Clinical trial results:
A Randomized, 4-Arm, Placebo-Controlled Phase 2 Trial of AMG 386 in Combination with Bevacizumab and Paclitaxel or AMG386 plus Paclitaxel as First-Line Therapy in Subjects with Her2-Negative, Metastatic or Locally Recurrent Breast Cancer

Summary

EudraCT number	2007-003384-51
Trial protocol	FR GB AT BE DK FI NL ES HU
Global end of trial date	19 May 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	20060341

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00511459
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	19 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the treatment effect as measured by progression free survival (PFS) of subjects receiving trebananib (at two doses) in combination with paclitaxel and bevacizumab relative to paclitaxel plus bevacizumab and placebo.

Protection of trial subjects:

This study was conducted in accordance with United States Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations Parts 11, 50, 54, 56, and 312 and 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	27 June 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
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	Netherlands: 2
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 53
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	India: 14
Country: Number of subjects enrolled	United States: 45

Worldwide total number of subjects	228
EEA total number of subjects	162

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	185
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 263 subjects were screened; 7 of these were rescreened, for a total of 270 screening assessments. Of these, 42 subjects failed screening and a total of 228 subjects were randomized to 1 of 4 treatment arms.

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

Blinding implementation details:

Treatment arms A, B, and C were double-blinded. Treatment arm D (Open-label [OL] Trebananib 10 mg/kg + Paclitaxel) was not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Paclitaxel + Bevacizumab

Arm description:

Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

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

Dosage and administration details:

Administered as an intravenous infustion (IV) infusion weekly

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

Dosage and administration details:

Paclitaxel 90 mg/m² administered as a ≥ 1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 10 mg/kg administered as a 90-minute IV infusion on Weeks 1 and 3 of each 4-week cycle.

Arm title	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab

Arm description:

Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Arm type	Experimental
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:

Trebananib administered by IV infusion weekly

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

Dosage and administration details:

Paclitaxel 90 mg/m² administered as a ≥ 1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 10 mg/kg administered as a 90-minute IV infusion on Weeks 1 and 3 of each 4-week cycle.

Arm title	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab

Arm description:

Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Arm type	Experimental
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:

Trebananib administered by IV infusion weekly

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

Dosage and administration details:

Paclitaxel 90 mg/m² administered as a ≥ 1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 10 mg/kg administered as a 90-minute IV infusion on Weeks 1 and 3 of each 4-week cycle.

Arm title	OL Trebananib 10 mg/kg + Paclitaxel

Arm description:

Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Arm type	Experimental
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:

Trebananib administered by IV infusion weekly

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

Dosage and administration details:

Paclitaxel 90 mg/m² administered as a ≥ 1-hour IV infusion on Weeks 1, 2, and 3 of every 4-week cycle.

Number of subjects in period 1	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab
Started	58	57	56
Received study drug	58	57	55
Completed	58	57	55
Not completed	0	0	1
Did not receive study drug	-	-	1

Number of subjects in period 1	OL Trebananib 10 mg/kg + Paclitaxel
Started	57
Received study drug	56
Completed	56
Not completed	1
Did not receive study drug	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	OL Trebananib 10 mg/kg + Paclitaxel

Reporting group description:

Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab
Number of subjects	58	57	56
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	51.4	56.2	55.1
standard deviation	± 11.1	± 10.6	± 10.5
Gender categorical Units: Subjects			
Female	58	57	56
Male	0	0	0
Race Units: Subjects			
White or Caucasian	48	55	45
Black or African American	2	0	1
Hispanic or Latino	1	0	2
Asian	6	2	7
Other	1	0	1
Extent of Disease Units: Subjects			
≤ 3 metastatic sites	48	47	47

≥ 3 metastatic sites	10	10	9
Prior Adjuvant Taxane Exposure Units: Subjects			
Yes	14	15	14
No	44	42	42

Reporting group values	OL Trebananib 10 mg/kg + Paclitaxel	Total	
Number of subjects	57	228	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.9		
standard deviation	± 11.8	-	
Gender categorical Units: Subjects			
Female	57	228	
Male	0	0	
Race Units: Subjects			
White or Caucasian	52	200	
Black or African American	1	4	
Hispanic or Latino	0	3	
Asian	4	19	
Other	0	2	
Extent of Disease Units: Subjects			
≤ 3 metastatic sites	44	186	
≥ 3 metastatic sites	13	42	
Prior Adjuvant Taxane Exposure Units: Subjects			
Yes	14	57	
No	43	171	

End points

End points reporting groups

Reporting group title	Placebo + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	OL Trebananib 10 mg/kg + Paclitaxel

Reporting group description:

Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Primary: Progression-free Survival

End point title	Progression-free Survival

End point description:

The time from the randomization date to the date of disease progression per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria assessed by the investigator or death from any cause. Progression-free survival was analyzed using the Kaplan-Meier method. Subjects not meeting the criteria for disease progression by the data cutoff date were censored at the last evaluable disease assessment date.

End point type	Primary

End point timeframe:

Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the cut-off date of 22 March 2013; median time on study was 118 weeks.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	57	56	57
Units: months				
median (confidence interval 80%)	12.7 (10.8 to 14.6)	9.2 (7.1 to 12.9)	12.8 (10.9 to 14.5)	8.6 (7.5 to 12.8)

Statistical analyses

Statistical analysis title	Blinded Trebananib Combined Versus Placebo

Statistical analysis description:

A Cox regression model stratified by adjuvant taxane exposure (yes or no) and number of metastatic sites (≤ 3 or > 3) was used to estimate the hazard ratio and 2-sided 80% confience intervals (CI) for both blinded trebananib + paclitaxel + bevacizumab dose groups combined versus placebo + paclitaxel + bevacizumab.
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 + Paclitaxel + Bevacizumab v Placebo + Paclitaxel + Bevacizumab v Trebananib 10 mg/kg + Paclitaxel + Bevacizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.532
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.118
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.889
upper limit	1.407

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.
The analysis of ORR was conducted on the Evaluable for Tumor Response analysis set consist of all subjects in the ITT analysis set with at least 1 unidimensionally measurable lesion at baseline per modified RECIST v 1.0.

End point type	Secondary

End point timeframe:

Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the cut-off date of 22 March 2013; median time on study was 118 weeks.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	49	41	46
Units: percentage of subjects				
number (confidence interval 80%)	59.5 (48.5 to 69.9)	49 (39 to 59)	70.7 (59.8 to 80.1)	45.7 (35.5 to 56.1)

Statistical analyses

Statistical analysis title	Trebananib Combined vs Placebo Response Rates

Statistical analysis description:

Wilson's score method with continuity correction was used to calculate 80% confidence intervals for the difference in response rates between both trebananib + paclitaxel + bevacizumab dose groups combined and the placebo + paclitaxel + bevacizumab group.

Comparison groups	Placebo + Paclitaxel + Bevacizumab v Trebananib 3 mg/kg + Paclitaxel + Bevacizumab v Trebananib 10 mg/kg + Paclitaxel + Bevacizumab
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in response rates
Point estimate	-0.6
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-13.2
upper limit	12.4

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Calculated only for those subjects with an objective response as the time from the first objective response (subsequently confirmed within no less than 4 weeks) to first observed disease progression per modified-RECIST criteria or death due to any cause.
Subjects not meeting these criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date. Duration of response was analyzed using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the primary analysis cut-off date of 17 May 2010; median time on study was 66 weeks.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	29	21
Units: months				
median (confidence interval 80%)	9 (7.4 to 9.4)	11 (7.4 to 11.2)	9.6 (7.9 to 11.2)	7.4 (6 to 12.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Time from the randomization date to the date of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at their last contact date. Overall survival was analyzed using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Data are reported as of the cut-off date of 22 March 2013; median time on study was 118 weeks.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	57	56	57
Units: months				
median (confidence interval 80%)	35.1 (25 to 37.3)	27.1 (24.2 to 35.1)	28.5 (24.5 to 32.3)	30.7 (25.1 to 34.9)

Statistical analyses

Statistical analysis title	Blinded Trebananib Combined Versus Placebo

Statistical analysis description:

A Cox regression model stratified by adjuvant taxane exposure (yes or no) and number of metastatic sites (≤ 3 or > 3) was used to estimate the hazard ratio and 2-sided 80% confience intervals (CI) for both blinded trebananib + paclitaxel + bevacizumab dose groups combined versus placebo + paclitaxel + bevacizumab.
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	Placebo + Paclitaxel + Bevacizumab v Trebananib 3 mg/kg + Paclitaxel + Bevacizumab v Trebananib 10 mg/kg + Paclitaxel + Bevacizumab

Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.046
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.823
upper limit	1.33

Secondary: Time to Response

End point title	Time to Response

End point description:

Time from randomization date to first objective response (subsequently confirmed within no less than 4 weeks); subjects with a best response of Stable Disease (SD) at their last evaluable assessment date were censored at this date and subjects with all other categories of best response while on study were censored at the maximum observed time to a first confirmed response among all responders. Time to reponse was analyzed using the Kaplan-Meier method for subjects with a confirmed objective response.

End point type	Secondary

End point timeframe:

Radiological assessments were performed every 8 weeks throughout the treatment period. Data are reported as of the primary analysis cut-off date of 17 May 2010; median time on study was 66 weeks.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	29	21
Units: weeks				
median (inter-quartile range (Q1-Q3))	8.7 (7.6 to 15.9)	8.1 (7.7 to 17)	8 (7.6 to 15.1)	15.3 (7.6 to 16.4)

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 performed every 8 weeks throughout the treatment period. Data are reported as of the primary analysis cut-off date of 17 May 2010; median time on study was 66 weeks.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40[1]	44[2]	40[3]	41[4]
Units: percent reduction				
median (inter-quartile range (Q1-Q3))	-50.3 (-66.3 to -28.2)	-49.1 (-65.5 to -22.3)	-52 (-76.8 to -34.1)	-41.1 (-59.5 to -16.4)

Notes:

[1] - Subjects with available data

[2] - Subjects with available data

[3] - Subjects with available data

[4] - Subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events

End point description:

Related, trebananib-related, paclitaxel-related, and bevacizumab-related adverse events are those events for which the investigator considered there to be a reasonable possibility that the event may have been caused by the study treatment, trebananib, paclitaxel, or bevacizumab respectively.
The intensity of each adverse event was 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/placebo treatment was 9.0, 6.0, 9.0 and 8.0 months in each treatment group respectively.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[5]	57[6]	55[7]	56[8]
Units: subjects				
Any adverse event (AE)	58	57	55	56
Worst grade of 3	37	35	40	30
Worst grade of 4	9	8	4	3
Worst grade of 5	1	3	1	4
Serious adverse event (SAE)	21	24	13	18

Leading to discontinuation from therapy or study	9	12	9	3
Any treatment-related adverse event	57	57	52	51
Treatment-related worst grade of 3	30	29	37	23
Treatment-related worst grade of 4	10	7	3	3
Treatment-related worst grade of 5	0	2	0	0
Serious treatment-related AE	12	13	8	6
Treatment-related leading to discontinuation	5	11	7	0

Notes:

[5] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel or bevacizumab.

[6] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel or bevacizumab.

[7] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel or bevacizumab.

[8] - All randomized subjects who received at least 1 dose of trebananib or paclitaxel.

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:

Textbook laboratory ranges were utilized to determine National Cancer Institute Common Toxicity Criteria version 3.0 (CTC) grades.

End point type	Secondary

End point timeframe:

From first dose of study treatment until the last dose, until the data cut-off date of 22 March 2013.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	57	55	56
Units: subjects				
Alanine amino transferase increased	3	2	0	1
Albumin decreased	0	0	0	1
Alkaline phosphatase increased	0	2	3	1
Aspartate amino transferase increased	2	3	2	2
Calcium decreased	0	0	3	0
Glucose increased	3	0	4	2
Glucose decreased	1	0	0	0
Magnesium increased	1	1	1	2
Magnesium decreased	1	1	0	0
Phosphorus decreased	3	3	0	2
Potassium increased	1	0	2	1
Potassium decreased	1	0	3	1
Sodium decreased	0	2	1	1
Hemoglobin decreased	0	0	1	2
International normalized ratio increased	1	0	1	0

Lymphocytes decreased	18	12	9	10
Partial thromboplastin time increased	2	5	1	3
Platelets decreased	1	1	1	1
Segmented neutrophils decreased	2	0	0	2
Total neutrophils decreased	13	8	14	11
White blood cells decreased	17	12	9	11

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Trebananib/Placebo, Paclitaxel and/or Bevacizumab Cycles Administered

End point title	Number of Trebananib/Placebo, Paclitaxel and/or Bevacizumab Cycles Administered

End point description:

Two subjects randomized to open label trebananib arm received at least one dose of bevacizumab due to dosing error.

End point type	Secondary

End point timeframe:

Up until the cut-off date date of 22 March 2013.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	57	55	56
Units: cycles				
median (inter-quartile range (Q1-Q3))				
Trebananib / Placebo	9 (5 to 13)	6 (4 to 13)	9 (6 to 16)	8 (5 to 14)
Paclitaxel	6 (5 to 9)	6 (4 to 7)	6 (4 to 9)	6 (5 to 8)
Bevacizumab	8.5 (5 to 14)	6 (4 to 13)	9 (5 to 16)	2.5 (2 to 3)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Trebananib/Placebo, Paclitaxel and/or Bevacizumab Dose Modifications

End point title	Number of Subjects with Trebananib/Placebo, Paclitaxel and/or Bevacizumab Dose Modifications

End point description:

If a subject developed a ≥ grade 3 (per CTCAE, version 3.0) toxicity considered to be related to trebananib, placebo, paclitaxel or bevacizumab, then trebananib, placebo paclitaxel or bevacizumab was to be held until the toxicity resolved. One permanent dose reduction of paclitaxel to 65 mg/m² was permitted. No dose level reductions for trebananib, placebo or bevacizumab were permitted.

Two subjects randomized to open label trebananib arm received at least one dose of bevacizumab due to dosing error.

End point type	Secondary

End point timeframe:

Up until the data cut-off date of 22 March 2013

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	57	55	56
Units: subjects				
Trebananib / placebo dose withholdings	49	39	47	44
Paclitaxel dose withholdings	49	43	44	46
Paclitaxel dose reductions	35	33	30	29
Bevacizumab dose withholdings	46	37	39	2

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Maximum and Minimum Observed Concentration of Trebaninib

End point title	Steady-State Maximum and Minimum Observed Concentration of Trebaninib[9]

End point description:

Steady-state serum concentration of trebaninib was measured at the end of infusion (maximum observed serum concentration [Cmax]) at Weeks 5 and 15; and predose (minimum observed serum concentration [Cmin], ie, prior to AMG 386 or placebo, bevacizumab, and paclitaxel infusion) on Weeks 5, 9, and 15. Serum concentration was measured using a validated enzyme-linked immunosorbent (ELISA) assay; The lower limit of quantification (LLOQ) of the serum assay was 20 ng/mL. Only samples collected at the protocol-specified dose regimen were included, and concentrations that were below the LLOQ were set to 0.

End point type	Secondary

End point timeframe:

Weeks 5, 9, and 15

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Observed Concentration of Trebaninib was assessed in the Trebaninib treatment groups only.

End point values	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	45	40	
Units: µg/mL				
median (full range (min-max))				

Cmax at Week 5 (N=44, 43, 40)	79 (52.2 to 167)	260 (65.2 to 809)	270 (125 to 376)	
Cmax at Week 15 (N=23, 20, 17)	90.7 (50.5 to 139)	296 (107 to 387)	294 (122 to 471)	
Cmin at Week 5 (N=46, 49, 38)	3.99 (1.5 to 17.7)	14.4 (1.63 to 43)	13.8 (0.808 to 30.1)	
Cmin at Week 9 (N=44, 45, 37)	4.04 (1.73 to 19.3)	14.6 (0.613 to 81.8)	14.6 (0.998 to 40.8)	
Cmin at Week 15 (N=36, 33, 28)	4.2 (1.38 to 22.6)	15.2 (6.43 to 34.7)	18 (2.18 to 40.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Maximum and Minimum Observed Concentration of Bevacizumab

End point title	Steady-State Maximum and Minimum Observed Concentration of Bevacizumab[10]

End point description:

Steady-state bevacizumab concentration was measured at the end of infusion (maximum observed serum concentration [Cmax]) on Weeks 5, and 15; and predose (minimum observed serum concentration [Cmin], ie, prior to AMG 386 or placebo, bevacizumab, and paclitaxel infusion) at Week 15. Serum bevacizumab samples were not measured in subjects receiving open-label trebaninib. Bevacizumab concentration was measured using a validated indirect ELISA; the LLOQ of the serum assay was 19.5 ng/mL.

End point type	Secondary

End point timeframe:

Weeks 5, 9 and 15

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Observed Concentration of Bevacizumab was assessed in the Bevacizumab treatment groups only.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	26	
Units: µg/mL				
median (full range (min-max))				
Cmax at Week 15 (N=18, 24, 19)	491 (232 to 727)	545 (327 to 785)	525 (93.6 to 901)	
Cmin at Week 15 (N=25, 24, 26)	218 (79.7 to 428)	200 (98.5 to 310)	193 (81.7 to 434)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Developed Antibodies to Trebaninib Post-Baseline

End point title	Number of Subjects Who Developed Antibodies to Trebaninib Post-Baseline

End point description:

Samples were first tested in a validated electrochemiluminescent (ECL) immunoassay to detect and confirm the presence of antibodies capable of binding to trebaninib. Samples that were positive in the immunoassay were then further tested in a validated ECL receptor-binding assay to measure 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:

Week 1, Week 5, Week 9, Week 23 and every 16 weeks thereafter until the data cut-off date of 22 March 2013.

End point values	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab	OL Trebananib 10 mg/kg + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56[11]	55[12]	52[13]	49[14]
Units: subjects				
Binding antibody positive	1	6	2	5
Neutralizing antibody positive	0	0	0	0

Notes:

[11] - Subjects with at least one post-baseline immunoassay result

[12] - Subjects with at least one post-baseline immunoassay result

[13] - Subjects with at least one post-baseline immunoassay result

[14] - Subjects with at least one post-baseline immunoassay 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded placebo administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded trebananib 3 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab

Reporting group description:

Subjects received blinded trebananib 10 mg/kg administered as an IV infusion weekly, paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle and bevacizumab 10 mg/kg IV on Weeks 1 and 3 of each 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Reporting group title	OL Trebananib 10 mg/kg QW + Paclitaxel

Reporting group description:

Subjects received open-label (OL) trebananib 10 mg/kg administered as an IV infusion weekly and paclitaxel 90 mg/m² IV infusion on Weeks 1, 2, and 3 of every 4-week cycle continuing until disease progression, clinical progression, unacceptable toxicity, withdrawal of subject consent, or death.

Serious adverse events	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 58 (36.21%)	24 / 57 (42.11%)	13 / 55 (23.64%)
number of deaths (all causes)	46	40	42
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
BREAST NEOPLASM			

subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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 EYE			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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 MENINGES			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
JUGULAR VEIN THROMBOSIS			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
VENOUS THROMBOSIS			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	0 / 55 (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

CHILLS			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
DEVICE DISLOCATION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
FATIGUE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
FEELING OF BODY TEMPERATURE CHANGE			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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	1 / 58 (1.72%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMPAIRED HEALING			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
LOCAL SWELLING			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
PAIN			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
PYREXIA			
subjects affected / exposed	3 / 58 (5.17%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
DYSPNOEA			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
EPISTAXIS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

LUNG INFILTRATION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NASAL SEPTUM PERFORATION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
PNEUMOTHORAX			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY DISTRESS			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
SUICIDAL IDEATION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
Injury, poisoning and procedural			

complications			
ANKLE FRACTURE			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
FEMORAL NECK FRACTURE			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT DISLOCATION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
RIB FRACTURE			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
Cardiac disorders			
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYCARDIA			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIOMYOPATHY			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
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	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
EPILEPSY			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
HEADACHE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
MENINGEAL DISORDER			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARESIS			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
SPEECH DISORDER			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOPENIA			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
NEUTROPENIA			
subjects affected / exposed	2 / 58 (3.45%)	2 / 57 (3.51%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
ASCITES			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
DIARRHOEA			

subjects affected / exposed	1 / 58 (1.72%)	2 / 57 (3.51%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL PERFORATION			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
ILEUS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 58 (1.72%)	2 / 57 (3.51%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
VOMITING			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	2 / 55 (3.64%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			

subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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 ACUTE			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
RASH			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBCUTANEOUS EMPHYSEMA			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	0 / 55 (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
BACK PAIN			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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

BONE PAIN			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
MUSCLE SPASMS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECK PAIN			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEONECROSIS			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
Infections and infestations			
ASPERGILLUS INFECTION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			

subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
CATHETER SITE INFECTION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
CELLULITIS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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
DEVICE RELATED SEPSIS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
GASTROENTERITIS			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
INFECTION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
LOBAR PNEUMONIA			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
NAIL INFECTION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (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 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
SKIN INFECTION			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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			
DECREASED APPETITE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
DEHYDRATION			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (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
FLUID RETENTION			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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
HYPOCALCAEMIA			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (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

Serious adverse events	OL Trebananib 10 mg/kg QW + Paclitaxel		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 56 (32.14%)		
number of deaths (all causes)	35		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
BREAST NEOPLASM			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
METASTASES TO EYE			

subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
METASTASES TO MENINGES				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
DEEP VEIN THROMBOSIS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
JUGULAR VEIN THROMBOSIS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VENOUS THROMBOSIS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
CHEST PAIN				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CHILLS				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DEVICE DISLOCATION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

FATIGUE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FEELING OF BODY TEMPERATURE CHANGE				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
IMPAIRED HEALING				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
INFLUENZA LIKE ILLNESS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LOCAL SWELLING				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PAIN				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PYREXIA				
subjects affected / exposed	2 / 56 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				

HYPERSENSITIVITY				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
COUGH				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
DYSPNOEA EXERTIONAL				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
EPISTAXIS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HAEMOPTYSIS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LUNG INFILTRATION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NASAL SEPTUM PERFORATION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

PNEUMOTHORAX				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY DISTRESS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY FAILURE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
DEPRESSION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUICIDAL IDEATION				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
ANKLE FRACTURE				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FEMORAL NECK FRACTURE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

JOINT DISLOCATION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RIB FRACTURE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
ATRIOVENTRICULAR BLOCK SECOND DEGREE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRADYCARDIA				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CARDIAC FAILURE CONGESTIVE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CARDIOMYOPATHY				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LEFT VENTRICULAR DYSFUNCTION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
MITRAL VALVE INCOMPETENCE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 56 (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	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
EPILEPSY			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HEADACHE			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MENINGEAL DISORDER			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PARESIS			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SPEECH DISORDER			
subjects affected / exposed	0 / 56 (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 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FEBRILE NEUTROPENIA				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
LEUKOPENIA				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
NEUTROPENIA				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
ABDOMINAL PAIN				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ASCITES				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL PERFORATION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ILEUS				

subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NAUSEA				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RECTAL HAEMORRHAGE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VOMITING				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
CHOLECYSTITIS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CHOLECYSTITIS ACUTE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HEPATIC FUNCTION ABNORMAL				

subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RASH			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUBCUTANEOUS EMPHYSEMA			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BACK PAIN			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BONE PAIN			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MUSCLE SPASMS			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

MUSCULOSKELETAL CHEST PAIN				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NECK PAIN				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OSTEONECROSIS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PAIN IN EXTREMITY				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PATHOLOGICAL FRACTURE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
ASPERGILLUS INFECTION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRONCHOPNEUMONIA				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CATHETER SITE INFECTION				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CELLULITIS				

subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DEVICE RELATED SEPSIS			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HERPES ZOSTER			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INFECTION			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NAIL INFECTION			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			

subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SEPSIS				
subjects affected / exposed	2 / 56 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
SKIN INFECTION				
subjects affected / exposed	0 / 56 (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 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
DECREASED APPETITE				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DEHYDRATION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
FLUID RETENTION				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
HYPOCALCAEMIA				

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo + Paclitaxel + Bevacizumab	Trebananib 3 mg/kg + Paclitaxel + Bevacizumab	Trebananib 10 mg/kg + Paclitaxel + Bevacizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 58 (96.55%)	57 / 57 (100.00%)	54 / 55 (98.18%)
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	3 / 55 (5.45%)
occurrences (all)	0	0	3
FLUSHING			
subjects affected / exposed	4 / 58 (6.90%)	3 / 57 (5.26%)	4 / 55 (7.27%)
occurrences (all)	23	8	30
HOT FLUSH			
subjects affected / exposed	12 / 58 (20.69%)	3 / 57 (5.26%)	5 / 55 (9.09%)
occurrences (all)	20	7	8
HYPERTENSION			
subjects affected / exposed	22 / 58 (37.93%)	22 / 57 (38.60%)	24 / 55 (43.64%)
occurrences (all)	42	33	42
HYPOTENSION			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
LYMPHOEDEMA			
subjects affected / exposed	4 / 58 (6.90%)	7 / 57 (12.28%)	8 / 55 (14.55%)
occurrences (all)	5	9	10
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	19 / 58 (32.76%)	19 / 57 (33.33%)	17 / 55 (30.91%)
occurrences (all)	87	74	76
CATHETER SITE PAIN			

subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	3 / 55 (5.45%)
occurrences (all)	1	0	3
CHEST DISCOMFORT			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	4 / 55 (7.27%)
occurrences (all)	1	1	5
CHEST PAIN			
subjects affected / exposed	5 / 58 (8.62%)	4 / 57 (7.02%)	3 / 55 (5.45%)
occurrences (all)	5	5	6
FACE OEDEMA			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	6 / 55 (10.91%)
occurrences (all)	0	5	6
FATIGUE			
subjects affected / exposed	22 / 58 (37.93%)	33 / 57 (57.89%)	27 / 55 (49.09%)
occurrences (all)	40	67	44
GAIT DISTURBANCE			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	2 / 55 (3.64%)
occurrences (all)	3	1	2
GENERALISED OEDEMA			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	1	0	2
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	4 / 58 (6.90%)	1 / 57 (1.75%)	4 / 55 (7.27%)
occurrences (all)	5	1	4
MUCOSAL INFLAMMATION			
subjects affected / exposed	13 / 58 (22.41%)	11 / 57 (19.30%)	9 / 55 (16.36%)
occurrences (all)	21	20	14
OEDEMA PERIPHERAL			
subjects affected / exposed	11 / 58 (18.97%)	26 / 57 (45.61%)	18 / 55 (32.73%)
occurrences (all)	26	55	37
PAIN			
subjects affected / exposed	9 / 58 (15.52%)	6 / 57 (10.53%)	2 / 55 (3.64%)
occurrences (all)	11	6	3
PYREXIA			
subjects affected / exposed	11 / 58 (18.97%)	9 / 57 (15.79%)	14 / 55 (25.45%)
occurrences (all)	19	12	22
Immune system disorders			

DRUG HYPERSENSITIVITY			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences (all)	3	1	2
HYPERSENSITIVITY			
subjects affected / exposed	1 / 58 (1.72%)	3 / 57 (5.26%)	4 / 55 (7.27%)
occurrences (all)	2	3	5
Reproductive system and breast disorders			
VULVOVAGINAL DRYNESS			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	0 / 55 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	20 / 58 (34.48%)	15 / 57 (26.32%)	18 / 55 (32.73%)
occurrences (all)	40	23	36
DYSPHONIA			
subjects affected / exposed	19 / 58 (32.76%)	8 / 57 (14.04%)	11 / 55 (20.00%)
occurrences (all)	37	10	13
DYSPNOEA			
subjects affected / exposed	11 / 58 (18.97%)	11 / 57 (19.30%)	12 / 55 (21.82%)
occurrences (all)	20	22	23
DYSPNOEA EXERTIONAL			
subjects affected / exposed	6 / 58 (10.34%)	3 / 57 (5.26%)	4 / 55 (7.27%)
occurrences (all)	10	5	5
EPISTAXIS			
subjects affected / exposed	29 / 58 (50.00%)	35 / 57 (61.40%)	25 / 55 (45.45%)
occurrences (all)	55	53	44
NASAL DRYNESS			
subjects affected / exposed	5 / 58 (8.62%)	4 / 57 (7.02%)	1 / 55 (1.82%)
occurrences (all)	5	5	1
OROPHARYNGEAL PAIN			
subjects affected / exposed	11 / 58 (18.97%)	11 / 57 (19.30%)	6 / 55 (10.91%)
occurrences (all)	17	14	10
PLEURAL EFFUSION			
subjects affected / exposed	0 / 58 (0.00%)	4 / 57 (7.02%)	3 / 55 (5.45%)
occurrences (all)	0	4	4
PRODUCTIVE COUGH			

subjects affected / exposed	2 / 58 (3.45%)	2 / 57 (3.51%)	2 / 55 (3.64%)
occurrences (all)	2	2	2
RHINORRHOEA			
subjects affected / exposed	6 / 58 (10.34%)	6 / 57 (10.53%)	10 / 55 (18.18%)
occurrences (all)	10	6	13
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	6 / 58 (10.34%)	4 / 57 (7.02%)	6 / 55 (10.91%)
occurrences (all)	7	7	6
DEPRESSION			
subjects affected / exposed	2 / 58 (3.45%)	4 / 57 (7.02%)	5 / 55 (9.09%)
occurrences (all)	2	5	5
INSOMNIA			
subjects affected / exposed	10 / 58 (17.24%)	8 / 57 (14.04%)	9 / 55 (16.36%)
occurrences (all)	13	10	10
SLEEP DISORDER			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences (all)	8	1	1
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 58 (3.45%)	4 / 57 (7.02%)	3 / 55 (5.45%)
occurrences (all)	2	7	4
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 58 (5.17%)	4 / 57 (7.02%)	2 / 55 (3.64%)
occurrences (all)	3	9	2
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	4 / 55 (7.27%)
occurrences (all)	0	3	9
WEIGHT DECREASED			
subjects affected / exposed	5 / 58 (8.62%)	6 / 57 (10.53%)	4 / 55 (7.27%)
occurrences (all)	8	12	13
WEIGHT INCREASED			
subjects affected / exposed	1 / 58 (1.72%)	2 / 57 (3.51%)	3 / 55 (5.45%)
occurrences (all)	2	3	5
WHITE BLOOD CELL COUNT DECREASED			

subjects affected / exposed	4 / 58 (6.90%)	0 / 57 (0.00%)	2 / 55 (3.64%)
occurrences (all)	8	0	6
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	3 / 58 (5.17%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	3	0	1
TACHYCARDIA			
subjects affected / exposed	1 / 58 (1.72%)	3 / 57 (5.26%)	3 / 55 (5.45%)
occurrences (all)	1	3	3
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	5 / 58 (8.62%)	11 / 57 (19.30%)	8 / 55 (14.55%)
occurrences (all)	6	14	11
DYSAESTHESIA			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	2 / 55 (3.64%)
occurrences (all)	3	1	4
DYSGEUSIA			
subjects affected / exposed	18 / 58 (31.03%)	10 / 57 (17.54%)	17 / 55 (30.91%)
occurrences (all)	34	15	23
HEADACHE			
subjects affected / exposed	27 / 58 (46.55%)	24 / 57 (42.11%)	16 / 55 (29.09%)
occurrences (all)	88	48	43
HYPOAESTHESIA			
subjects affected / exposed	5 / 58 (8.62%)	4 / 57 (7.02%)	4 / 55 (7.27%)
occurrences (all)	6	5	4
MEMORY IMPAIRMENT			
subjects affected / exposed	4 / 58 (6.90%)	0 / 57 (0.00%)	2 / 55 (3.64%)
occurrences (all)	4	0	2
NEUROPATHY PERIPHERAL			
subjects affected / exposed	16 / 58 (27.59%)	23 / 57 (40.35%)	19 / 55 (34.55%)
occurrences (all)	49	61	68
PARAESTHESIA			
subjects affected / exposed	8 / 58 (13.79%)	10 / 57 (17.54%)	11 / 55 (20.00%)
occurrences (all)	17	19	33
PERIPHERAL SENSORY NEUROPATHY			

subjects affected / exposed	10 / 58 (17.24%)	12 / 57 (21.05%)	11 / 55 (20.00%)
occurrences (all)	24	36	28
POLYNEUROPATHY			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	3	0	0
SCIATICA			
subjects affected / exposed	4 / 58 (6.90%)	2 / 57 (3.51%)	3 / 55 (5.45%)
occurrences (all)	4	2	5
SPEECH DISORDER			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	0 / 55 (0.00%)
occurrences (all)	0	3	0
SYNCOPE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences (all)	0	1	1
TREMOR			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	5 / 55 (9.09%)
occurrences (all)	0	1	5
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	5 / 58 (8.62%)	5 / 57 (8.77%)	4 / 55 (7.27%)
occurrences (all)	22	7	17
LEUKOPENIA			
subjects affected / exposed	4 / 58 (6.90%)	3 / 57 (5.26%)	4 / 55 (7.27%)
occurrences (all)	35	6	8
NEUTROPENIA			
subjects affected / exposed	24 / 58 (41.38%)	23 / 57 (40.35%)	19 / 55 (34.55%)
occurrences (all)	135	61	82
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	2 / 55 (3.64%)
occurrences (all)	3	2	3
TINNITUS			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	0 / 55 (0.00%)
occurrences (all)	3	3	0
VERTIGO			

subjects affected / exposed	3 / 58 (5.17%)	10 / 57 (17.54%)	2 / 55 (3.64%)
occurrences (all)	4	13	2
Eye disorders			
DRY EYE			
subjects affected / exposed	4 / 58 (6.90%)	1 / 57 (1.75%)	2 / 55 (3.64%)
occurrences (all)	4	1	3
EYELID OEDEMA			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	2 / 55 (3.64%)
occurrences (all)	0	2	2
LACRIMATION INCREASED			
subjects affected / exposed	5 / 58 (8.62%)	5 / 57 (8.77%)	5 / 55 (9.09%)
occurrences (all)	6	7	5
VISION BLURRED			
subjects affected / exposed	1 / 58 (1.72%)	3 / 57 (5.26%)	4 / 55 (7.27%)
occurrences (all)	1	3	4
VISUAL ACUITY REDUCED			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	1 / 55 (1.82%)
occurrences (all)	3	2	1
VISUAL IMPAIRMENT			
subjects affected / exposed	2 / 58 (3.45%)	4 / 57 (7.02%)	2 / 55 (3.64%)
occurrences (all)	3	4	7
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 58 (1.72%)	7 / 57 (12.28%)	5 / 55 (9.09%)
occurrences (all)	1	9	5
ABDOMINAL PAIN			
subjects affected / exposed	15 / 58 (25.86%)	13 / 57 (22.81%)	14 / 55 (25.45%)
occurrences (all)	36	17	28
ABDOMINAL PAIN UPPER			
subjects affected / exposed	13 / 58 (22.41%)	11 / 57 (19.30%)	8 / 55 (14.55%)
occurrences (all)	19	12	17
CONSTIPATION			
subjects affected / exposed	22 / 58 (37.93%)	24 / 57 (42.11%)	14 / 55 (25.45%)
occurrences (all)	36	31	25
DENTAL CARIES			

subjects affected / exposed	3 / 58 (5.17%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	4	0	0
DIARRHOEA			
subjects affected / exposed	35 / 58 (60.34%)	31 / 57 (54.39%)	27 / 55 (49.09%)
occurrences (all)	83	59	57
DRY MOUTH			
subjects affected / exposed	5 / 58 (8.62%)	4 / 57 (7.02%)	6 / 55 (10.91%)
occurrences (all)	7	4	11
DYSPEPSIA			
subjects affected / exposed	11 / 58 (18.97%)	8 / 57 (14.04%)	9 / 55 (16.36%)
occurrences (all)	14	25	16
DYSPHAGIA			
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)	4 / 55 (7.27%)
occurrences (all)	4	1	4
FLATULENCE			
subjects affected / exposed	2 / 58 (3.45%)	3 / 57 (5.26%)	3 / 55 (5.45%)
occurrences (all)	2	3	3
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	5 / 58 (8.62%)	3 / 57 (5.26%)	5 / 55 (9.09%)
occurrences (all)	6	4	5
GINGIVAL BLEEDING			
subjects affected / exposed	5 / 58 (8.62%)	1 / 57 (1.75%)	2 / 55 (3.64%)
occurrences (all)	6	2	2
HAEMORRHOIDS			
subjects affected / exposed	3 / 58 (5.17%)	6 / 57 (10.53%)	3 / 55 (5.45%)
occurrences (all)	5	6	3
NAUSEA			
subjects affected / exposed	26 / 58 (44.83%)	25 / 57 (43.86%)	34 / 55 (61.82%)
occurrences (all)	70	58	90
ORAL PAIN			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	1 / 55 (1.82%)
occurrences (all)	0	5	1
STOMATITIS			
subjects affected / exposed	13 / 58 (22.41%)	12 / 57 (21.05%)	10 / 55 (18.18%)
occurrences (all)	21	16	13

TOOTHACHE			
subjects affected / exposed	2 / 58 (3.45%)	3 / 57 (5.26%)	4 / 55 (7.27%)
occurrences (all)	2	4	4
VOMITING			
subjects affected / exposed	17 / 58 (29.31%)	21 / 57 (36.84%)	19 / 55 (34.55%)
occurrences (all)	45	37	40
Hepatobiliary disorders			
HEPATIC PAIN			
subjects affected / exposed	1 / 58 (1.72%)	2 / 57 (3.51%)	1 / 55 (1.82%)
occurrences (all)	1	3	1
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	4 / 58 (6.90%)	5 / 57 (8.77%)	4 / 55 (7.27%)
occurrences (all)	8	5	4
ALOPECIA			
subjects affected / exposed	36 / 58 (62.07%)	35 / 57 (61.40%)	35 / 55 (63.64%)
occurrences (all)	64	62	53
DERMATITIS ACNEIFORM			
subjects affected / exposed	5 / 58 (8.62%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	6	0	1
DRY SKIN			
subjects affected / exposed	6 / 58 (10.34%)	5 / 57 (8.77%)	4 / 55 (7.27%)
occurrences (all)	10	5	5
ERYTHEMA			
subjects affected / exposed	5 / 58 (8.62%)	6 / 57 (10.53%)	10 / 55 (18.18%)
occurrences (all)	9	13	26
NAIL DISCOLOURATION			
subjects affected / exposed	2 / 58 (3.45%)	3 / 57 (5.26%)	1 / 55 (1.82%)
occurrences (all)	2	3	2
NAIL DISORDER			
subjects affected / exposed	14 / 58 (24.14%)	20 / 57 (35.09%)	20 / 55 (36.36%)
occurrences (all)	49	39	47
NAIL TOXICITY			
subjects affected / exposed	4 / 58 (6.90%)	6 / 57 (10.53%)	2 / 55 (3.64%)
occurrences (all)	8	11	10
PAIN OF SKIN			

subjects affected / exposed	1 / 58 (1.72%)	3 / 57 (5.26%)	0 / 55 (0.00%)
occurrences (all)	1	3	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	2 / 55 (3.64%)
occurrences (all)	2	1	3
PRURITUS			
subjects affected / exposed	6 / 58 (10.34%)	7 / 57 (12.28%)	12 / 55 (21.82%)
occurrences (all)	8	9	12
RASH			
subjects affected / exposed	17 / 58 (29.31%)	13 / 57 (22.81%)	13 / 55 (23.64%)
occurrences (all)	51	17	20
SKIN DISCOLOURATION			
subjects affected / exposed	1 / 58 (1.72%)	4 / 57 (7.02%)	0 / 55 (0.00%)
occurrences (all)	1	4	0
SKIN FISSURES			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	2	0	0
SKIN HYPERPIGMENTATION			
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)	4 / 55 (7.27%)
occurrences (all)	3	1	4
Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	6 / 58 (10.34%)	1 / 57 (1.75%)	5 / 55 (9.09%)
occurrences (all)	7	1	7
PROTEINURIA			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	3 / 55 (5.45%)
occurrences (all)	5	3	3
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	16 / 58 (27.59%)	22 / 57 (38.60%)	15 / 55 (27.27%)
occurrences (all)	26	36	29
BACK PAIN			
subjects affected / exposed	13 / 58 (22.41%)	15 / 57 (26.32%)	13 / 55 (23.64%)
occurrences (all)	30	27	17
BONE PAIN			

subjects affected / exposed	11 / 58 (18.97%)	3 / 57 (5.26%)	6 / 55 (10.91%)
occurrences (all)	15	5	12
MUSCLE FATIGUE			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	2 / 55 (3.64%)
occurrences (all)	0	1	5
MUSCLE SPASMS			
subjects affected / exposed	10 / 58 (17.24%)	2 / 57 (3.51%)	4 / 55 (7.27%)
occurrences (all)	12	3	6
MUSCULAR WEAKNESS			
subjects affected / exposed	4 / 58 (6.90%)	3 / 57 (5.26%)	2 / 55 (3.64%)
occurrences (all)	9	3	3
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	6 / 58 (10.34%)	8 / 57 (14.04%)	4 / 55 (7.27%)
occurrences (all)	7	10	4
MUSCULOSKELETAL PAIN			
subjects affected / exposed	9 / 58 (15.52%)	6 / 57 (10.53%)	7 / 55 (12.73%)
occurrences (all)	15	8	15
MUSCULOSKELETAL STIFFNESS			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences (all)	4	2	1
MYALGIA			
subjects affected / exposed	15 / 58 (25.86%)	16 / 57 (28.07%)	13 / 55 (23.64%)
occurrences (all)	38	32	35
NECK PAIN			
subjects affected / exposed	3 / 58 (5.17%)	4 / 57 (7.02%)	3 / 55 (5.45%)
occurrences (all)	4	7	3
PAIN IN EXTREMITY			
subjects affected / exposed	14 / 58 (24.14%)	14 / 57 (24.56%)	9 / 55 (16.36%)
occurrences (all)	25	24	14
SPINAL PAIN			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	2 / 55 (3.64%)
occurrences (all)	4	2	2
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 58 (1.72%)	4 / 57 (7.02%)	2 / 55 (3.64%)
occurrences (all)	1	4	2

CELLULITIS			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	1 / 55 (1.82%)
occurrences (all)	0	2	2
CONJUNCTIVITIS			
subjects affected / exposed	5 / 58 (8.62%)	3 / 57 (5.26%)	0 / 55 (0.00%)
occurrences (all)	7	3	0
CYSTITIS			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	2 / 55 (3.64%)
occurrences (all)	1	0	2
EAR INFECTION			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	4	1	0
FOLLICULITIS			
subjects affected / exposed	4 / 58 (6.90%)	3 / 57 (5.26%)	2 / 55 (3.64%)
occurrences (all)	8	3	8
FUNGAL INFECTION			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	3	1	0
GASTROENTERITIS			
subjects affected / exposed	4 / 58 (6.90%)	2 / 57 (3.51%)	2 / 55 (3.64%)
occurrences (all)	5	2	3
GINGIVITIS			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	4 / 55 (7.27%)
occurrences (all)	3	7	4
HERPES VIRUS INFECTION			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	1 / 55 (1.82%)
occurrences (all)	0	3	1
HORDEOLUM			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences (all)	3	1	2
INFLUENZA			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	4 / 55 (7.27%)
occurrences (all)	6	1	5
NAIL INFECTION			
subjects affected / exposed	3 / 58 (5.17%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	4	0	1

NASOPHARYNGITIS			
subjects affected / exposed	8 / 58 (13.79%)	5 / 57 (8.77%)	8 / 55 (14.55%)
occurrences (all)	14	6	8
ORAL CANDIDIASIS			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
ORAL HERPES			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	2 / 55 (3.64%)
occurrences (all)	1	0	3
PHARYNGITIS			
subjects affected / exposed	4 / 58 (6.90%)	4 / 57 (7.02%)	2 / 55 (3.64%)
occurrences (all)	4	5	2
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 58 (1.72%)	3 / 57 (5.26%)	1 / 55 (1.82%)
occurrences (all)	1	5	1
RHINITIS			
subjects affected / exposed	7 / 58 (12.07%)	7 / 57 (12.28%)	6 / 55 (10.91%)
occurrences (all)	11	8	8
SINUSITIS			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	8 / 55 (14.55%)
occurrences (all)	3	2	9
TOOTH ABSCESS			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	1 / 55 (1.82%)
occurrences (all)	0	5	1
TOOTH INFECTION			
subjects affected / exposed	1 / 58 (1.72%)	4 / 57 (7.02%)	2 / 55 (3.64%)
occurrences (all)	1	5	2
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 58 (18.97%)	4 / 57 (7.02%)	8 / 55 (14.55%)
occurrences (all)	23	6	11
URINARY TRACT INFECTION			
subjects affected / exposed	7 / 58 (12.07%)	6 / 57 (10.53%)	12 / 55 (21.82%)
occurrences (all)	15	9	17
Metabolism and nutrition disorders			

DECREASED APPETITE			
subjects affected / exposed	17 / 58 (29.31%)	16 / 57 (28.07%)	13 / 55 (23.64%)
occurrences (all)	36	27	19
DEHYDRATION			
subjects affected / exposed	1 / 58 (1.72%)	4 / 57 (7.02%)	2 / 55 (3.64%)
occurrences (all)	1	4	2
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 58 (1.72%)	3 / 57 (5.26%)	0 / 55 (0.00%)
occurrences (all)	1	3	0
HYPOCALCAEMIA			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	3 / 55 (5.45%)
occurrences (all)	0	0	3
HYPOKALAEMIA			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	1 / 55 (1.82%)
occurrences (all)	5	3	1

Non-serious adverse events	OL Trebananib 10 mg/kg QW + Paclitaxel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 56 (96.43%)		
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
FLUSHING			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
HOT FLUSH			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	14		
HYPERTENSION			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	8		
HYPOTENSION			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
LYMPHOEDEMA			

subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	10		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	23 / 56 (41.07%)		
occurrences (all)	95		
CATHETER SITE PAIN			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	3		
CHEST DISCOMFORT			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
CHEST PAIN			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	22		
FACE OEDEMA			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	12		
FATIGUE			
subjects affected / exposed	15 / 56 (26.79%)		
occurrences (all)	29		
GAIT DISTURBANCE			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
GENERALISED OEDEMA			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
MUCOSAL INFLAMMATION			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
OEDEMA PERIPHERAL			

subjects affected / exposed	30 / 56 (53.57%)		
occurrences (all)	72		
PAIN			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
PYREXIA			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	18		
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
HYPERSENSITIVITY			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Reproductive system and breast disorders			
VULVOVAGINAL DRYNESS			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	18 / 56 (32.14%)		
occurrences (all)	29		
DYSPHONIA			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
DYSPNOEA			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	20		
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
EPISTAXIS			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	16		
NASAL DRYNESS			

subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
OROPHARYNGEAL PAIN			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	5		
PLEURAL EFFUSION			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
PRODUCTIVE COUGH			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
RHINORRHOEA			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
DEPRESSION			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	7		
INSOMNIA			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	17		
SLEEP DISORDER			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	3		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	2		
NEUTROPHIL COUNT DECREASED			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	4		
WEIGHT DECREASED			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	3		
WEIGHT INCREASED			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	5		
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
TACHYCARDIA			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	11		
DYSAESTHESIA			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
DYSGEUSIA			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	13		
HEADACHE			
subjects affected / exposed	17 / 56 (30.36%)		
occurrences (all)	42		
HYPOAESTHESIA			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	7		
MEMORY IMPAIRMENT			

subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
NEUROPATHY PERIPHERAL			
subjects affected / exposed	21 / 56 (37.50%)		
occurrences (all)	46		
PARAESTHESIA			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	26		
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	11 / 56 (19.64%)		
occurrences (all)	26		
POLYNEUROPATHY			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	5		
SCIATICA			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
SPEECH DISORDER			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
SYNCOPE			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
TREMOR			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	8 / 56 (14.29%)		
occurrences (all)	8		
LEUKOPENIA			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	9		
NEUTROPENIA			
subjects affected / exposed	17 / 56 (30.36%)		
occurrences (all)	31		

Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
TINNITUS			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
VERTIGO			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	6		
Eye disorders			
DRY EYE			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
EYELID OEDEMA			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	8		
LACRIMATION INCREASED			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	8		
VISION BLURRED			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
VISUAL ACUITY REDUCED			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
ABDOMINAL PAIN			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	14		
ABDOMINAL PAIN UPPER			

subjects affected / exposed	6 / 56 (10.71%)			
occurrences (all)	15			
CONSTIPATION				
subjects affected / exposed	13 / 56 (23.21%)			
occurrences (all)	19			
DENTAL CARIES				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences (all)	0			
DIARRHOEA				
subjects affected / exposed	18 / 56 (32.14%)			
occurrences (all)	39			
DRY MOUTH				
subjects affected / exposed	2 / 56 (3.57%)			
occurrences (all)	2			
DYSPEPSIA				
subjects affected / exposed	8 / 56 (14.29%)			
occurrences (all)	15			
DYSPHAGIA				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	3			
FLATULENCE				
subjects affected / exposed	2 / 56 (3.57%)			
occurrences (all)	2			
GASTROOESOPHAGEAL REFLUX DISEASE				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences (all)	1			
GINGIVAL BLEEDING				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences (all)	0			
HAEMORRHOIDS				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences (all)	4			
NAUSEA				
subjects affected / exposed	26 / 56 (46.43%)			
occurrences (all)	44			

ORAL PAIN subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		
STOMATITIS subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 7		
TOOTHACHE subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 2		
VOMITING subjects affected / exposed occurrences (all)	12 / 56 (21.43%) 15		
Hepatobiliary disorders HEPATIC PAIN subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 4		
Skin and subcutaneous tissue disorders ACNE subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 9		
ALOPECIA subjects affected / exposed occurrences (all)	31 / 56 (55.36%) 43		
DERMATITIS ACNEIFORM subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0		
DRY SKIN subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 7		
ERYTHEMA subjects affected / exposed occurrences (all)	11 / 56 (19.64%) 37		
NAIL DISCOLOURATION subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0		
NAIL DISORDER			

subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	10		
NAIL TOXICITY			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	20		
PAIN OF SKIN			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
PRURITUS			
subjects affected / exposed	9 / 56 (16.07%)		
occurrences (all)	13		
RASH			
subjects affected / exposed	12 / 56 (21.43%)		
occurrences (all)	17		
SKIN DISCOLOURATION			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
SKIN FISSURES			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
SKIN HYPERPIGMENTATION			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
PROTEINURIA			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			

ARTHRALGIA				
subjects affected / exposed	14 / 56 (25.00%)			
occurrences (all)	24			
BACK PAIN				
subjects affected / exposed	12 / 56 (21.43%)			
occurrences (all)	23			
BONE PAIN				
subjects affected / exposed	7 / 56 (12.50%)			
occurrences (all)	8			
MUSCLE FATIGUE				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	7			
MUSCLE SPASMS				
subjects affected / exposed	5 / 56 (8.93%)			
occurrences (all)	5			
MUSCULAR WEAKNESS				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences (all)	4			
MUSCULOSKELETAL CHEST PAIN				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	4			
MUSCULOSKELETAL PAIN				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences (all)	6			
MUSCULOSKELETAL STIFFNESS				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences (all)	0			
MYALGIA				
subjects affected / exposed	16 / 56 (28.57%)			
occurrences (all)	31			
NECK PAIN				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences (all)	1			
PAIN IN EXTREMITY				
subjects affected / exposed	12 / 56 (21.43%)			
occurrences (all)	21			

SPINAL PAIN			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
CELLULITIS			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	8		
CONJUNCTIVITIS			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	5		
CYSTITIS			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
EAR INFECTION			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
FOLLICULITIS			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
FUNGAL INFECTION			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
GASTROENTERITIS			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
GINGIVITIS			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences (all)	0		
HERPES VIRUS INFECTION			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
HORDEOLUM			

subjects affected / exposed	0 / 56 (0.00%)			
occurrences (all)	0			
INFLUENZA				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences (all)	1			
NAIL INFECTION				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences (all)	1			
NASOPHARYNGITIS				
subjects affected / exposed	7 / 56 (12.50%)			
occurrences (all)	11			
ORAL CANDIDIASIS				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	3			
ORAL HERPES				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	5			
PHARYNGITIS				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	3			
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences (all)	5			
RHINITIS				
subjects affected / exposed	3 / 56 (5.36%)			
occurrences (all)	3			
SINUSITIS				
subjects affected / exposed	4 / 56 (7.14%)			
occurrences (all)	5			
TOOTH ABSCESS				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences (all)	1			
TOOTH INFECTION				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences (all)	0			
UPPER RESPIRATORY TRACT				

INFECTION			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	8		
URINARY TRACT INFECTION			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	13		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	12		
DEHYDRATION			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
HYPERGLYCAEMIA			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	3		
HYPOCALCAEMIA			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	10		
HYPOKALAEMIA			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2007	Amendment 1 included the following changes: • Prior malignancy (other than thyroid cancer, in situ cervical cancer, or basal cell cancer of the skin) was added as an exclusion criterion. • Clinical safety and efficacy experience and paclitaxel background were updated. • Baseline samples for anti-AMG 386 antibody tests (immunogenicity), biomarkers, and pharmacokinetic tests) were to be taken within 14 days prior to randomization or before dosing on day 1. • A MUGA scan or echocardiogram was to be performed on week 1 day 1, week 9, and week 21. • Radiological assessments were to include a CT scan or MRI of the chest, abdomen, and pelvis, and the modality selected was to be the same throughout the study. • The timing for the 12-lead ECG was defined: on day 1 of week 1, week 4, and week 21, 60 minutes after the completion of the infusion of AMG 386 and after the subject had been supine for at least 5 minutes. • Additional blood samples for biomarker development were to be drawn every 4 cycles (16 weeks) after cycle 3 (week 9). • All non-serious adverse events that occurred after the subject has signed the ICF were to be captured. • Additional statistical analyses included Arm A and/or B relative to Arm D; andArm C relative to Arm D.
11 July 2008	Amendment 2 included the following changes: • Baseline values and changes from baseline in pharmacogenetic markers were added as an exploratory endpoint. • Complete radiology and tumor measurements were to be performed within 28 days prior to randomization. • The brain CT or MRI inclusion criterion was changed to head or brain CT or MRI and was to be performed within 28 days before randomization. • The echocardiogram or MUGA scan was to be performed within 14 days prior to randomization. • aPTT and INR ≤ 1.0 x ULN per institutional laboratory range was added to the PTT laboratory inclusion criterion. • Renal function inclusion criterion was amended to include urinary protein quantitative value of ≤ 30 mg in urinalysis or ≤ 1+ on dipstick, unless quantitative protein is ≤ 1000 mg in a 24 hour urine sample. • Exceptions were added to the prior malignancy exclusion criterion: malignancy treated with curative intent and with no known active disease present for ≥ 3 years; adequately treated non-melanomatous skin cancer or lentigo maligna without evidence of disease; adequately treated cervical carcinoma in situ without evidence of disease. • Motesanib was added as an excluded medication, and concurrent or prior anticoagulation therapy, excluding aspirin and anti-platelet agents. • Concurrent therapy with any hormonal agents must have been discontinued 14 days before randomization. • Baseline samples for anti-AMG 386 antibody tests, biomarkers, and PK tests were to taken before dosing on day 1 cycle 1. • Treatment procedures were modified to include weight, CT or MRI of head or brain and bone metastases, and bone scan if a subject developed signs or symptoms suggestive of bony metastasis while on study treatment. • Randomization was to be stratified according to adjuvant taxane exposure and number of metastatic sites. • Addition of India and Australia. • Other clarifications regarding study procedures were added.

25 February 2009	The third amendment included the following changes: • The echocardiogram or MUGA scan was to be performed within 28 days prior to randomization (previously 14 days). • The sample size consideration for PFS hazard ratio was expanded and clarified. • Plans for two interim analyses of efficacy were changed to one interim analysis, to take place when 75 PFS events (RECIST v 1.0 with modifications progression or death) among subjects in Arms A, B, and C have occurred. • The status of studies listed in the table of clinical safety experience was updated. • The study accrual period was changed from approximately 12 months to approximately 22 months. • It was clarified that investigators could recalculate AMG 386 dose based on subject weight changes per institutional guidelines. • The paclitaxel and bevacizumab dose modification section was updated to include guidelines for dose withholding. • The venous thrombosis toxicity management section was modified to differentiate between symptomatic and asymptomatic grade 4 events. • The safety reporting procedures were expanded and clarified. • The time frame for the primary efficacy analysis was clarified. • The treatment effect statistical analyses were modified. • A description of the use of a peristaltic pump with an in-line filter for AMG 386 infusion was added for consistency with instructions in the Pharmacy Binder.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported