Clinical trial results:
A Randomized, Double Blinded, Multi-Center Phase 2 Study to Estimate the Efficacy and Evaluate the Safety and Tolerability of Sorafenib in Combination With AMG 386 or Placebo in Subjects With Metastatic Clear Cell Carcinoma of the Kidney

Summary

EudraCT number	2007-000147-98
Trial protocol	FR BE AT
Global end of trial date	10 June 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	20060159

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00467025
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	Final
Date of interim/final analysis	10 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the efficacy as measured by progression-free survival (PFS) of subjects receiving trebananib in combination with sorafenib compared to subjects receiving sorafenib plus placebo.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	48 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 26
Worldwide total number of subjects	152
EEA total number of subjects	110

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	103
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible subjects were men or women ≥ 18 years of age with histologically confirmed metastatic renal cell carcinoma (RCC) with a clear cell component, of low or intermediate risk according to the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk classification.

Pre-assignment

Screening details:

Two hundred one subjects were screened for enrollment, and 152 subjects were enrolled in the study: 51 in the Trebananib 3-mg/kg arm, 50 in the Trebananib 10-mg/kg arm, and 51 in the placebo arm. Subjects were stratified by risk classification (low vs intermediate) according to the MSKCC prognostic risk classification.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trebananib 3 mg/kg + Sorafenib

Arm description:

Subjects received trebananib 3 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).

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

Dosage and administration details:

Sorafenib was administered to subjects in all 3 arms of this clinical trial at a starting dose of 400 mg orally BID.

Investigational medicinal product name	Trebananib
Investigational medicinal product code	AMG 386
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion once weekly

Arm title	Trebananib 10 mg/kg + Sorafenib

Arm description:

Subjects received trebananib 10 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).

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

Dosage and administration details:

Sorafenib was administered to subjects in all 3 arms of this clinical trial at a starting dose of 400 mg orally BID.

Investigational medicinal product name	Trebananib
Investigational medicinal product code	AMG 386
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion once weekly

Arm title	Placebo + Sorafenib

Arm description:

Subjects received placebo IV infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion once weekly

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

Dosage and administration details:

Sorafenib was administered to subjects in all 3 arms of this clinical trial at a starting dose of 400 mg orally BID.

Number of subjects in period 1	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib
Started	51	50	51
Received Treatment	51	50	50
Crossover to open-label trebananib	0 [1]	0 [2]	32 [3]
Completed	51	50	50
Not completed	0	0	1
Did not receive study drug	-	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not applicable to Trebananib 3 mg/kg + Sorafenib treatment arm

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not applicable to Trebananib 10 mg/kg + Sorafenib treatment arm

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 32 subjects crossed over to open-label trebananib (10 mg/kg IV QW) and sorafenib upon disease progression

Baseline characteristics

Reporting groups	
Reporting group title	Trebananib 3 mg/kg + Sorafenib
Reporting group description:	
Subjects received trebananib 3 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).	
Reporting group title	Trebananib 10 mg/kg + Sorafenib
Reporting group description:	
Subjects received trebananib 10 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).	
Reporting group title	Placebo + Sorafenib
Reporting group description:	
Subjects received placebo IV infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).	

Reporting group values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib
Number of subjects	51	50	51
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	58.8	60.7	59.7
standard deviation	± 10.9	± 8.9	± 10.1
Gender categorical			
Units: Subjects			
Female	16	9	13
Male	35	41	38
Race			
Units: Subjects			
White or Caucasian	47	49	48
Black or African American	2	0	2
Hispanic or Latino	2	1	1
MSKCC Risk Classification			
The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk classification based on the following risk factors: - Karnofsky performance status < 80%; - Serum lactate dehydrogenase > 1.5 x upper limit of normal (ULN); - Serum hemoglobin < lower limit of normal (LLN) for their institutions; - Serum Calcium (corrected) > 10 mg/dL; - Time from diagnosis of RCC to first systemic treatment < 1 year. Low risk is defined as 0 risk factors; intermediate risk is defined as 1-2 risk factors.			
Units: Subjects			
Low	20	21	21
Intermediate	31	29	30

Reporting group values	Total		
Number of subjects	152		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	38		
Male	114		
Race Units: Subjects			
White or Caucasian	144		
Black or African American	4		
Hispanic or Latino	4		
MSKCC Risk Classification			
The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk classification based on the following risk factors: - Karnofsky performance status < 80%; - Serum lactate dehydrogenase > 1.5 x upper limit of normal (ULN); - Serum hemoglobin < lower limit of normal (LLN) for their institutions; - Serum Calcium (corrected) > 10 mg/dL; - Time from diagnosis of RCC to first systemic treatment < 1 year. Low risk is defined as 0 risk factors; intermediate risk is defined as 1-2 risk factors.			
Units: Subjects			
Low	62		
Intermediate	90		

End points

End points reporting groups

Reporting group title	Trebananib 3 mg/kg + Sorafenib
Reporting group description:	
Subjects received trebananib 3 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).	
Reporting group title	Trebananib 10 mg/kg + Sorafenib
Reporting group description:	
Subjects received trebananib 10 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).	
Reporting group title	Placebo + Sorafenib
Reporting group description:	
Subjects received placebo IV infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).	

Primary: Progression-Free Survival

End point title	Progression-Free Survival
End point description:	
Progression-free survival is calculated as the time between the randomization of protocol-specified treatment to the earliest date disease progression per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria or death, assessed by the Investigator. Progression-free survival was analyzed using the Kaplan-Meier method. Subjects who had not died and did not have an assessment of disease progression were censored at their last evaluable disease assessment date.	
End point type	Primary
End point timeframe:	
Radiological assessments were performd every 8 weeks for 2 years and then every 4 months thereafter. Data are reported as of the cut-off date of 28 February 2013; median time on study was 113 weeks.	

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	50	51	
Units: months				
median (confidence interval 80%)	8.5 (7.2 to 9.1)	9 (5.6 to 11)	9 (7.2 to 9.2)	

Statistical analyses

Statistical analysis title	Trebananib combined versus placebo
Statistical analysis description:	
A Cox regression model stratified by MSKCC prognostic risk classification was used to estimate the progression-free survival hazard ratio and 2-sided 80% confidence interval for both trebananib + sorafenib dose groups combined versus placebo + sorafenib. A hazard ratio of < 1.0 indicates a lower average event rate and longer time to event for the trebananib treatment group relative to the placebo group.	
Comparison groups	Trebananib 3 mg/kg + Sorafenib v Trebananib 10 mg/kg +

	Sorafenib v Placebo + Sorafenib
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.993
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.782
upper limit	1.261

Notes:

[1] - No adjustments for multiple testing were used. Stratifed by MSKCC risk category.

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective Response Rate (ORR) defined as either a confirmed complete response (CR) or partial response (PR) per modified RECIST (v 1.0) criteria (responder). A confirmed CR requires 2 assessments of CR at least 28 days apart. A confirmed PR requires 2 assessments at least 28 days apart of PR or CR. All subjects who did not meet the criteria for an objective response by the analysis cutoff date were considered non-responders.

End point type	Secondary

End point timeframe:

Radiological assessments were performd every 8 weeks for 2 years and then every 4 months thereafter. Data are reported as of the cut-off date of 28 February 2013; median time on study was 113 weeks.

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[2]	50[3]	51[4]	
Units: percentage of subjects				
number (confidence interval 80%)	37 (28 to 47)	40 (31 to 50)	27 (19 to 37)	

Notes:

[2] - Subjects with measurable disease at baseline

[3] - Subjects with measurable disease at baseline

[4] - Subjects with measurable disease at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of response was calculated only for those subjects with an objective response and is defined as the time from first confirmed objective response to first observed disease progression or death due to any cause. Subjects not meeting criteria for progression by the analysis data cutoff date or who had not

died were censored at their last evaluable disease assessment date. Duration of response was analyzed using the Kaplan-Meier method. "99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

Radiological assessments were performd every 8 weeks for 2 years and then every 4 months thereafter. Data are reported as of the primary analysis cut-off date of February 2010; median time on study was 75 weeks.

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19[5]	19[6]	13[7]	
Units: months				
median (confidence interval 80%)	7.4 (6.9 to 13)	8.9 (7.4 to 99999)	8.9 (7.4 to 12.9)	

Notes:

[5] - Subjects with a response

[6] - Subjects with a response

[7] - Subjects with a response

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Tumor Burden

End point title	Change in Tumor Burden

End point description:

Reduction in tumor burden was measured as the maximum percent reduction from Baseline (or, for subjects without a reduction, the minimum increase from Baseline) in the sum of the longest diameters (SLD) of target lesions. For each subject the maximum percent reduction in SLD from baseline to the post-baseline nadir was identified, and the mean of these values was then calculated.

End point type	Secondary

End point timeframe:

Radiological assessments were performd every 8 weeks for 2 years and then every 4 months thereafter. Data are reported as of the primary analysis cut-off date of 22 February 2010; median time on study was 72 weeks.

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47[8]	46[9]	47[10]	
Units: percent reduction				
arithmetic mean (confidence interval 80%)	-29.2 (-33.5 to -24.9)	-34.3 (-38.6 to -30)	-23.8 (-28 to -19.7)	

Notes:

[8] - Subjects with available data

[9] - Subjects with available data

[10] - Subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Time-adjusted Area Under the Curve (AUC) for Change From Baseline in Functional Assessment of Cancer Therapy-Kidney Symptom Index – 15 Items (FKSI-15) Scale Score

End point title	Time-adjusted Area Under the Curve (AUC) for Change From Baseline in Functional Assessment of Cancer Therapy-Kidney Symptom Index – 15 Items (FKSI-15) Scale Score

End point description:

The FKSI-15 is a validated symptom index for kidney cancer patients containing 15 questions, each scored on a 5-point scale (0 = not at all; 4 = very much). The FKSI-15 summary score ranges from 0 to 60, with higher scores indicating less severe symptoms or concerns.
The AUC was calculated using the trapezoidal rule and divided by the duration in weeks of the assessment period to obtain the time-adjusted AUC.
The patient-reported outcomes (PRO) analysis set includes all subjects with at least one PRO assessment prior to disease progression.

End point type	Secondary

End point timeframe:

Baseline to Week 57

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[11]	49[12]	50[13]	
Units: units on a scale				
least squares mean (confidence interval 95%)	-2 (-3.5 to -0.5)	-0.9 (-2.4 to 0.6)	-2.4 (-3.9 to -0.9)	

Notes:

[11] - PRO analysis set

[12] - PRO analysis set

[13] - PRO analysis set

Statistical analyses

Statistical analysis title	Difference Between Trebananib 3 mg/kg and 10 mg/kg

Statistical analysis description:

Mixed model analysis including fixed effects for treatment, visit, baseline PRO scale score, the interaction of treatment and visit, and a subject-specific random intercept.

Comparison groups	Trebananib 10 mg/kg + Sorafenib v Trebananib 3 mg/kg + Sorafenib

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	3.2

Statistical analysis title	Difference Between Trebananib 10 mg/kg and Placebo

Statistical analysis description:

Mixed model analysis including fixed effects for treatment, visit, baseline PRO scale score, the interaction of treatment and visit, and a subject-specific random intercept.

Comparison groups	Trebananib 10 mg/kg + Sorafenib v Placebo + Sorafenib
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	3.6

Statistical analysis title	Difference Between Trebananib 3 mg/kg and Placebo

Statistical analysis description:

Mixed model analysis including fixed effects for treatment, visit, baseline PRO scale score, the interaction of treatment and visit, and a subject-specific random intercept.

Comparison groups	Placebo + Sorafenib v Trebananib 3 mg/kg + Sorafenib
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	2.5

Secondary: Number of Subjects With Adverse Events (AE)

End point title	Number of Subjects With Adverse Events (AE)

End point description:

Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

End point type	Secondary

End point timeframe:

From first dose until 30 days after last dose of any study therapy. Median duration of trebananib treatment was 8.0, 9.5 and 9.5 months in each treatment group respectively.

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[14]	50[15]	50[16]	
Units: subjects				
Any adverse event	50	49	50	
Worst grade of 3	29	28	38	
Worst grade of 4	7	4	5	
Worst grade of 5	1	3	0	
Any serious adverse event	26	20	13	
Leading to discontinuation from therapy or study	7	8	3	
Any treatment-related adverse event	49	48	47	
Treatment-related worst grade of 3	27	25	39	
Treatment-related worst grade of 4	4	4	2	
Treatment-related worst grade of 5	1	0	0	
Serious treatment-related AE	16	14	7	
Treatment-related leading to discontinuation	6	5	2	

Notes:

[14] - Safety analysis set

[15] - Safety analysis set

[16] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Grade 3 or Higher Laboratory Toxicities

End point title	Number of Subjects with Grade 3 or Higher Laboratory Toxicities

End point description:

End point type	Secondary

End point timeframe:

From first dose of study treatment until the last dose.

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[17]	50[18]	50[19]	
Units: subjects				
Alanine amino transferase increased	1	1	2	
Albumin decreased	1	0	0	
Alkaline phosphatase increased	1	0	1	
Amylase increased	3	3	0	
Aspartate amino transferase increased	1	1	2	
Bicarbonate decreased	0	1	0	
Calcium decreased	1	3	2	
Creatinine increased	0	1	0	
Glucose increased	2	3	1	
Lipase increased	3	10	3	
Magnesium decreased	1	2	0	
Phosphorus decreased	12	9	9	
Potassium increased	1	1	3	
Potassium decreased	4	4	0	
Sodium decreased	2	3	0	
Absolute neutrophil count decreased	1	0	1	
Hemoglobin decreased	1	0	2	
Lymphocytes decreased	5	1	2	
Partial thromboplastin time increased	0	0	1	
Platelets decreased	0	0	1	
Segmented neutrophils decreased	1	0	0	
Total neutrophils decreased	0	0	1	
White blood cells decreased	0	0	0	

Notes:

[17] - Safety analysis set

[18] - Safety analysis set

[19] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Developed Anti-trebananib Antibodies Post-baseline

End point title	Number of Subjects Who Developed Anti-trebananib Antibodies Post-baseline

End point description:

Serum samples were first tested in an electrochemiluminescent immunoassay to detect and confirm the presence of antibodies capable of binding to trebananib. Samples that tested positive in the immunoassay were then subjected to an electrochemiluminescent receptor-binding assay to detect neutralizing or inhibitory effects of the antibodies in vitro. If a sample was positive in both assays, a subject was defined as positive for neutralizing antibodies. Additionally, if a sample was positive in the immunoassay, but negative in the receptor-binding assay, the sample was defined as positive for binding antibodies.

End point type	Secondary

End point timeframe:

Pre-dose, Cycle 3 (Week 9), and every 4 cycles (16 weeks) thereafter.

End point values	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	Placebo + Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[20]	48[21]	46[22]	
Units: subjects				
Binding antibody positive	2	1	3	
Neutralizing antibody positive	0	0	0	

Notes:

[20] - Subjects with a postbaseline result

[21] - Subjects with a postbaseline result

[22] - Subjects with a postbaseline result

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days after the last dose of any study therapy or up to the day before first dose of open-label trebananib. For crossover subjects, from start of open-label therapy until 30 days after the last dose of trebananib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo + Sorafenib

Reporting group description:

Subjects received placebo IV infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).

Reporting group title	Trebananib 3 mg/kg + Sorafenib

Reporting group description:

Subjects received trebananib 3 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).

Reporting group title	Trebananib 10 mg/kg + Sorafenib

Reporting group description:

Subjects received trebananib 10 mg/kg by intravenous infusion once a week and sorafenib at a starting dose of 400 mg orally twice a day (BID).

Reporting group title	Open-label Trebananib 10 mg/kg + Sorafenib

Reporting group description:

Subjects initially randomized to Placebo + Sorafenib who discontinued treatment due to disease progression crossed over and received trebananib 10 mg/kg by intravenous infusion once a week and the same dose of sorafenib that they were receiving immediately prior to documentation of disease progression.

Serious adverse events	Placebo + Sorafenib	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 50 (26.00%)	26 / 51 (50.98%)	20 / 50 (40.00%)
number of deaths (all causes)	11	31	31
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour necrosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular neoplasm			

subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device complication			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial restenosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary artery insufficiency			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 50 (4.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incoherent			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery thrombosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vascular thrombosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Large intestine perforation			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			

subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalised			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal disorder			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label Trebananib 10 mg/kg + Sorafenib		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 32 (31.25%)		
number of deaths (all causes)	26		
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Metastases to spine			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tumour necrosis			

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular neoplasm				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arterial thrombosis				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Death				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medical device complication				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Lung disorder				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Investigations				
Amylase increased				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Arterial restenosis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery insufficiency			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incoherent			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diplopia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal artery thrombosis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal vascular thrombosis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Visual acuity reduced			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal fissure			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct obstruction				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis toxic				

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Blister				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash generalised				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Urinary retention				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal disorder				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis bacterial				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				

subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Osteomyelitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo + Sorafenib	Trebananib 3 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	48 / 51 (94.12%)	48 / 50 (96.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	3 / 50 (6.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	3	0	1
Squamous cell carcinoma			
subjects affected / exposed	3 / 50 (6.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	3	0	4
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 50 (48.00%)	25 / 51 (49.02%)	22 / 50 (44.00%)
occurrences (all)	38	50	42
Hypotension			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	2 / 50 (4.00%)
occurrences (all)	1	4	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 50 (20.00%)	11 / 51 (21.57%)	14 / 50 (28.00%)
occurrences (all)	20	24	19
Chest discomfort			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	3 / 50 (6.00%)
occurrences (all)	1	0	3
Chest pain			
subjects affected / exposed	3 / 50 (6.00%)	6 / 51 (11.76%)	4 / 50 (8.00%)
occurrences (all)	4	9	6
Chills			
subjects affected / exposed	2 / 50 (4.00%)	4 / 51 (7.84%)	4 / 50 (8.00%)
occurrences (all)	2	4	6
Face oedema			
subjects affected / exposed	0 / 50 (0.00%)	4 / 51 (7.84%)	3 / 50 (6.00%)
occurrences (all)	0	5	7

Fatigue			
subjects affected / exposed	11 / 50 (22.00%)	12 / 51 (23.53%)	17 / 50 (34.00%)
occurrences (all)	20	24	27
General physical health deterioration			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Mucosal inflammation			
subjects affected / exposed	4 / 50 (8.00%)	10 / 51 (19.61%)	13 / 50 (26.00%)
occurrences (all)	4	14	25
Oedema peripheral			
subjects affected / exposed	5 / 50 (10.00%)	11 / 51 (21.57%)	7 / 50 (14.00%)
occurrences (all)	5	16	15
Pain			
subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	2 / 50 (4.00%)
occurrences (all)	5	1	2
Pyrexia			
subjects affected / exposed	8 / 50 (16.00%)	5 / 51 (9.80%)	9 / 50 (18.00%)
occurrences (all)	9	9	15
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 50 (10.00%)	2 / 51 (3.92%)	0 / 50 (0.00%)
occurrences (all)	6	2	0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 50 (10.00%)	7 / 51 (13.73%)	13 / 50 (26.00%)
occurrences (all)	10	7	21
Dysphonia			
subjects affected / exposed	2 / 50 (4.00%)	4 / 51 (7.84%)	6 / 50 (12.00%)
occurrences (all)	2	4	8
Dyspnoea			
subjects affected / exposed	6 / 50 (12.00%)	8 / 51 (15.69%)	10 / 50 (20.00%)
occurrences (all)	12	9	15

Dyspnoea exertional			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	1	3	3
Epistaxis			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	2 / 50 (4.00%)
occurrences (all)	5	1	3
Oropharyngeal pain			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	9 / 50 (18.00%)
occurrences (all)	0	3	11
Pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	4 / 50 (8.00%)
occurrences (all)	0	2	6
Productive cough			
subjects affected / exposed	3 / 50 (6.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	3	0	2
Rhinorrhoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	5 / 50 (10.00%)
occurrences (all)	0	1	7
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	5 / 50 (10.00%)
occurrences (all)	4	1	5
Depression			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	5 / 50 (10.00%)
occurrences (all)	2	3	6
Insomnia			
subjects affected / exposed	3 / 50 (6.00%)	9 / 51 (17.65%)	12 / 50 (24.00%)
occurrences (all)	7	9	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 50 (8.00%)	2 / 51 (3.92%)	1 / 50 (2.00%)
occurrences (all)	10	6	1
Amylase increased			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	3 / 50 (6.00%)
occurrences (all)	6	5	4
Aspartate aminotransferase increased			

subjects affected / exposed	4 / 50 (8.00%)	2 / 51 (3.92%)	1 / 50 (2.00%)
occurrences (all)	7	4	1
Blood creatinine increased			
subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	4 / 50 (8.00%)
occurrences (all)	5	2	4
Blood uric acid increased			
subjects affected / exposed	2 / 50 (4.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	2	2	4
Lipase increased			
subjects affected / exposed	4 / 50 (8.00%)	4 / 51 (7.84%)	3 / 50 (6.00%)
occurrences (all)	7	8	4
Weight decreased			
subjects affected / exposed	8 / 50 (16.00%)	7 / 51 (13.73%)	9 / 50 (18.00%)
occurrences (all)	13	12	13
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 50 (4.00%)	4 / 51 (7.84%)	3 / 50 (6.00%)
occurrences (all)	2	5	4
Dysgeusia			
subjects affected / exposed	2 / 50 (4.00%)	6 / 51 (11.76%)	2 / 50 (4.00%)
occurrences (all)	2	6	2
Headache			
subjects affected / exposed	7 / 50 (14.00%)	10 / 51 (19.61%)	5 / 50 (10.00%)
occurrences (all)	15	15	8
Hyperaesthesia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	6
Hypoaesthesia			
subjects affected / exposed	5 / 50 (10.00%)	2 / 51 (3.92%)	2 / 50 (4.00%)
occurrences (all)	7	7	2
Paraesthesia			

subjects affected / exposed	4 / 50 (8.00%)	2 / 51 (3.92%)	2 / 50 (4.00%)
occurrences (all)	7	5	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 50 (8.00%)	5 / 51 (9.80%)	3 / 50 (6.00%)
occurrences (all)	9	12	3
Thrombocytopenia			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	0 / 50 (0.00%)
occurrences (all)	7	3	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 50 (0.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences (all)	0	3	1
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	4 / 50 (8.00%)
occurrences (all)	0	17	4
Vision blurred			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	1	2	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 50 (10.00%)	9 / 51 (17.65%)	9 / 50 (18.00%)
occurrences (all)	8	18	12
Abdominal pain upper			
subjects affected / exposed	2 / 50 (4.00%)	5 / 51 (9.80%)	9 / 50 (18.00%)
occurrences (all)	2	6	11
Constipation			
subjects affected / exposed	12 / 50 (24.00%)	6 / 51 (11.76%)	13 / 50 (26.00%)
occurrences (all)	20	6	18
Diarrhoea			
subjects affected / exposed	28 / 50 (56.00%)	35 / 51 (68.63%)	36 / 50 (72.00%)
occurrences (all)	71	110	135
Dry mouth			
subjects affected / exposed	2 / 50 (4.00%)	2 / 51 (3.92%)	4 / 50 (8.00%)
occurrences (all)	2	2	5
Dyspepsia			

subjects affected / exposed	5 / 50 (10.00%)	5 / 51 (9.80%)	5 / 50 (10.00%)
occurrences (all)	6	5	18
Flatulence			
subjects affected / exposed	2 / 50 (4.00%)	1 / 51 (1.96%)	5 / 50 (10.00%)
occurrences (all)	2	4	6
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 50 (8.00%)	2 / 51 (3.92%)	2 / 50 (4.00%)
occurrences (all)	4	5	2
Haemorrhoids			
subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	3 / 50 (6.00%)
occurrences (all)	4	1	3
Nausea			
subjects affected / exposed	11 / 50 (22.00%)	16 / 51 (31.37%)	15 / 50 (30.00%)
occurrences (all)	15	29	26
Stomatitis			
subjects affected / exposed	8 / 50 (16.00%)	7 / 51 (13.73%)	10 / 50 (20.00%)
occurrences (all)	12	8	13
Vomiting			
subjects affected / exposed	9 / 50 (18.00%)	9 / 51 (17.65%)	10 / 50 (20.00%)
occurrences (all)	12	15	32
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 51 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Alopecia			
subjects affected / exposed	25 / 50 (50.00%)	23 / 51 (45.10%)	25 / 50 (50.00%)
occurrences (all)	38	30	29
Blister			
subjects affected / exposed	3 / 50 (6.00%)	2 / 51 (3.92%)	0 / 50 (0.00%)
occurrences (all)	13	3	0
Dry skin			
subjects affected / exposed	9 / 50 (18.00%)	12 / 51 (23.53%)	12 / 50 (24.00%)
occurrences (all)	12	14	24
Erythema			
subjects affected / exposed	6 / 50 (12.00%)	4 / 51 (7.84%)	7 / 50 (14.00%)
occurrences (all)	8	7	11

Hair texture abnormal			
subjects affected / exposed	1 / 50 (2.00%)	3 / 51 (5.88%)	1 / 50 (2.00%)
occurrences (all)	1	3	1
Hyperkeratosis			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	5 / 50 (10.00%)
occurrences (all)	4	13	6
Nail disorder			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	1 / 50 (2.00%)
occurrences (all)	0	4	1
Night sweats			
subjects affected / exposed	0 / 50 (0.00%)	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	4 / 50 (8.00%)	7 / 51 (13.73%)	3 / 50 (6.00%)
occurrences (all)	4	7	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	26 / 50 (52.00%)	23 / 51 (45.10%)	27 / 50 (54.00%)
occurrences (all)	72	88	78
Pruritus			
subjects affected / exposed	12 / 50 (24.00%)	13 / 51 (25.49%)	13 / 50 (26.00%)
occurrences (all)	18	19	17
Rash			
subjects affected / exposed	15 / 50 (30.00%)	16 / 51 (31.37%)	16 / 50 (32.00%)
occurrences (all)	28	30	29
Rash erythematous			
subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	4	1	0
Rash generalised			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	0	5	3
Rash maculo-papular			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences (all)	6	1	1
Skin exfoliation			

subjects affected / exposed	3 / 50 (6.00%)	3 / 51 (5.88%)	2 / 50 (4.00%)
occurrences (all)	4	4	8
Skin lesion			
subjects affected / exposed	1 / 50 (2.00%)	4 / 51 (7.84%)	2 / 50 (4.00%)
occurrences (all)	1	8	4
Skin toxicity			
subjects affected / exposed	6 / 50 (12.00%)	5 / 51 (9.80%)	2 / 50 (4.00%)
occurrences (all)	13	7	3
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 50 (8.00%)	7 / 51 (13.73%)	8 / 50 (16.00%)
occurrences (all)	6	16	22
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 50 (4.00%)	4 / 51 (7.84%)	5 / 50 (10.00%)
occurrences (all)	2	6	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 50 (22.00%)	5 / 51 (9.80%)	8 / 50 (16.00%)
occurrences (all)	16	6	13
Back pain			
subjects affected / exposed	6 / 50 (12.00%)	7 / 51 (13.73%)	9 / 50 (18.00%)
occurrences (all)	8	10	12
Bone pain			
subjects affected / exposed	2 / 50 (4.00%)	1 / 51 (1.96%)	4 / 50 (8.00%)
occurrences (all)	4	1	10
Flank pain			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences (all)	4	1	1
Muscle spasms			
subjects affected / exposed	4 / 50 (8.00%)	4 / 51 (7.84%)	2 / 50 (4.00%)
occurrences (all)	5	7	2
Muscular weakness			
subjects affected / exposed	0 / 50 (0.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	0	2	8
Musculoskeletal chest pain			

subjects affected / exposed	5 / 50 (10.00%)	6 / 51 (11.76%)	3 / 50 (6.00%)
occurrences (all)	5	10	3
Musculoskeletal pain			
subjects affected / exposed	6 / 50 (12.00%)	5 / 51 (9.80%)	8 / 50 (16.00%)
occurrences (all)	7	5	12
Myalgia			
subjects affected / exposed	6 / 50 (12.00%)	7 / 51 (13.73%)	1 / 50 (2.00%)
occurrences (all)	6	10	2
Neck pain			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	1	2	3
Pain in extremity			
subjects affected / exposed	9 / 50 (18.00%)	8 / 51 (15.69%)	11 / 50 (22.00%)
occurrences (all)	25	10	25
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	4 / 50 (8.00%)
occurrences (all)	1	2	5
Nasopharyngitis			
subjects affected / exposed	1 / 50 (2.00%)	4 / 51 (7.84%)	4 / 50 (8.00%)
occurrences (all)	1	10	6
Rhinitis			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	1	4	3
Upper respiratory tract infection			
subjects affected / exposed	3 / 50 (6.00%)	2 / 51 (3.92%)	1 / 50 (2.00%)
occurrences (all)	3	5	3
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)	3 / 51 (5.88%)	1 / 50 (2.00%)
occurrences (all)	0	5	1
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences (all)	3	1	1
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	11 / 50 (22.00%)	13 / 51 (25.49%)	20 / 50 (40.00%)
occurrences (all)	13	17	31
Dehydration			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	1	2	3
Hyperglycaemia			
subjects affected / exposed	3 / 50 (6.00%)	3 / 51 (5.88%)	4 / 50 (8.00%)
occurrences (all)	4	5	4
Hyperkalaemia			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	2 / 50 (4.00%)
occurrences (all)	2	4	3
Hyperuricaemia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 51 (1.96%)	4 / 50 (8.00%)
occurrences (all)	3	1	8
Hypoalbuminaemia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	4	3	0
Hypocalcaemia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 51 (3.92%)	3 / 50 (6.00%)
occurrences (all)	1	9	3
Hypokalaemia			
subjects affected / exposed	2 / 50 (4.00%)	6 / 51 (11.76%)	5 / 50 (10.00%)
occurrences (all)	2	10	6
Hyponatraemia			
subjects affected / exposed	0 / 50 (0.00%)	4 / 51 (7.84%)	2 / 50 (4.00%)
occurrences (all)	0	9	3
Hypophosphataemia			
subjects affected / exposed	3 / 50 (6.00%)	4 / 51 (7.84%)	1 / 50 (2.00%)
occurrences (all)	4	5	1

Non-serious adverse events	Open-label Trebananib 10 mg/kg + Sorafenib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 32 (87.50%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Melanocytic naevus subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Squamous cell carcinoma subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 16		
Hypotension subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		
Chest discomfort subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Chest pain subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 5		
Chills subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Face oedema subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Fatigue subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 8		
General physical health deterioration subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Mucosal inflammation			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	4		
Amylase increased			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Blood uric acid increased			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Hyperaesthesia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Thrombocytopenia			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	7 / 32 (21.88%)		
occurrences (all)	12		
Dry mouth			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	5		
Stomatitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Blister			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hair texture abnormal			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hyperkeratosis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		

Nail disorder				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Night sweats				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Pain of skin				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	4 / 32 (12.50%)			
occurrences (all)	11			
Pruritus				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Rash				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	2			
Rash erythematous				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Rash generalised				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Rash maculo-papular				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Skin exfoliation				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Skin lesion				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Skin toxicity				

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	5		
Bone pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Flank pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Myalgia			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	5		
Dehydration			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	3		
Hyperuricaemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	5		
Hypoalbuminaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2007	• The informed consent template: – In the Safety section: listed in detail the expected adverse events for sorafenib. – In the Alternative Therapy section: listed the alternative therapies available instead of indicating that the subject's doctor will discuss them. • Clarified the fasting requirements for sorafenib administration. • The wording on the storage conditions for sorafenib in the Pharmacy Guide (Appendix C) was revised to improve the consistency with the approved sorafenib label. • The confidentiality language in the pharmacogenetic consent was updated.
13 August 2008	• Updated Informed Consent and Introduction • Clarified unblinding details • Updated and clarified inclusion/exclusion criteria (serum creatinine, hemostatic function, prior malignancies, concurrent anticoagulation therapy, surgical procedures, pancreatitis) • Revised the sorafenib toxicity management instructions to allow for potential re-escalation of the sorafenib dose, at the investigator's discretion, in subjects who had undergone a dose reduction due to skin toxicity • Added requirement for all non-serious and serious adverse events to be collected from the time subjects signed the informed consent • Revised AMG 386/placebo pharmacokinetic and immunogenicity sample collection time points • Removed requirement that post-dose ECGs be performed in triplicate • Clarified that all ECG reports were to include the heart rate and QRS, QT, QTc, RR and PR intervals • Clarified time frames for screening safety laboratory assessments and radiological imaging • Required that baseline samples for immunogenicity, biomarker, and pharmacokinetic assessments be taken before infusion • Removed PRO Questionnaires from the screening procedures • Clarified the definition of cycles • Clarified how the dose of AMG 386 was to be calculated • Clarified that long-term follow-up radiographic assessment for subjects who discontinued treatment before disease progression would stop if subjects commence new therapy • Revised the hypothesis statement • Clarified on which CRFs deaths were to be reported and how signs and symptoms of disease progression were to be reported • Reduced the analyses performed on data subsets that were not deemed useful or relevant in this subject population • Included pairwise comparisons between treatment arms for data subsets of interest and removed closed testing procedures throughout the statistical analysis section • Added language encouraging sites to repeat confirmatory scans within 28 to 35 days after initial observation of a P

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported