved on 23-AUG-2008. Sorafenib/placebo was restarted on 26-AUG-2008. The dosage of capecitabine was reduced by 25% as of 26-AUG-2008.

On 05-SEP-2008, the patient once again experienced HAND-FOOT SKIN SYNDROME (CTC GRADE 3), with peeling, edema, and pain in her feet and hands. Sorafenib/placebo and capecitabine therapies were interrupted on 05-SEP-2008 as a result of this event, which resolved on 15-SEP-2008. Cycle 4 was delayed because of non-serious increase in creatinine on 15-SEP-2008; study drugs were restarted on 24-SEP-2008. Sorafenib/placebo dosage was reduced to 400 mg once daily.

On 23-OCT-2008, the patient yet again experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain in her feet. Sorafenib/placebo and capecitabine therapies were interrupted as a result of this event, which improved on 25-OCT-2008. Study drugs were restarted on 28-OCT-2008. Capecitabine dosage was reduced to 500 mg/m2 (650 mg) BID.

On 29-OCT-2008, laboratory results once again showed elevated creatinine at 1.9 mg/dL (normal 0.6 - 1.1). The patient was hypertensive as well. She was diagnosed with RENAL INSUFFICIENCY (CTC GRADE 3), considered serious because of medical importance. Both sorafenib/placebo and capecitabine therapies were interrupted. The patient received nifedipine 40mg daily for hypertension from 13-NOV-2008. On 14-NOV-2008, laboratory results still showed elevated creatinine (1.8 mg/dL), so on 15-NOV-2008 study drugs were reintroduced for clinical benefit/disease control. The event resolved on 04-DEC-2008, creatinine having dropped to 1.4 mg/dL, considered abnormal but not clinically significant.

On 08-DEC-2008, the patient again experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain in her feet. Sorafenib/placebo and capecitabine therapies were interrupted on 09-DEC-2008 as a result of this event, which improved on 14-DEC-2008.

Study drugs were restarted on 15-DEC-2008. Sorafenib/placebo dosage was reduced to 400 mg every other day.

The investigator considered all events of hand-foot skin syndrome and hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine. The investigator considered the event of renal insufficiency to be RELATED to both sorafenib/placebo and capecitabine but also thought it might be related to a CT contrast procedure.

On 24-SEP-2010, the patient was unblinded after the end of the study. The patient received PLACEBO.

Study SOLTI 0701
Center 50-334
Subject 50-334-1027
53-year-old woman

SAE(s): Hand and foot syndrome (related)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 18-NOV-2002. On 19-MAY-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the chest wall, lung, and lymph nodes. Primary therapy for non-metastatic disease included surgery, radiotherapy, endocrine therapy, adjuvant chemotherapy, and anthracyclines (total dose of 3000 mg/m^2). No prior metastatic treatment was reported. The date of the final dose of the most recent radiotherapy was not reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 24-JUL-2008.

On 15-AUG-2008, the patient began experiencing grade 1 hand and foot syndrome that worsened to HAND AND FOOT SYNDROME (CTC GRADE 3) on 28-AUG-2008, now assessed as resulting in significant disability. Sorafenib/placebo therapy was interrupted on 29-AUG-2008 due to the event; no action was taken with capecitabine since the patient was between cycles. The event resolved on 01-SEP-2008. Study drugs were restarted on 03-SEP-2008 with capecitabine dosage reduced by 25% and sorafenib/placebo dosage the same.

The investigator considered the event of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1030
69-year-old woman

SAE(s): Hand and foot syndrome (related)

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.The patient was diagnosed with stage II infiltrating ductal breast cancer on 29-SEP-2003. On 06-MAY-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, chest wall, lymph nodes, and pleura. Primary therapy for non-metastatic disease included surgery, radiotherapy, and adjuvant chemotherapy. No prior metastatic treatment was reported. The date of the final dose of the most recent radiotherapy was not reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 19-AUG-2008.

On 02-OCT-2008, the patient experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain in her walk. Sorafenib/placebo and capecitabine therapies were interrupted as a result of this event, which resolved on 07-OCT-2008. Study drugs were restarted on 09-OCT-2008 with capecitabine at a reduced dosage of 750 mg/m^2 (1150 mg) and sorafenib/placebo at the same dosage.

The investigator considered the event to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-334
Subject 50-334-1033
72-year-old woman

SAE(s): Hand and foot syndrome, Hand and foot syndrome (related)

On 21-FEB-2000, the patient was diagnosed with stage II infiltrating ductal breast cancer. Primary treatment for breast cancer was surgery, radiotherapy, adjuvant and neo-adjuvant chemotherapy, taxanes, and anthracyclines (540 mg/m^2). On 13-DEC-2001, she was diagnosed with stage IV metastatic breast cancer with metastases to the lung. Prior metastatic treatment was reported as surgery, radiotherapy, and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 26-AUG-2008. The final dose of the most recent radiotherapy was administered on 08-NOV-2006.

No past medical history or concomitant medications were reported. On 28-AUG-2008, the patient began therapy with sorafenib/placebo 400 mg by mouth BID and capecitabine 1000 mg/m^2 (1450 mg) by mouth BID.

On 18-SEP-2008, the patient began experiencing HAND AND FOOT SYNDROME (CTC GRADE 3) with pain on her hands, considered to result in significant disability for the patient. Sorafenib/placebo and capecitabine therapies were interrupted on 25-SEP-2008 in response to the event, which improved to a grade 1 event on 29-SEP-2008. Sorafenib/placebo therapy was restarted on 02-OCT-2008 with no change in dosage, and capecitabine therapy was restarted on 09-OCT-2008 at a reduced dosage of 750 mg/m^2 (1000 mg).

On 04-DEC-2008, the patient developed a subsequent event of HAND AND FOOT SYNDROME (CTC GRADE 3) with peeling and painful walking. Sorafenib/placebo therapy was interrupted on 09-DEC-2008 as a result of this event. No action was initially taken with capecitabine because the patient was between cycles, but capecitabine therapy was interrupted on 11-DEC-2008. The event improved on 18-DEC-2008. Study drugs were restarted on 20-DEC-2008 with sorafenib/placebo at a reduced dosage of 400 mg once a day.

The investigator considered both events of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1035
63-year-old woman

SAE(s): Hand and foot syndrome (related); Worsening of diabetes (unrelated)

The patient was diagnosed with infiltrating ductal breast cancer on 05-AUG-2008. On 23-JUL-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, liver, and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, taxanes, and anthracyclines (total dose of 400mg/m^2). No prior metastatic treatment was reported. The date of the final dose of the most recent radiotherapy was not reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 12-SEP-2008.

On 07-OCT-2008, the patient experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with erythema and pain in her walk. Sorafenib/placebo and capecitabine therapies were interrupted on 07-OCT-2008 as a result of this event, which resolved on 11-OCT-2008. Study drugs were reintroduced on 13-OCT-2008; dosage of capecitabine was reduced by 25%.

The investigator considered the event of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

Sorafenib/placebo dosage was reduced to 400 mg once daily on 22-OCT-2008 and further reduced to 400 mg every other day on 17-DEC-2008. Capecitabine dosage was reduced to 500 mg/m^2 on 12-NOV-2008 in response to an adverse event.

On 11-APR-2009, the patient was hospitalized for WORSENING DIABETES (CTC GRADE 2). The patient reported symptoms of polyuria and polydipsia and stated that she had not taken her diabetes medications correctly. On 11-APR-2009, laboratory investigations revealed an elevated glucose level of 423 mg/dL and an elevated amylase of 95 U/L (lipase level was not drawn). On 12-APR-2009, she was treated with insulin subcutaneously and oral Metformin and Glibenclamide. Glibenclamide was discontinued on the same date, and insulin and Metformin were continued until discharge. On 17-APR-2009, the patient was discharged in “good general status,” the event having resolved, and was referred to an endocrinologist for follow-up.

The investigator considered the event to be UNRELATED to both sorafenib/placebo and capecitabine, citing concomitant disease as an alternate explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1037
46-year-old woman

SAE(s): Hand and foot syndrome, Hand and foot syndrome (related)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 28-DEC-2005. On 05-JUN-2008, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the bone, lung, and lymph nodes. Primary therapy for non-metastatic disease included surgery and adjuvant chemotherapy including anthracyclines (total dose of 300 mg/m^2). Prior metastatic treatment included radiotherapy. The final dose of the most recent radiotherapy was administered on 11-AUG-2008.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1950 mg) BID by mouth on 08-OCT-2008. On 15-OCT-2008, dosage of capecitabine was reduced to 750 mg/m^2 (1500 mg) BID because of non-serious, grade 3 epigastralgia.

On 21-OCT-2008, the patient experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain on her hands and a burning sensation and bullas on her feet. Both sorafenib/placebo and capecitabine therapies were interrupted as a result of this event, which improved to a grade 1 event on 24-OCT-2008. Sorafenib/placebo was restarted on 27-OCT-2008 at a reduced dosage of 400 mg once daily, and capecitabine was restarted on 27-OCT-2008 with no change in dosage since the dosage had recently been reduced.

On 02-NOV-2008, the patient once again experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain during walking and pain in her hands. Both sorafenib/placebo and capecitabine therapies were interrupted on 03-NOV-2008 as a result of this event, which improved on 06-NOV-2008. Sorafenib/placebo was reintroduced on 10-NOV-2008 with no change in dosage, and capecitabine was restarted on 19-NOV-2008 (the beginning of Cycle 3) with a 25% reduction in dosage.

On 23-DEC-2008, the patient experienced non-serious hand and foot syndrome with pain and bubbles on her feet and difficulty walking. No action was taken with study medications because she did not contact the site, and the event improved on 31-DEC-2008. When she contacted the site on 05-JAN-2009, both study medications were interrupted.

The investigator considered all events of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-334
Subject 50-334-1039
53-year-old woman

SAE(s): Hand and foot syndrome, Hand and foot syndrome (related); Stenosis of trachea (unrelated)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 27-OCT-2005. On 28-SEP-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, lung, and skin. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, taxanes, and anthracyclines. Prior metastatic treatment included endocrine therapy. The final dose of the most recent metastatic treatment was administered on 15-OCT-2008. The date of the final dose of the most recent radiotherapy was not reported.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1650 mg) BID by mouth on 29-OCT-2008.

On 30-NOV-2008, the patient experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain in her walk. The patient notified the site of this event on 03-DEC-2008, and sorafenib/placebo and capecitabine therapies were interrupted on 03-DEC-2008 as a result of this event, which improved on 06-DEC-2008. Study drugs were restarted on 10-DEC-2008 with capecitabine at reduced dosage of 750 mg/m^2 (1300 mg) BID. Sorafenib/placebo dosage was not changed.

On 31-DEC-2008, the patient once again experienced HAND AND FOOT SYNDROME (CTC GRADE 3) with pain in her walk, hand peeling, and pain when holding objects. Sorafenib/placebo therapy was interrupted as a result of the event. No action was immediately taken with capecitabine since the patient was between cycles, but the next cycle of treatment was delayed. The event improved to a grade 1 event on 03-JAN-2009. Study drugs were restarted on 08-JAN-2009 with sorafenib/placebo at a reduced dosage of 400 mg once daily.

The investigator considered both events of hand and foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 03-JUN-2009, the patient received her last doses of sorafenib/placebo and capecitabine, having discontinued treatment because of progressive disease.

On 08-JUN-2009, the patient was hospitalized for STENOSIS OF TRACHEA (CTC GRADE 3) and underwent a tracheostomy. On 10-JUN-2009, a chest tomography revealed a bilateral pleural effusion. Pleural effusion was treated with furosemide from 21-JUN-2009 to 27-JUN-2009. On 25-JUN-2009, a thoracentesis was performed (result not available). No action as taken with study drugs in response to the event, as they had already been discontinued. The patient was discharged from the hospital on 01-JUL-2009, the event having improved.

The investigator considered the event of stenosis of trachea to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternate explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-335
Subject 50-335-1001
42-year-old woman

SAE(s): Edema lower extremities (related)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 15-MAR-2005. On 13-FEB-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, taxanes, and anthracyclines (total dose of 412 mg/m^2). No prior metastatic treatment was reported.

No past medical history was reported. Concomitant medications included dipyrone, dimethicone, omeprazole, morphine, and zoledronic acid. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (3300 mg) daily by mouth on 07-MAR-2008.

On 07-MAR-2008, the patient began experiencing non-serious edema of lower extremities. A Doppler ultrasound performed on 26-MAR-2008 showed no abnormal diagnosis. On 24-APR-2008, the event worsened to serious EDEMA LOWER EXTREMITIES (CTC GRADE 3). Sorafenib/placebo therapy was interrupted on 25-APR-2008 on the patient's request; no action was taken with capecitabine. A Doppler ultrasound performed on 28-APR-2008 did not confirm the diagnosis of thrombosis. The event improved on 07-MAY-2008, but the patient chose to withdraw from the study on 09-MAY-2008, with the patient's last doses of sorafenib/placebo and capecitabine having been administered on 24-APR-2008 and 02-MAY-2008, respectively. On 09-JUN-2008, the patient presented with no symptoms.

The investigator considered the event of edema lower extremities to be RELATED to sorafenib/placebo and UNRELATED to capecitabine.

On 12-JUN-2008, the patient was unblinded; she had received PLACEBO.

Study SOLTI 0701
Center 50-336
Subject 50-336-1001
32-year-old woman

SAE(s): Intracranial hypertension, Respiratory insufficiency (unrelated)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 22-DEC-2005. On 14-JAN-2008, she was diagnosed with stage IIIb or IIIc metastatic breast cancer with metastases to the bone, lung, and lymph nodes. Primary therapy for non-metastatic disease included surgery, radiotherapy, endocrine therapy, neo-adjuvant chemotherapy, and anthracyclines (total dose of 392 mg/m^2). No prior metastatic treatment was reported.

No past medical history or concomitant medications were reported. The patient received sorafenib/placebo 400 mg BID by mouth from 26-FEB-2008 to 29-APR-2008 and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth from 26-FEB-2008 to 22-APR-2008. She discontinued from the study because of progressive disease.

On 28-MAY-2008, the patient was hospitalized for INTRACRANIAL HIPERTENSION (CTC GRADE 3). Computed tomography of the brain showed a significant lesion. No action was taken with either study drug and the event resolved on 06-JUN-2008. The patient was discharged.

On 09-JUN-2008, the patient was re-hospitalized for RESPIRATORY INSUFFICIENCY (CTC GRADE 5) with presenting factors of dyspnea and complete atalectasis of the left lung. No action was taken with either study drug and the patient died on 11-JUN-2008. According to the death certificate, the causes of death were acute respiratory failure, pneumonia, metastatic cancer, and breast cancer.

The investigator considered the events of respiratory insufficiency and intracranial hypertension to be UNRELATED to both sorafenib/placebo and capecitabine, citing intercurrent disease as an alternative explanation for respiratory insufficiency and underlying disease as an alternative explanation for intracranial hypertension.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-338
Subject 50-338-1001
31-year-old woman

SAE(s): Facial paralysis, Vaginal hemorrhage, Vomiting (unrelated)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 28-DEC-2006. On 05-OCT-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, neo-adjuvant chemotherapy, anthracyclines (total dose of 504 mg/m^2), and endocrine therapy. Prior metastatic treatment included endocrine therapy. The final dose of the most recent metastatic treatment was administered on 14-FEB-2008. The final dose of the most recent radiotherapy was administered on 16-OCT-2007.

No past medical history or concomitant medications were reported. From 13-MAR-2008 to 01-MAY-2008, the patient received sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (3000 mg) BID by mouth.

On 01-MAY-2008, the patient was hospitalized for FACIAL PARALYSIS (CTC GRADE 2), VAGINAL HEMORRHAGE (CTC GRADE 2), and VOMITING (CTC GRADE 2), all of which began on 29-APR-2008. The event of vaginal hemorrhage resolved on 01-MAY-2008. No action was taken with sorafenib/placebo or capecitabine as a result of the events of facial paralysis and vaginal hemorrhage, but both study drugs were interrupted as a result of the event of vomiting. The event of facial paralysis resolved on 05-MAY-2008. The patient was discharged on 08-MAY-2008, at which time the event of vomiting was resolved. Magnetic resonance imaging of the brain on 15-MAY-2008 revealed a small intra-axial nodular lesion in the white periventricular substance in the left frontal lobe, adjacent to the frontal cornu of the related lateral ventricle and probable metastatic destructive lesions in the skull in regions bilaterally fronto-parietal, consistent with metastasis to the brain. The patient discontinued treatment because of disease progression; her last dose of both study drugs was on 01-MAY-2008.

The investigator considered all three events to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-338
Subject 50-338-1002
52-year-old woman

SAE(s): Congestive heart failure (related)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 13-SEP-2004. On 11-OCT-2007, she was diagnosed with stage IIIb or IIIc metastatic breast cancer with metastases to the breast, lymph nodes, and skin. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, endocrine therapy, and anthracyclines (total dose of 420 mg/m^2). Prior metastatic treatment included chemotherapy (neither taxane nor anthracycline). The final dose of the most recent metastatic treatment was administered on 12-FEB-2008. The final dose of the most recent radiotherapy was administered on 10-DEC-2004.

The patient's past medical history included a cardiac catheterization in OCT-2007, a history of smoking since age 12, a significant history of alcohol use (but only occasional alcohol use currently), and a family history of coronary disease. No concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (2900 mg) daily by mouth on 03-APR-2008.

On 21-APR-2008, the patient was hospitalized for dyspnea. The single episode of mild dyspnea improved after nasal O2. A chest X-ray on 22-APR-2008 showed an atherosclerotic aorta, peri-bronchovascular interstitial thickening, intrascissural effusion, and the costo-phrenic sinus free on the left and covered on the right (pleural effusion). An echocardiographic study on 30-APR-2008 revealed left ventricular dilated cardiomyopathy with significant deficit on the left ventricular globalsystolic function, moderate tricuspid and mitral regurgitation, pulmonary hypertension (PSAP [pulmonary systolic artery pressure] 52 mmHg), and LVEF (left ventricular ejection fraction) 30%. An ECG was performed, but results were not available. The investigator considered the patient to have significant dilated myocardiopathy leading to a CONGESTIVE HEART FAILURE (CTC GRADE 2) Class II of NYHA that could possibly have an ischemic etiology. In addition, she also has moderate tricuspid and mitral failure secondary to heart dilatation. On an unknown date, the patient was started on the following medication to treat suspected congestive heart failure: captopril 12.5 mg Q12H, atenolol 25 mg Q12H, and aldactone 25 mg daily. Both sorafenib/placebo and capecitabine therapies were discontinued as a result of the event of congestive heart failure, with the last doses of each having been administered on 21-APR-2008 and 17-APR-2008, respectively. The patient was discharged on 06-MAY-2008, the event having improved.

The investigator considered the event of congestive heart failure to be RELATED to sorafenib/placebo but UNRELATED to capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-338
Subject 50-338-1005
74-year-old woman

SAE(s): Hepatic metastases (unrelated)

The patient was diagnosed with stage IV intraductal colloid carcinoma breast cancer on 28-MAR-2002. On 17-NOV-2004, she was diagnosed with stage IV metastatic breast cancer with metastases to the lung and lymph nodes. Primary therapy for non-metastatic disease included surgery and endocrine therapy. Prior metastatic treatment included endocrine therapy and 7 regimens of chemotherapy including anthracyclines (total dose of 525 mg/m^2). The final dose of the most recent metastatic treatment was administered on 22-MAY-2007.

No past medical history or concomitant medications were reported. The patient received sorafenib/placebo 400 mg BID by mouth from 29-APR-2008 to 20-MAY-2008 and capecitabine 1000 mg/m^2 (2600 mg) daily by mouth from 29-APR-2008 to 13-MAY-2008. The patient withdrew consent.

On 29-MAY-2008, the patient was hospitalized for HEPATIC METASTASES (CTC GRADE 5). She presented with symptoms of melena, icterus, and coagulation disturbance. On 31-MAY-2008, an endoscopy with biopsy indicated hematochezia and erosive esophagitis with no bleeding activity. The patient received intravenous omeprazole and plasma and blood transfusion, but no improvement of her clinical status was observed. No action was taken with study drugs because they had already been discontinued. The patient died on 01-JUN-2008. The causes of death were listed as respiratory failure and bleeding due to liver metastasis and breast cancer. Coagulation disorder was listed as a significant contributing factor.

The investigator considered the event of hepatic metastases to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-338
Subject 50-338-1022
52-year-old woman

SAE(s): Meningeal metastases (unrelated)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 28-APR-2005. On 28-MAY-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone and liver. Primary therapy for non-metastatic disease included surgery, adjuvant chemotherapy including taxanes and anthracyclines (total dose 270 mg/m^2), and endocrine therapy. Prior metastatic treatment included radiotherapy, 1 regimen of chemotherapy including taxanes, and endocrine therapy. The final dose of the most recent metastatic treatment was administered on 08-AUG-2008. The final dose of the most recent radiotherapy was administered on 20-AUG-2007.

No past medical history or concomitant medications were reported. On 20-NOV-2008, the patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1450 mg) BID by mouth. Dosage of sorafenib/placebo was reduced to 400 mg once daily on 22-APR-2009 in response to an adverse event, and dosage of capecitabine was reduced to 750 mg/m^2 (1150 mg) BID on 05-JAN-2009 in response to an adverse event. The patient's last doses of sorafenib/placebo and capecitabine were received on 18-JUL-2009.

On 21-JUL-2009, the patient experienced vomiting and dizziness. Magnetic resonance imagining revealed meningeal metastases, and on 22-JUL-2009, the patient was hospitalized for MENINGEAL METASTASES (CTC GRADE 2). No action was taken with study drugs in response to these events, but the patient discontinued study treatment because of progressive disease. The event remained ongoing and unchanged at the end of study treatment.

The investigator considered the event of meningeal metastases to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-339
Subject 50-339-1007
36-year-old woman

SAE(s): Hand and foot skin reaction (related)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 25-MAR-2003. On 12-DEC-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, liver, and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, anthracyclines (total dose of 360 mg/m^2), and endocrine therapy. Prior metastatic treatment included 1 regimen of taxanes. The final dose of the most recent metastatic treatment was administered on 08-MAY-2008. The final dose of the most recent radiotherapy was administered on 30-JUL-2003.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 30-MAY-2008.

From 10-JUN-2008 to 19-JUN-2008, the patient experienced non-serious grade 1 hand and foot skin reaction (HFSR). On 20-JUN-2008, the HFSR worsened to grade 2, and study drugs were interrupted on 27-JUN-2008. On 30-JUN-2008, however, the patient contacted the site and the investigator diagnosed HAND AND FOOT SKIN REACTION (CTC GRADE 3), now considered an important medical event. Study drugs were not reintroduced. On 11-JUL-2008, the patient visited the site, and the event was still grade 3, so study drugs remained interrupted. The event resolved on 15-JUL-2008. Both study drugs were reintroduced on 17-JUL-2008, with capecitabine at a reduced dosage of 750 mg/m^2 (1150 mg).

The investigator considered the event of hand and foot skin reaction to be RELATED to both sorafenib/placebo and capecitabine.

On 24-Sep-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

Study SOLTI 0701
Center 50-339
Subject 50-339-1010
51-year-old woman

SAE(s): Pleural effusion (unrelated)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 15-AUG-2006. Primary therapy included surgery, radiotherapy, neo-adjuvant chemotherapy including taxanes and anthracyclines (total dose of 200 mg/m^2), and endocrine therapy. On 25-JUL-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the lung and lymph nodes. Prior metastatic treatment included radiotherapy with the final dose administered on 07-AUG-2007.

No past medical history or concomitant medications were reported. On 30-JUL-2008, the patient began therapy with sorafenib/placebo 400 mg BID orally and capecitabine 1000 mg/m^2 (1650 mg) BID orally for 14 days, with a seven-day rest period. On 22-OCT-2008, sorafenib/placebo dosage was reduced to 400 mg once a day in response to an adverse event. On 08-OCT-2008, capecitabine dosage was reduced to a reduced dose of 750 mg/m^2 (1300 mg) BID in response to an adverse event, on 03-DEC-2008, capecitabine dosage was further reduced to 500 mg/m^2 (1100 mg) in response to an adverse event. Capecitabine therapy was interrupted on 17-MAR-2009.

On 24-MAR-2009, the patient came to the hospital for a Cycle 12 visit and tumor evaluation. A computed tomography (CT) scan completed on that day revealed PLEURAL EFFUSION (CTC GRADE 2) and a grade 2 pericardial effusion, considered to be non-serious. The patient was hospitalized for evaluation of disease progression. Therapy with both study drugs was interrupted in response to the event of pleural effusion. On 30-MAR-2009, disease progression was diagnosed by biopsy, and the patient discontinued treatment. She received her last dose of sorafenib/placebo on 23-MAR-2009 and her last dose of capecitabine on 17-MAR-2009. On 08-APR-2009, the pleural effusion and pericardial effusion resolved, and the patient was discharged.

The investigator considered the event of pleural effusion to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternate explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-339
Subject 50-339-1013
46-year-old woman

SAE(s): Diarrhea (related)

The patient was diagnosed with stage III infiltrating ductal breast cancer on 22-SEP-2006. On 08-FEB-2008, she was diagnosed with stage IV metastatic breast cancer with metastases to the liver and lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, and neo-adjuvant chemotherapy including anthracyclines (total dose of 300 mg/m^2). Prior metastatic treatment included 1 regimen of taxanes. The final dose of the most recent metastatic treatment was administered on 14-JUL-2008. The final dose of the most recent radiotherapy was administered on 26-SEP-2007.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 16-OCT-2008.

On 23-NOV-2008, the patient began experiencing diarrhea with incontinence and more than 7 stools per day. She was hospitalized on the evening of 27-NOV-2008 for DIARRHEA (CTC GRADE 3) to receive intravenous fluids. Both study drug therapies were interrupted on 27-NOV-2008 as a result of this event. She was discharged on 28-NOV-2008, the event having improved to a grade 2 event. On 03-DEC-2008, the patient discontinued because of progressive disease. Her last dose of sorafenib/placebo was administered on 26-NOV-2008 and her last dose of capecitabine was administered on 20-NOV-2008.

The investigator considered the event of diarrhea to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received SORAFENIB.

Study SOLTI 0701
Center 50-340
Subject 50-340-1002
42-year-old woman

SAE(s): Brain metastasis (unrelated)

On 22-AUG-2006, the patient was diagnosed with stage III infiltrating ductal breast cancer. On 24-MAR-2008, the patient was diagnosed with stage IV metastatic breast cancer with metastases to the lung. Primary therapy for non-metastatic disease included surgery, radiotherapy, adjuvant chemotherapy, neo-adjuvant chemotherapy, and anthracyclines (total dose of 390 mg/m^2). No prior metastatic treatment was reported. The final dose of the most recent radiotherapy was administered on 11-JUN-2007.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1150 mg) BID by mouth on 14-MAY-2008.

On 19-JUL-2008, the patient presented to the hospital with headache, nausea, and vomitus. Computed tomography of the brain revealed edema and BRAIN METASTASIS (CTC GRADE 5). The patient was hospitalized to receive medication (NOS) and neurological evaluation. No action was taken with study drugs as a result of this event, as they had been discontinued because of progressive disease on 19-JUL-2008. The patient died in her sleep on 21-JUL-2008.

The investigator considered the event of brain metastases to be UNRELATED to both sorafenib/placebo and capecitabine, citing underlying disease as an alternative explanation.

On 24-SEP-2010, the patient was unblinded at the end of the study; the patient received PLACEBO.

Study SOLTI 0701
Center 50-340
Subject 50-340-1004
61-year-old woman

SAE(s): Hand foot syndrome (related)

The patient was diagnosed with stage II infiltrating ductal breast cancer on 07-OCT-2002. On 26-JUL-2007, she was diagnosed with stage IV metastatic breast cancer with metastases to the bone, breast, liver, lung, and lymphangitis in right breast. Primary therapy for non-metastatic disease included surgery, radiotherapy, endocrine therapy, adjuvant chemotherapy, and anthracyclines (total dose of 480 mg/m^2). Prior metastatic treatment included radiotherapy, endocrine therapy, and 1 cycle of taxanes. The final dose of the most recent metastatic treatment was administered on 03-JUN-2008. The final dose of the most recent radiotherapy was administered on 06-NOV-2007.

No past medical history or concomitant medications were reported. The patient began receiving sorafenib/placebo 400 mg BID by mouth and capecitabine 1000 mg/m^2 (1500 mg) BID by mouth on 03-JUL-2008.

On 10-JUL-2008, the patient began experiencing grade 2 hand foot syndrome that worsened to HAND FOOT SYNDROME (CTC GRADE 3) on 18-AUG-2008. The patient's pain interfered with her normal function. Sorafenib/placebo and capecitabine therapies were interrupted on 18-AUG-2008 as a result of this event, which improved to a grade 1 event on 22-AUG-2008. Study medications were reintroduced with capecitabine dosage reduced by 25%. No change was made to the dosage of sorafenib/placebo.

The investigator considered the event of hand foot syndrome to be RELATED to both sorafenib/placebo and capecitabine.

On 24-SEP-2010, the patient was unblinded at the end of the study. The patient received SORAFENIB.

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