Clinical trial results:
A Phase III Randomized, Double-blind, Placebo-controlled Trial Comparing Capecitabine Plus Sorafenib Versus Capecitabine Plus Placebo in the Treatment of Locally Advanced or Metastatic HER2-Negative Breast Cancer

Summary

EudraCT number	2010-018501-10
Trial protocol	BE DE GB AT CZ IE ES HU IT GR SE
Global end of trial date	

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	28 May 2015

Trial information

Trial identification

Sponsor protocol code	BAY43-9006/12444

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01234337
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	12 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy endpoint was to compare the Progression Free Survival (PFS) as assessed by the independent review panel according to Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 between the treatment groups (sorafenib in combination of capecitabine versus placebo in combination of capecitabine).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Capecitabine was administered orally at a dose of 1,000 milligram per square meter (mg/m^2) twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Capecitabine dose was escalated to 1,250 mg/m^2 twice daily if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received sorafenib at a total daily dose of 800 mg/4 tablets (400 mg/2 tablets, twice daily) were Grade 1 or less as per the common terminology criteria for adverse events version 4.0 (CTCAE v4.0).

Evidence for comparator: -

Actual start date of recruitment	21 February 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	39 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Ireland: 17

Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	China: 34
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Japan: 62
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	Spain: 111
Country: Number of subjects enrolled	South Africa: 13
Worldwide total number of subjects	537
EEA total number of subjects	321

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	447
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At 154 sites in 22 countries, subjects with histologically or cytologically confirmed human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma of the breast, and locally advanced or metastatic disease, were screened.

Pre-assignment

Screening details:

Of 707 subjects screened, 537 subjects were randomized and 527 subjects received at least 1 dose of study treatment. The reasons for 170 screen failures were adverse event in 21 subjects, disease progression, recurrence or relapse in 2, consent withdrawn in 16, death in 4, and protocol violation in 127 subjects.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Blinding implementation details:

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSARs) that was considered to be related to the blinded treatment, the subject's treatment code was usually unblinded before reporting to the health authorities, ethic committees, and investigators. Unblinding occurred for emergency purposes only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib (Nexavar, BAY43-9006) + Capecitabine

Arm description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and sorafenib dose to a total daily dose of 800 mg for that subject.

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Capecitabine dose was escalated to 1,250 mg/m^2 twice daily if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received sorafenib at a dose of 800 mg (400 mg twice daily) were Grade 1 or less as per the CTCAE v4.0.

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). Sorafenib dose was escalated to 800 mg (400 mg twice daily) in Cycle 2 or beyond if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a

prior cycle in which the subject received sorafenib at a total daily dose of 600 mg were Grade 1 or less as per CTCAE v4.0.

Arm title	Placebo + Capecitabine

Arm description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject.

Arm type	Placebo
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Capecitabine dose was escalated to 1,250 mg/m^2 twice daily if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received placebo at a dose of 4 tablets (2 tablets twice daily) were Grade 1 or less as per the CTCAE v4.0.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). Placebo dose was escalated to 4 tablets (2 tablets twice daily) in Cycle 2 or beyond if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received placebo at a total daily dose of 3 tablets were Grade 1 or less as per CTCAE v4.0.

Number of subjects in period 1	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine
Started	266	271
Subjects received treatment	260	267
Completed	169	207
Not completed	97	64
Consent withdrawn by subject	11	7
Randomized but not treated	6	4
Protocol violation	2	3
Non-compliant with study medication	3	2
Ongoing	16	24

Adverse event	55	20
Investigator decision not protocol driven	4	3
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Capecitabine
Reporting group description:	
Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and sorafenib dose to a total daily dose of 800 mg for that subject.	
Reporting group title	Placebo + Capecitabine
Reporting group description:	
Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject.	

Reporting group values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine	Total
Number of subjects	266	271	537
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.3	54.4	
standard deviation	± 10.2	± 10.9	-
Gender categorical Units: Subjects			
Female	265	268	533
Male	1	3	4
Race Units: Subjects			
White	205	212	417
Black	7	4	11
Asian	50	50	100
Hispanic	4	5	9
Region			
Other countries in the below category included Argentina, Australia, China, Israel and Japan.			
Units: Subjects			
Europe	166	168	334
North America	23	26	49
Other	77	77	154
Baseline performance status (Eastern Cooperative Oncology Group [ECOG]) Units: Subjects			
ECOG status=0	152	161	313
ECOG status=1	114	110	224
Number of prior chemotherapies for metastatic disease			

Assessed by Interactive voice response system (IVRS). Subjects with more than 1 actual number of prior chemotherapies were combined with subjects with 1 prior chemotherapy.			
Units: Subjects			
Prior chemotherapies=0	114	118	232
Prior chemotherapies=1	152	153	305
Hormone receptor status			
The hormone receptor status was assessed by IVRS, and considered as follows: in case, the tumor expressed estrogen and/or progesterone receptor, the subject was considered to have positive hormone receptor status. Otherwise, if both receptors were not expressed, then subject was considered to have a negative hormone receptor status.			
Units: Subjects			
Negative	83	84	167
Positive	183	187	370
Visceral disease at baseline Units: Subjects			
Missing	1	1	2
No	66	57	123
Yes	199	213	412

End points

End points reporting groups

Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Capecitabine

Reporting group description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and sorafenib dose to a total daily dose of 800 mg for that subject.

Reporting group title	Placebo + Capecitabine

Reporting group description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS (also considered the Intent-to-treat (ITT) analysis set) population (N=537) was defined as all randomized subjects. Subjects were analyzed as randomized, that is, even if a subject was randomized and received no drug or if randomized and initially received incorrect drug prior to switching to correct study drug, these subjects were still analyzed for efficacy under FAS, as randomized.

Subject analysis set title	Pharmacokinetic analysis set (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PKS (N=182) included all subjects with a valid pharmacokinetic profile of capecitabine.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF (N=527) was comprised of all randomized subjects who received at least one dose of study medication (sorafenib, placebo or capecitabine). Subjects were analyzed as treated.

Primary: Progression-free Survival (PFS) Assessed by the Independent Review Panel According to Response Evaluation Criteria for Solid Tumors (RECIST) 1.1

End point title	Progression-free Survival (PFS) Assessed by the Independent Review Panel According to Response Evaluation Criteria for Solid Tumors (RECIST) 1.1

End point description:

PFS was defined as the time from date of randomization to disease progression, radiological or death due to any cause, whichever occurs first. Subjects without progression or death at the time of analysis were censored at their last date of evaluable tumor evaluation. Median and other 95% CIs computed using Kaplan-Meier estimates.

End point type	Primary

End point timeframe:

From randomization of the first subject until approximately 3 years or until disease radiological progression

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[1]	271[2]		
Units: days				
median (confidence interval 95%)	166 (131 to 206)	165 (126 to 204)		

Notes:

[1] - FAS.

[2] - FAS.

Statistical analyses

Statistical analysis title	PFS by central review panel

Statistical analysis description:

PFS was compared using a stratified log-rank test with a one-sided alpha of 0.005, stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease. The hazard ratio (sorafenib + capecitabine / placebo + capecitabine) and its 95 percent (%) confidence intervals (CIs) were calculated using the Cox model, stratified by the above factors.

Comparison groups	Sorafenib (Nexavar, BAY43-9006) + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.405618 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.973
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.779
upper limit	1.217

Notes:

[3] - A Hazard ratio of less than (<) 1 indicates superiority of Sorafenib + Capecitabine over Placebo + Capecitabine.

[4] - One-sided p-value from log rank test (stratified per randomization as in interactive voice response system [IVRS]).

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from date of randomization to death due to any cause. Subjects still alive at the time of analysis were censored at their last known alive date. Median and other 95% CIs computed using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

From randomization of the first subject until approximately 3 years later

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[5]	271[6]		
Units: days				
median (confidence interval 95%)	575 (467 to 645)	616 (546 to 687)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis for Overall Survival

Statistical analysis description:

At the time of PFS final analysis, it was OS interim analysis (IA) with 285 total death events. According to protocol specified O'Brien-Fleming type alpha spending function and 285 death events at IA, the pre-specified alpha for this analysis was 0.0075 (one-sided).The hazard ratio (sorafenib + capecitabine / placebo + capecitabine) and its 95% CIs were calculated using the Cox model, stratified by randomization factors.

Comparison groups	Sorafenib (Nexavar, BAY43-9006) + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.930088 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.943
upper limit	1.513

Notes:

[7] - A Hazard ratio < 1 indicates superiority of Sorafenib+Capecitabine over Placebo+Capecitabine.

[8] - One-sided p-value from log rank test (stratified per randomization as in IVRS). OS was compared using a stratified log-rank test, stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease.

Secondary: Time to Progression (TTP) by Central Review

End point title	Time to Progression (TTP) by Central Review

End point description:

TTP was defined as the time from date of randomization to disease radiological progression by central review. Subjects without progression at the time of analysis were censored at their last evaluable tumor assessment date. Median and its 95% CIs were computed using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[9]	271[10]		
Units: days				
median (confidence interval 95%)	168 (139 to 215)	165 (127 to 208)		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	TTP by central review panel

Statistical analysis description:

TTP was compared using a stratified log-rank test with a one-sided alpha of 0.025, stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease. The hazard ratio (sorafenib + capecitabine / placebo + capecitabine) and its 95% CIs were calculated using the Cox model, stratified by the above factors.

Comparison groups	Sorafenib (Nexavar, BAY43-9006) + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.2105 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.723
upper limit	1.146

Notes:

[11] - A Hazard ratio <1 indicates superiority of Sorafenib+Capecitabine over Placebo+Capecitabine.

[12] - One-sided p-value from log rank test (stratified per randomization as in IVRS).

Secondary: Objective Response Rate (ORR) by Central Review

End point title	Objective Response Rate (ORR) by Central Review

End point description:

ORR was defined as the best tumor response (Complete Response [CR] or Partial Response [PR]) observed during treatment or within 30 days after termination of study treatment, assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. CR and PR needed to be confirmed by another scan at least 4 weeks later.

End point type	Secondary

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[13]	271[14]		
Units: percentage (%) of subjects				
number (confidence interval 95%)	13.5 (9.7 to 18.2)	15.5 (11.4 to 20.4)		

Notes:

[13] - FAS

[14] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis for Objective Tumor Response

Statistical analysis description:

ORR and 95% CI based on Cochran Mantel-Haenszel Test stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease. Difference = (Placebo + Capecitabine) - (Sorafenib + Capecitabine).

Comparison groups	Placebo + Capecitabine v Sorafenib (Nexavar, BAY43-9006) + Capecitabine
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.257412 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percent Difference
Point estimate	1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	7.77

Notes:

[15] - One-sided p-value from Cochran-Mantel-Haenszel test (stratified per randomization as in IVRS)

Secondary: Disease Control Rate (DCR) by Central Review

End point title	Disease Control Rate (DCR) by Central Review

End point description:

Disease control rate (DCR) was defined as the proportion of subjects whose best response was complete response (CR), partial response (PR), stable disease (SD) or Non CR/Non progressive disease (PD). CR and PR needed to be confirmed by another scan at least 4 weeks later. SD and Non CR/Non PD had to be documented at least 6 weeks after randomization.

End point type	Secondary

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[16]	271[17]		
Units: percentage (%) of subjects				
number (confidence interval 95%)	60.5 (54.4 to 66.4)	58.3 (52.2 to 64.2)		

Notes:

[16] - FAS

[17] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis for Disease Control Rate

Statistical analysis description:

DCR and 95% CI based on "general association Cochran-Mantel-Haenszel statistic" with one-sided alpha of 0.025 stratified by number of prior chemotherapies for metastatic disease, hormone receptor status, and region.
Difference = Placebo + Capecitabine - Sorafenib + Capecitabine.

Comparison groups	Placebo + Capecitabine v Sorafenib (Nexavar, BAY43-9006) + Capecitabine
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.284674 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percent Difference
Point estimate	-2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	5.72

Notes:

[18] - One-sided p-value from Cochran-Mantel-Haenszel test (stratified per randomization as in IVRS).

Secondary: Duration of Response (DOR) by Central Reader

End point title	Duration of Response (DOR) by Central Reader

End point description:

DOR was defined as the time from date of first response (CR or PR) to the date when Progressive Disease (PD) is first documented, or to the date of death, whichever occurred first according to RECIST version 1.1. Subjects still having CR or PR and have not died at the time of analysis were censored at their last date of tumor evaluation. Duration of response defined for confirmed responders only (that is, CR or PR). '99999' indicates that value could not be estimated due to censored data. Median and 95% CIs were computed using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[19]	42[20]		
Units: days				
median (confidence interval 95%)	313 (209 to 99999)	290 (169 to 99999)		

Notes:

[19] - Only responders in FAS

[20] - Only responders in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient Reported Outcomes: Functional Assessment of Cancer Therapy-Breast Symptom Index (8 item) (FBSI-8)

End point title	Patient Reported Outcomes: Functional Assessment of Cancer Therapy-Breast Symptom Index (8 item) (FBSI-8)

End point description:

The FBSI-8 was an 8-item questionnaire. Subjects responded to each item using a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). A total scale score was calculated (range from 0 to 32), with higher scores indicating low symptomatology and reflecting a better Health-Related Quality of Life (HRQoL). The results on the analysis of covariance (ANCOVA) of time-adjusted area under curve (AUC) for the FBSI-8 score were reported. Only subjects with a baseline assessment and at least one post-baseline assessment during the study were used for the AUC-based analyses.
Please find the statistical analyses in the attachment below.

End point type	Other pre-specified

End point timeframe:

Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 16, 19, 22, 25, 28, 31, 34, 37, and end of treatment (EOT, 21 days after last dose of study drug)

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233[21]	243[22]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	20.915 (20.459 to 21.37)	21.356 (20.911 to 21.801)		

Notes:

[21] - FAS

[22] - FAS

Attachments (see zip file)	Statistical Analyses_Other_FBSI-8/12444_Statistical

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Index Score

End point title	Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Index Score

End point description:

The EQ-5D was a generic Quality of life (QoL) preference based instrument and has been validated in the cancer populations. EQ-5D questionnaire contained a 5-item descriptive system of health states (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale (VAS). From the answers to these 5 health states a single HRQoL score ranging from -0.59 to 1 were generated according to the standard scoring algorithm developed by the EuroQoL Group for the instrument. This single score was referred to as the EQ-5D index score. For the EQ-5D, higher scores represented better health status. A change of at least 0.10 to 0.12 points on the EQ-5D index is considered clinically meaningful. The results on ANCOVA of time-adjusted AUC were reported. Only subjects with a baseline assessment and at least one post-baseline assessment during the study were used for the AUC-based analyses.
Please find the statistical analyses in the attachment below.

End point type	Other pre-specified

End point timeframe:

Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 16, 19, 22, 25, 28, and EOT (21 days after last dose of study drug)

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[23]	247[24]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	0.665 (0.641 to 0.688)	0.69 (0.667 to 0.713)		

Notes:

[23] - FAS

[24] - FAS

Attachments (see zip file)	12444_Statistical Analyses_Other_EQ-5D

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score

End point title	Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score

End point description:

The EQ-5D was a generic QoL preference based instrument and has been validated in the cancer populations. VAS was generated from 0 (worst imaginable health state) to 100 (best imaginable health state). This VAS score was referred to as the EQ-5D self-reported health status score. The results on ANCOVA of time-adjusted AUC were reported. Only subjects with a baseline assessment and at least one post-baseline assessment during the study were used for the AUC-based analyses.
Please find the statistical analyses in the attachment below.

End point type	Other pre-specified

End point timeframe:

Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 16, 19, 22, 25, 28, and EOT (21 days after last dose of study drug)

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235[25]	244[26]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	67.532 (65.87 to 69.19)	69.228 (67.6 to 70.86)		

Notes:

[25] - FAS

[26] - FAS

Attachments (see zip file)	Statistical Analyses_Other_EQ-5D-VAS/12444_Statistical

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Observed Drug Concentration (Cmax) of Capecitabine and 5-fluorouracil

End point title	Maximum Observed Drug Concentration (Cmax) of Capecitabine and 5-fluorouracil

End point description:

Maximum observed drug concentration, directly taken from analytical data.
Geometric mean and percentage geometric coefficient of variation (%CV) were reported.
In the listed categories below, 'N' signifies the number of evaluable subjects for the drug administered.
Please find the statistical analyses in the attachments below.

End point type	Other pre-specified

End point timeframe:

Pre-dose and 0.5, 1, 2, and 4 hours after capecitabine dosing at Cycle 2, Day 14

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[27]	104[28]		
Units: milligram per liter				
geometric mean (geometric coefficient of variation)				
Capecitabine (N=56, 84)	6.05 (± 79)	4.68 (± 72)		
5-fluorouracil (N=51, 84)	0.434 (± 105)	0.382 (± 67)		

Notes:

[27] - PKS

[28] - PKS

Attachments (see zip file)	12444_Statistical Analyses_Other_Cmax of 5- 12444_Statistical Analyses_Other_Cmax of

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Area Under Curve From Time Zero to Last Quantifiable Concentration (AUC[0-tlast]) of Capecitabine and 5-fluorouracil

End point title	Area Under Curve From Time Zero to Last Quantifiable Concentration (AUC[0-tlast]) of Capecitabine and 5-fluorouracil

End point description:

AUC(0-tlast) is defined as AUC from time 0 to the last data point, calculated up by linear trapezoidal rule, down by logarithmic trapezoidal rule. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In the listed categories below, 'N' signifies the number of evaluable subjects for the drug administered.
Please find the statistical analyses in the attachments below.

End point type	Other pre-specified

End point timeframe:

Pre-dose and 0.5, 1, 2, and 4 hours after capecitabine dosing at Cycle 2, Day 14

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[29]	104[30]		
Units: milligram*hour per liter				
geometric mean (geometric coefficient of variation)				
Capecitabine (N=56, 84)	7.12 (± 50)	5.13 (± 48)		
5-fluorouracil (N=51, 84)	0.621 (± 71)	0.557 (± 47)		

Notes:

[29] - PKS

[30] - PKS

Attachments (see zip file)	12444_Statistical Analyses_Other_AUC(0-tlast) 5- 12444_Statistical Analyses_Other_AUC(0-tlast) of

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-emergent Grade 3 and 4 Laboratory Abnormalities

End point title	Number of Subjects With Treatment-emergent Grade 3 and 4 Laboratory Abnormalities

End point description:

Hematological (anemia, hemoglobin, international normalized ratio [INR], lymphocyte, neutrophil, platelet, white blood cell [WBC]) and biochemical (ALT [alanine aminotransferase], AST [aspartate aminotransferase], GGT [gamma-glutamyl-transferase], bilirubin, lipase, serum amylase, hypoalbuminemia, hypocalcemia, hypokalemia, hyponatremia, hypophosphatemia, hyperglycemia,

hyperuricemia) evaluations were done.
CTCAE v4.0-Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to selfcare ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
CTCAE v4.0-Grade 4: life-threatening consequences; urgent intervention is indicated.
'99999' in the below table indicates that the lab parameter has no grade 4 (hemoglobin) or grade 3 (uric acid).

End point type	Other pre-specified

End point timeframe:

From the start of study treatment up to 30 days after the last dose

End point values	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260[31]	267[32]		
Units: Subjects				
Anemia (grade 3)	12	7		
Hemoglobin increased (grade 3)	0	3		
INR increased (grade 3)	9	9		
Lymphocyte count decreased (grade 3)	20	17		
Neutrophil count decreased (grade 3)	11	19		
Platelet count decreased (grade 3)	6	2		
WBC decreased (grade 3)	15	13		
ALT increased (grade 3)	4	5		
AST increased (grade 3)	10	5		
Alkaline phosphatase increased (grade 3)	12	13		
Bilirubin increased (grade 3)	9	1		
GGT increased (grade 3)	22	21		
Lipase increased (grade 3)	19	12		
Serum amylase increased (grade 3)	8	4		
Hypoalbuminemia (grade 3)	4	2		
Hypocalcemia (grade 3)	9	6		
Hypokalemia (grade 3)	20	11		
Hyponatremia (grade 3)	9	7		
Hypophosphatemia (grade 3)	46	14		
Hyperglycemia (grade 3)	9	10		
Hypercalcemia (grade 3)	0	2		
Hyperkalemia (grade 3)	0	2		
Lymphocyte count decreased (grade 4)	3	2		
Neutrophil count decreased (grade 4)	7	7		
Platelet count decreased (grade 4)	1	7		
WBC decreased (grade 4)	2	3		
ALT increased (grade 4)	3	0		
AST increased (grade 4)	1	0		
Bilirubin increased (grade 4)	1	2		
Creatinine increased (grade 4)	0	1		
GGT increased (grade 4)	6	2		
Lipase increased (grade 4)	5	1		

Hypocalcemia (grade 4)	1	2		
Hypokalemia (grade 4)	2	4		
Hyponatremia (grade 4)	3	0		
Hypophosphatemia (grade 4)	5	0		
Hyperuricemia (grade 4)	5	0		
Hypercalcemia (grade 4)	0	1		
Hyperkalemia (grade 4)	2	1		

Notes:

[31] - SAF

[32] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Received the first dose to 30 days after the last dose up to 3.2 years

Adverse event reporting additional description:

A treatment-emergent adverse event was defined as any event arising or worsening after the start of study drug administration until 30 days after the last study medication intake.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Sorafenib (Nexavar, BAY43-9006) + Capecitabine

Reporting group description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and sorafenib dose to a total daily dose of 800 mg for that subject.

Reporting group title	Placebo + Capecitabine

Reporting group description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Placebo matching with sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle copnsisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject.

Serious adverse events	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 260 (30.77%)	67 / 267 (25.09%)	
number of deaths (all causes)	141	138	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant pleural effusion			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to liver			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer metastatic			
subjects affected / exposed	1 / 260 (0.38%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Tumour associated fever			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral artery occlusion			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 260 (0.38%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurodesis			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatectomy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenectomy			

subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer surgery			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheterisation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 260 (0.77%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 260 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Mucosal inflammation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 260 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	3 / 260 (1.15%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 2	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	8 / 260 (3.08%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	1 / 9	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	6 / 260 (2.31%)	10 / 267 (3.75%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	1 / 260 (0.38%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 260 (1.15%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary microemboli			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 260 (1.15%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Tracheal obstruction extrinsic			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy lung			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count decreased			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			

subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 260 (0.00%)	5 / 267 (1.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 260 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lethargy			

subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system mass			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytotoxic oedema			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 260 (0.77%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 260 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	1 / 260 (0.38%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 260 (0.38%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 260 (1.15%)	8 / 267 (3.00%)	
occurrences causally related to treatment / all	3 / 3	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 260 (1.15%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen tongue			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	7 / 260 (2.69%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	5 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 260 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Gallbladder pain			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	2 / 260 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Jaundice cholestatic			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 260 (0.38%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 260 (1.15%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis viral			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 260 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus enterocolitis			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 260 (0.77%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 260 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 260 (0.38%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 260 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 260 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Sorafenib (Nexavar, BAY43-9006) + Capecitabine	Placebo + Capecitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	256 / 260 (98.46%)	248 / 267 (92.88%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	68 / 260 (26.15%)	15 / 267 (5.62%)	
occurrences (all)	91	20	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	49 / 260 (18.85%)	51 / 267 (19.10%)	
occurrences (all)	66	68	
Influenza like illness			

subjects affected / exposed	5 / 260 (1.92%)	15 / 267 (5.62%)	
occurrences (all)	9	19	
Fatigue			
subjects affected / exposed	76 / 260 (29.23%)	81 / 267 (30.34%)	
occurrences (all)	96	102	
Oedema peripheral			
subjects affected / exposed	9 / 260 (3.46%)	23 / 267 (8.61%)	
occurrences (all)	10	29	
Pyrexia			
subjects affected / exposed	28 / 260 (10.77%)	32 / 267 (11.99%)	
occurrences (all)	30	39	
Mucosal inflammation			
subjects affected / exposed	39 / 260 (15.00%)	18 / 267 (6.74%)	
occurrences (all)	48	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 260 (9.23%)	23 / 267 (8.61%)	
occurrences (all)	24	25	
Dyspnoea			
subjects affected / exposed	32 / 260 (12.31%)	40 / 267 (14.98%)	
occurrences (all)	34	46	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	19 / 260 (7.31%)	12 / 267 (4.49%)	
occurrences (all)	19	12	
Insomnia			
subjects affected / exposed	16 / 260 (6.15%)	12 / 267 (4.49%)	
occurrences (all)	16	12	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 260 (10.00%)	20 / 267 (7.49%)	
occurrences (all)	33	23	
Aspartate aminotransferase increased			
subjects affected / exposed	27 / 260 (10.38%)	22 / 267 (8.24%)	
occurrences (all)	32	25	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	14 / 260 (5.38%)	4 / 267 (1.50%)	
occurrences (all)	14	4	
Blood bilirubin increased			
subjects affected / exposed	19 / 260 (7.31%)	17 / 267 (6.37%)	
occurrences (all)	27	26	
Lipase increased			
subjects affected / exposed	13 / 260 (5.00%)	5 / 267 (1.87%)	
occurrences (all)	14	5	
Neutrophil count decreased			
subjects affected / exposed	14 / 260 (5.38%)	10 / 267 (3.75%)	
occurrences (all)	27	17	
White blood cell count decreased			
subjects affected / exposed	17 / 260 (6.54%)	12 / 267 (4.49%)	
occurrences (all)	23	19	
Weight decreased			
subjects affected / exposed	28 / 260 (10.77%)	12 / 267 (4.49%)	
occurrences (all)	28	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 260 (8.08%)	21 / 267 (7.87%)	
occurrences (all)	25	25	
Headache			
subjects affected / exposed	35 / 260 (13.46%)	36 / 267 (13.48%)	
occurrences (all)	49	45	
Dysgeusia			
subjects affected / exposed	12 / 260 (4.62%)	20 / 267 (7.49%)	
occurrences (all)	13	20	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	12 / 260 (4.62%)	24 / 267 (8.99%)	
occurrences (all)	22	46	
Anaemia			
subjects affected / exposed	30 / 260 (11.54%)	32 / 267 (11.99%)	
occurrences (all)	36	37	
Eye disorders			

Lacrimation increased			
subjects affected / exposed	0 / 260 (0.00%)	15 / 267 (5.62%)	
occurrences (all)	0	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	33 / 260 (12.69%)	28 / 267 (10.49%)	
occurrences (all)	39	41	
Abdominal pain upper			
subjects affected / exposed	35 / 260 (13.46%)	19 / 267 (7.12%)	
occurrences (all)	44	22	
Constipation			
subjects affected / exposed	53 / 260 (20.38%)	32 / 267 (11.99%)	
occurrences (all)	67	35	
Diarrhoea			
subjects affected / exposed	123 / 260 (47.31%)	98 / 267 (36.70%)	
occurrences (all)	287	186	
Dyspepsia			
subjects affected / exposed	17 / 260 (6.54%)	25 / 267 (9.36%)	
occurrences (all)	20	29	
Nausea			
subjects affected / exposed	101 / 260 (38.85%)	97 / 267 (36.33%)	
occurrences (all)	165	149	
Vomiting			
subjects affected / exposed	65 / 260 (25.00%)	53 / 267 (19.85%)	
occurrences (all)	118	83	
Stomatitis			
subjects affected / exposed	45 / 260 (17.31%)	24 / 267 (8.99%)	
occurrences (all)	54	29	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	44 / 260 (16.92%)	6 / 267 (2.25%)	
occurrences (all)	49	6	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	206 / 260 (79.23%)	158 / 267 (59.18%)	
occurrences (all)	277	227	
Dry skin			

subjects affected / exposed	19 / 260 (7.31%)	17 / 267 (6.37%)	
occurrences (all)	21	19	
Rash			
subjects affected / exposed	48 / 260 (18.46%)	22 / 267 (8.24%)	
occurrences (all)	58	29	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 260 (13.46%)	25 / 267 (9.36%)	
occurrences (all)	54	31	
Back pain			
subjects affected / exposed	32 / 260 (12.31%)	30 / 267 (11.24%)	
occurrences (all)	37	31	
Musculoskeletal pain			
subjects affected / exposed	10 / 260 (3.85%)	19 / 267 (7.12%)	
occurrences (all)	10	22	
Muscle spasms			
subjects affected / exposed	17 / 260 (6.54%)	5 / 267 (1.87%)	
occurrences (all)	24	5	
Pain in extremity			
subjects affected / exposed	23 / 260 (8.85%)	20 / 267 (7.49%)	
occurrences (all)	32	26	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 260 (9.23%)	24 / 267 (8.99%)	
occurrences (all)	30	30	
Upper respiratory tract infection			
subjects affected / exposed	13 / 260 (5.00%)	10 / 267 (3.75%)	
occurrences (all)	13	11	
Urinary tract infection			
subjects affected / exposed	16 / 260 (6.15%)	14 / 267 (5.24%)	
occurrences (all)	21	15	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	22 / 260 (8.46%)	15 / 267 (5.62%)	
occurrences (all)	24	19	
Decreased appetite			

subjects affected / exposed	53 / 260 (20.38%)	38 / 267 (14.23%)	
occurrences (all)	63	40	
Hypophosphataemia			
subjects affected / exposed	16 / 260 (6.15%)	4 / 267 (1.50%)	
occurrences (all)	22	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 December 2010	1. Several changes were made to the inclusion criterion concerning subjects who were (1) resistant to or failed prior taxane and an anthracycline OR (2) resistant to or failed prior taxane and for whom further anthracycline therapy was not indicated 2. Clarification of Consent to Long-Term Follow-up as information on overall survival (a secondary study objective) must be collected for all subjects 3. Subjects in the Long-term Follow-up Period should have regular computed tomography (CT) scans/magnetic resonance images (MRIs) until disease progression is documented 4. The IVRS used in this study has a built-in 3-day time period for the screening phase 5. Participation in the pharmacokinetics part of the study is not mandatory 6. To allow collection of pharmacokinetic samples at the scheduled Day 15 visit of appropriate cycles rather than Day 14 to enhance subject convenience by eliminating the need for this additional Day-14 visit 7. Anti-cancer drugs or device therapy for the treatment of breast cancer was prohibited within 4 weeks (28 days) or 5 half-lives, whichever was longer, prior to randomization 8. Allowed for the use of hematopoietic growth factor (only cycles subsequent to Cycle 1) in study subjects at the discretion of the investigator 9. To emphasize that a subject may decline to participate in the optional genetic biomarker study and yet still participate in the study trial.
03 May 2011	1. Clarifications on inclusion criteria regarding radiological evaluations, dose range of doxorubicin equivalents, eligibility following taxane and anthracycline therapy, discontinuation of prior chemotherapy, and pregnancy test 2. Clarifications on exclusion criteria regarding testing of subjects with unknown HER2 status, breast cancer types, subjects with brain metastases, baseline infections, prior radiation, excluded therapies, hemorrhage/bleeding events 3. To allow dose re-escalation of sorafenib/placebo only under the specific circumstances that are clearly defined in protocol 4. Included detailed guidelines on dose modifications, dose interruptions, and criteria for reintroduction of study medications in response to hematologic toxicities 5. To allow subjects for collection of pharmacokinetic samples, to attend their weekly clinic visit scheduled for Cycle 2/Day 15 to be conducted on Cycle 2/Day 14 6. To state that, if 10 slides are not available, fewer slides may be accepted for formalin-fixed paraffin embedded biopsy after discussion and agreement with the sponsor 7. In the interest of increasing the subject safety the protocol was modified to specify that subjects should undergo electrocardiograms (ECGs) on Day 1 of each cycle in addition to previously specified baseline, end-of-treatment, and as-required ECGs 8. The text on excluded concurrent therapies was clarified for consistency with the remainder of the protocol 9. The inclusion criterion regarding cancer-evaluation imaging at baseline was amended to allow a bone scan to be conducted up to 8 weeks before randomization to be used as the baseline scan 10. Screening study assessments should be performed within specified time periods relative to randomization 11. The instructions regarding HER2 status determination were changed in order to reflect the current practices regarding laboratory accreditation and usage of testing kits.

26 January 2012	Amendment 6 modified inclusion criteria defining the specification for prior treatment with taxane and anthracycline therapy in subjects who relapsed over 12 months following the end of treatment and clarifications were made. 1. The inclusion criterion regarding baseline cancer evaluation imaging was amended to allow the baseline bone scan to have been conducted up to 12 weeks before randomization 2. Detailed guidelines on baseline criteria for laboratory evaluations were provided. 3. Re-screening was permitted in cases in which the subject's eligibility for the study depended on the completion of further treatment, or to allow protocol compliant time lines for assessment or washout periods 4. Detailed guidelines on dose modifications, dose interruptions, and criteria for re-introduction of study medications in response to hematologic toxicities based on the CTCAE v4.0 grade of events
03 September 2013	1. The original assumption of a 1-sided alpha of 0.025, power of 98% and a randomization ratio of 1:1 between treatments for 363 PFS events (for progression events based on central radiology review) to detect a 66.7% increase in PFS was amended to an assumption of a 1-sided alpha of 0.025, power of 92.8% and a randomization ratio of 1:1 between treatments for 250 PFS events (including progression events based on central radiology review and death, if death occurs before disease progression) to detect a 66.7% increase in PFS 2. The following statement: "assuming a median OS of 12 months for the control group, approximately 270 deaths would be expected at the time of the PFS analysis. For the final analysis of OS, 405 deaths are projected to occur by approximately 43.3 months after the first subject is randomized" was amended to "assuming a median of 12 months for the control group, approximately 270 deaths would be expected at the time of the PFS analysis. However, at the time approximately 250 PFS events are reached, if the observed number of deaths is less than approximately 270, the trial will continue and remain blinded until approximately 270 deaths are observed. In such a case, the analysis of PFS will include all PFS data up to the later data cutoff date for approximately 270 deaths. For the final analysis of OS, and based on actual events, 405 deaths are projected to occur by approximately 56.2 months after the first subject was randomized." 3. DCR was added as a secondary end-point.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Results of exploratory analysis of biomarkers are anticipated in the month of February, 2016.
Occurrence of "±" in relation with geometric CV (%) is auto-generated and cannot be deleted.

Notes: