Clinical trial results:
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

Estudio fase 2b, multinacional, doble ciego y aleatorizado para evaluar la eficacia y seguridad de sorafenib frente a placebo administrados junto con capecitabina en pacientes con cáncer de mama localmente avanzado o metastásico

Summary

EudraCT number	2007-000290-32
Trial protocol	ES FR
Global end of trial date	27 March 2009

Results information

Result version number	v1 (current)
This version publication date	05 May 2022
First version publication date	05 May 2022
Summary attachment (see zip file)	Summary (0701-C~1.PDF)

Trial information

Trial identification

Sponsor protocol code	SOLTI-0701

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	SOLTI
Sponsor organisation address	C/ Balmes 89 3-7, Barcelona, Spain, 08008
Public contact	INVESTIGACION CLINICA, SOLTI, +34 933436302, regsolti@gruposolti.org
Scientific contact	INVESTIGACION CLINICA, SOLTI, 34 933436302, regsolti@gruposolti.org

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 November 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2009
Global end of trial reached?	Yes
Global end of trial date	27 March 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:
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.

Protection of trial subjects:

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.

Background therapy:

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-beta), 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].

Evidence for comparator: -

Actual start date of recruitment	28 May 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 80
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	Brazil: 112
Worldwide total number of subjects	229
EEA total number of subjects	117

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)	175
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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.

Pre-assignment

Screening details:

A total of 273 patients were screened: 44 patients failed screening and 2

Pre-assignment period milestones

Number of subjects started	229
Number of subjects completed	229

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Capecitabine + Sorafenib

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	SUB12474MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine will be administered at a dose of 1,000 mg/m2 orally, twice daily (morning and evening; equivalent to 2,000 mg/m2 total daily dose) for 14 days followed by a 7 day rest period

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	L01EX02
Other name	o
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg (2 tablets) BID continuous administration

Arm title	Group B

Arm description:

Capecitabine + Placebo

Arm type	Placebo

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	SUB12474MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine will be administered at a dose of 1,000 mg/m2 orally, twice daily (morning and evening; equivalent to 2,000 mg/m2 total daily dose) for 14 days followed by a 7 day rest period

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

Dosage and administration details:

(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

Number of subjects in period 1	Group A	Group B
Started	115	114
Completed	112	112
Not completed	3	2
Consent withdrawn by subject	2	-
Physician decision	-	1
Lost to follow-up	1	-
Not receive treatment	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description: Capecitabine + Sorafenib	
Reporting group title	Group B
Reporting group description: Capecitabine + Placebo	

Reporting group values	Group A	Group B	Total
Number of subjects	115	114	229
Age categorical Units: Subjects			
<40 years	7	11	18
40-64 years	81	76	157
65-74 years	23	19	42
>75 years	4	8	12
Age continuous Units: years			
geometric mean	55.1	55.4	
standard deviation	± 11.3	± 11.9	-
Gender categorical Units: Subjects			
Female	0	1	1
Male	115	113	228
Race Units: Subjects			
Caucasian	98	98	196
Black	5	7	12
Asian	2	0	2
American Indian or Native Alaskan	0	1	1
Mestizo	6	7	13
Mulato	4	0	4
Other	0	1	1
ECOG Performance Status Units: Subjects			
zero	79	77	156
one	34	34	68
>2	1	1	2
Missing	1	2	3
Measurable disease Units: Subjects			
Yes	95	96	191
No	20	17	37
Missing	0	1	1
Stage of disease at initial diagnosis Units: Subjects			
Stage I	8	9	17

Stage II	48	42	90
Stage III	49	47	96
Stage IV	10	14	24
Missing	0	2	2
Stage of disease at enrollment Units: Subjects			
Stage IIIB or IIIC	11	9	20
Stage IV	104	104	208
Missing	0	1	1
Months since metastatic diagnosis Units: Subjects			
0 - 12 Months	61	56	117
>12 - <24 Months	15	21	36
≥24 Months	39	36	75
Missing	0	1	1
Months from adjuvant treatment to recurrence or metastatic diagnosis Units: Subjects			
0 - 12 Months	37	50	87
>12 - <24 Months	16	15	31
≥24 Months	57	45	102
Missing	5	4	9
Location of metastatic sites Units: Subjects			
Non-visceral	28	30	58
Visceral	87	84	171
Number of metastatic sites Units: Subjects			
one	31	34	65
two	41	45	86
three	36	23	59
>3	7	11	18
Missing	0	1	1
Brain metastasis Units: Subjects			
Yes	1	1	2
No	114	112	226
Missing	0	1	1
Estrogen receptor Units: Subjects			
Positive	91	77	168
Negative	23	35	58
Unknown	1	1	2
Missing	0	1	1
Progesterone receptor Units: Subjects			
Positive	66	51	117
Negative	43	60	103
Unknown	6	2	8
Missing	0	1	1
Hormone receptor status			

Units: Subjects			
ER-, PgR-	20	33	53
ER+, PgR-	23	27	50
ER-, PgR+	3	2	5
ER+, PgR+	63	49	112
Unknown	6	2	8
Missing	0	1	1
Weight			
Units: kilogram(s)			
geometric mean	66.6	67.3	
standard deviation	± 13.4	± 12.6	-
BSA			
Units: square meter			
geometric mean	1.7	1.7	
standard deviation	± 0.2	± 0.1	-
Months since initial diagnosis			
Units: month			
geometric mean	71	63.9	
standard deviation	± 52.6	± 58.6	-
Months since metastatic diagnosis			
Units: month			
geometric mean	19.4	23.1	
standard deviation	± 22.2	± 31.3	-
FACT-B total score			
Units: unit(s)			
geometric mean	97.1	99.9	
standard deviation	± 21	± 16.7	-
FACT-B breast cancer subscale score			
Units: unit(s)			
geometric mean	22.6	23.2	
standard deviation	± 6.1	± 5.2	-

End points

End points reporting groups	
Reporting group title	Group A
Reporting group description: Capecitabine + Sorafenib	
Reporting group title	Group B
Reporting group description: Capecitabine + Placebo	

Primary: PFS	
End point title	PFS
End point description:	
End point type	Primary
End point timeframe: PFS will be measured from the date of randomization to the date of first documented disease progressionor the date of death due to any cause, if before progression	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	71		
Units: day				
median (confidence interval 95%)	183 (133 to 234)	121 (85 to 160)		

Attachments (see zip file)	Analyses of progression-free survival.docx

Statistical analyses

Statistical analysis title	Analyses of progression-free survival
Comparison groups	Group A v Group B
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0005
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.576

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.809

Statistical analysis title	Un-stratified analysis
Comparison groups	Group A v Group B
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.573
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.573
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.799

Statistical analysis title	NPT considered as PFS event
Comparison groups	Group A v Group B
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0005
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.599
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.438
upper limit	0.819

Statistical analysis title	NPT not considered PFS or censor PFS
Comparison groups	Group A v Group B

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.599
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.614
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.443
upper limit	0.851

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

At the time of the data cutoff date of 30 June 2010

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: day				
median (confidence interval 95%)	675 (550 to 812)	637 (489 to 734)		

Statistical analyses

Statistical analysis title	Analysis of overall survival
Comparison groups	Group B v Group A
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2075
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	1.228

Secondary: Time to progression

End point title	Time to progression

End point description:

End point type	Secondary

End point timeframe:

At the time of the data cutoff date of 27 March 2009, the 229 patients in the ITT population had 132 progression events.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: day				
geometric mean (confidence interval 95%)	207 (167 to 253)	126 (105 to 179)		

Statistical analyses

Statistical analysis title	Analysis of time to progression
Comparison groups	Group A v Group B
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0005
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.562
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.394
upper limit	0.799

Secondary: Overall response rate

End point title	Overall response rate

End point description:

End point type	Secondary

End point timeframe:

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.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: day				
median (confidence interval 91%)				
Treatment Group	188 (93 to 255)	124 (88 to 189)		

Statistical analyses

Statistical analysis title	Analysis of duration of response rate
Comparison groups	Group A v Group B
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1229
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.635
upper limit	1.127

Secondary: Overall response rate: Patients with measurable disease

End point title	Overall response rate: Patients with measurable disease

End point description:

End point type	Secondary

End point timeframe:

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.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	96		
Units: day				
median (confidence interval 95%)	188 (93 to 255)	124 (88 to 189)		

Statistical analyses

Statistical analysis title	Analysis of duration of response rate
Comparison groups	Group A v Group B
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0336
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.799
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.579
upper limit	1.102

Secondary: Duration of overall response

End point title	Duration of overall response

End point description:

End point type	Secondary

End point timeframe:

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).

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	114		
Units: day				
median (confidence interval 95%)	232 (147 to 255)	127 (87 to 189)		

Statistical analyses

Statistical analysis title	Analysis of duration of objective response
Comparison groups	Group A v Group B

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.877
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.665
upper limit	1.158

Secondary: Duration of overall response: Patients with Measurable Disease

End point title	Duration of overall response: Patients with Measurable Disease

End point description:

End point type	Secondary

End point timeframe:

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).

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	96		
Units: day				
median (confidence interval 95%)	232 (147 to 255)	127 (87 to 189)		

Statistical analyses

Statistical analysis title	Analysis of duration of objective response
Comparison groups	Group B v Group A
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0417
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.843

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.619
upper limit	1.147

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Since Inclusion until End of Treatment	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	3.0
Reporting groups	
Reporting group title	Sorafenib
Reporting group description: Sorafenib + Capecitabine	
Reporting group title	Placebo
Reporting group description: Sorafenib + Capecitabine	

Serious adverse events	Sorafenib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 112 (32.14%)	30 / 112 (26.79%)	
number of deaths (all causes)	5	5	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 112 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 112 (1.79%)	4 / 112 (3.57%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 112 (0.00%)	3 / 112 (2.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	4 / 112 (3.57%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 112 (2.68%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	14 / 112 (12.50%)	5 / 112 (4.46%)	
occurrences causally related to treatment / all	14 / 14	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 112 (0.89%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 112 (0.89%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sorafenib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 112 (99.11%)	106 / 112 (94.64%)	
Investigations			
Weight decreased			
subjects affected / exposed	9 / 112 (8.04%)	0 / 112 (0.00%)	
occurrences (all)	9	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 112 (16.96%)	13 / 112 (11.61%)	
occurrences (all)	19	13	
Nervous system disorders			

Headache			
subjects affected / exposed	18 / 112 (16.07%)	17 / 112 (15.18%)	
occurrences (all)	18	17	
Paraesthesia			
subjects affected / exposed	14 / 112 (12.50%)	10 / 112 (8.93%)	
occurrences (all)	14	10	
Dizziness			
subjects affected / exposed	7 / 112 (6.25%)	3 / 112 (2.68%)	
occurrences (all)	7	3	
Myalgia			
subjects affected / exposed	5 / 112 (4.46%)	6 / 112 (5.36%)	
occurrences (all)	5	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 112 (24.11%)	30 / 112 (26.79%)	
occurrences (all)	27	30	
Mucosal inflammation			
subjects affected / exposed	36 / 112 (32.14%)	20 / 112 (17.86%)	
occurrences (all)	36	20	
Fatigue			
subjects affected / exposed	16 / 112 (14.29%)	14 / 112 (12.50%)	
occurrences (all)	16	14	
Oedema peripheral			
subjects affected / exposed	11 / 112 (9.82%)	7 / 112 (6.25%)	
occurrences (all)	11	7	
Pyrexia			
subjects affected / exposed	10 / 112 (8.93%)	8 / 112 (7.14%)	
occurrences (all)	10	8	
Chest pain			
subjects affected / exposed	5 / 112 (4.46%)	9 / 112 (8.04%)	
occurrences (all)	5	9	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	11 / 112 (9.82%)	3 / 112 (2.68%)	
occurrences (all)	11	3	
Anaemia			

subjects affected / exposed	9 / 112 (8.04%)	6 / 112 (5.36%)	
occurrences (all)	9	6	
Thrombocytopenia			
subjects affected / exposed	2 / 112 (1.79%)	5 / 112 (4.46%)	
occurrences (all)	2	5	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 112 (0.89%)	8 / 112 (7.14%)	
occurrences (all)	1	8	
Lacrimation increased			
subjects affected / exposed	0 / 112 (0.00%)	6 / 112 (5.36%)	
occurrences (all)	0	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	57 / 112 (50.89%)	30 / 112 (26.79%)	
occurrences (all)	57	30	
Nausea			
subjects affected / exposed	30 / 112 (26.79%)	35 / 112 (31.25%)	
occurrences (all)	30	35	
Vomiting			
subjects affected / exposed	23 / 112 (20.54%)	16 / 112 (14.29%)	
occurrences (all)	23	16	
Constipation			
subjects affected / exposed	2 / 112 (1.79%)	11 / 112 (9.82%)	
occurrences (all)	25	11	
Abdominal pain upper			
subjects affected / exposed	17 / 112 (15.18%)	12 / 112 (10.71%)	
occurrences (all)	17	12	
Abdominal pain			
subjects affected / exposed	11 / 112 (9.82%)	11 / 112 (9.82%)	
occurrences (all)	11	11	
Stomatitis			
subjects affected / exposed	6 / 112 (5.36%)	7 / 112 (6.25%)	
occurrences (all)	6	7	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	12 / 112 (10.71%)	13 / 112 (11.61%)	
occurrences (all)	12	13	
Cough			
subjects affected / exposed	13 / 112 (11.61%)	7 / 112 (6.25%)	
occurrences (all)	13	7	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	86 / 112 (76.79%)	65 / 112 (58.04%)	
occurrences (all)	86	65	
Alopecia			
subjects affected / exposed	32 / 112 (28.57%)	5 / 112 (4.46%)	
occurrences (all)	32	5	
Dry skin			
subjects affected / exposed	10 / 112 (8.93%)	8 / 112 (7.14%)	
occurrences (all)	10	8	
Pruritus			
subjects affected / exposed	6 / 112 (5.36%)	5 / 112 (4.46%)	
occurrences (all)	6	5	
Skin hyperpigmentation			
subjects affected / exposed	2 / 112 (1.79%)	8 / 112 (7.14%)	
occurrences (all)	2	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 112 (8.04%)	6 / 112 (5.36%)	
occurrences (all)	9	6	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 112 (8.93%)	12 / 112 (10.71%)	
occurrences (all)	10	12	
Musculoskeletal pain			
subjects affected / exposed	13 / 112 (11.61%)	7 / 112 (6.25%)	
occurrences (all)	13	7	
Pain in extremity			
subjects affected / exposed	7 / 112 (6.25%)	6 / 112 (5.36%)	
occurrences (all)	7	6	

Arthralgia subjects affected / exposed occurrences (all)	5 / 112 (4.46%) 5	6 / 112 (5.36%) 6	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	22 / 112 (19.64%) 22	13 / 112 (11.61%) 13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2007	-Increase in the patient sample size is done in order to achieve 120 PFS events in a shorter time than with the original sample size of 180. -Include the health related quality of life HF-QoL in order to compare the effect of sorafenib and capecitabine versus placebo and capecitabine on hand-foot skin reaction symptoms
18 April 2008	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
18 April 2008	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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported