Clinical trial results:
A Randomized Double-Blinded Phase II Study of Carboplatin/Paclitaxel/CT-322 versus Carboplatin/Paclitaxel/Bevacizumab as First-Line Treatment for Recurrent or Advanced Non-Small Cell Lung Cancer with Non-Squamous Histology

Summary

EudraCT number	2008-007768-41
Trial protocol	GB IT
Global end of trial date	08 November 2011

Results information

Result version number	v1 (current)
This version publication date	30 October 2016
First version publication date	30 October 2016

Trial information

Trial identification

Sponsor protocol code	CA196-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00850577
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb International Corporation
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb Study Director, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, clinical.trials@bms.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	08 November 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 November 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the progression free survival (PFS) of CT-322 versus bevacizumab in combination with carboplatin and paclitaxel in chemonaive subjects with recurrent or advanced non-small cell lung cancer with non-squamous histology.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 95
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Brazil: 17
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	South Africa: 36
Worldwide total number of subjects	255
EEA total number of subjects	73

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	164
From 65 to 84 years	90
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 48 sites in 8 countries.

Pre-assignment

Screening details:

A total of 338 subjects were enrolled in the study, out of which 255 were randomized and treated (127 CT-322 arm, 128 Bevacizumab arm). 83 were not randomized because 3 experienced adverse events, 9 withdrew consent, 1 was lost to follow-up, 2 died, 64 no longer met study criteria, 1 for poor/non-compliance and 3 for other non-specified reasons

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Paclitaxel/Carboplatin/CT-322

Arm description:

Paclitaxel (200 mg/m2) and carboplatin (area under the plasma concentration versus time curve [AUC]=6) on Day 1 of a 21-day cycle, plus blinded CT-322 (2 mg/kg) weekly on Days 1, 8, and 15 of the 21-day cycle as an intravenous [IV] infusion.

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 200 mg/m^2 was administered intravenously, over 3 hours on Day 1 of a 21-day cycle.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin 10 mg/mL (AUC=6) was administered intravenously on day 1 of a 21 day cycle.

Investigational medicinal product name	CT-322
Investigational medicinal product code	
Other name	BMS-844203
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CT-322 2 mg/kg was administered intravenously weekly on Days 1,8, and 15 of the 21-day cycle

Arm title	Paclitaxel/Carboplatin/Bevacizumab/Placebo

Arm description:

Paclitaxel (200 mg/m2) and carboplatin (AUC=6) on Day 1 of a 21-day cycle, plus blinded bevacizumab (15 mg/kg IV) on Day 1 and placebo (IV) on Day 8 and 15 of a 21-day cycle

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

Dosage and administration details:

Paclitaxel 200 mg/m^2 was administered intravenously, over 3 hours on Day 1 of a 21-day cycle.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin 10 mg/mL (AUC=6) was administered intravenously on day 1 of a 21 day cycle.

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

Dosage and administration details:

Bevacizumab 15 mg/kg on Day 1 of a 21-day cycle

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Saline (Bevacizumab equivalent volume) was administered intravenously on Days 8 and 15 of a 21-day cycle

Number of subjects in period 1	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo
Started	127	128
Completed	0	0
Not completed	127	128
Subject request to discontinue treatment	5	2
Subject withdrew consent	1	-
Consent withdrawn by subject	-	1
Disease progression	77	63
Study drug toxicity	13	20
Adverse event, non-fatal	9	8
Death	7	4
Various other reasons	3	2
Maximum clinical benefit	-	1

On study therapy	9	24
Subject no longer meets study criteria	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Paclitaxel/Carboplatin/CT-322
Reporting group description:	
Paclitaxel (200 mg/m2) and carboplatin (area under the plasma concentration versus time curve [AUC]=6) on Day 1 of a 21-day cycle, plus blinded CT-322 (2 mg/kg) weekly on Days 1, 8, and 15 of the 21-day cycle as an intravenous [IV] infusion.	
Reporting group title	Paclitaxel/Carboplatin/Bevacizumab/Placebo
Reporting group description:	
Paclitaxel (200 mg/m2) and carboplatin (AUC=6) on Day 1 of a 21-day cycle, plus blinded bevacizumab (15 mg/kg IV) on Day 1 and placebo (IV) on Day 8 and 15 of a 21-day cycle	

Reporting group values	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo	Total
Number of subjects	127	128	255
Age categorical Units: Subjects			
< 65 years	87	77	164
>= 65 years	40	51	91
Age continuous Units: years			
arithmetic mean	59.6	60.9	
standard deviation	± 9.33	± 10.27	-
Gender categorical Units: Subjects			
Female	50	57	107
Male	77	71	148

End points

End points reporting groups

Reporting group title	Paclitaxel/Carboplatin/CT-322
Reporting group description:	
Paclitaxel (200 mg/m2) and carboplatin (area under the plasma concentration versus time curve [AUC]=6) on Day 1 of a 21-day cycle, plus blinded CT-322 (2 mg/kg) weekly on Days 1, 8, and 15 of the 21-day cycle as an intravenous [IV] infusion.	
Reporting group title	Paclitaxel/Carboplatin/Bevacizumab/Placebo
Reporting group description:	
Paclitaxel (200 mg/m2) and carboplatin (AUC=6) on Day 1 of a 21-day cycle, plus blinded bevacizumab (15 mg/kg IV) on Day 1 and placebo (IV) on Day 8 and 15 of a 21-day cycle	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
PFS was defined as the time from randomization to the time of disease progression (as assessed by CT/MRI scans) or death, whichever occurred first. The analysis was performed in all randomized subjects.	
End point type	Primary
End point timeframe:	
Day of randomization to end of study	

End point values	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	128		
Units: Months				
median (confidence interval 95%)	5.6 (4.2 to 6.4)	6.8 (6 to 8.2)		

Statistical analyses

Statistical analysis title	CT-322 Arm vs Bevacizumab Arm
Comparison groups	Paclitaxel/Carboplatin/CT-322 v Paclitaxel/Carboplatin/Bevacizumab/Placebo
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.997
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	2.02

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time from randomization to death. The analysis was performed in all the subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Date of randomization to date of death

End point values	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	128		
Units: Months				
median (confidence interval 95%)	12.5 (10.2 to 15.7)	15.2 (12.2 to 16.8)		

Statistical analyses

Statistical analysis title	CT-322 Arm vs Bevacizumab Arm
Comparison groups	Paclitaxel/Carboplatin/CT-322 v Paclitaxel/Carboplatin/Bevacizumab/Placebo
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.703
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.61

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective response rate was defined as the proportion of randomized subjects in each treatment arm, whose best response was complete response (CR) or partial response (PR). The analysis population included all randomized subjects.

End point type	Secondary

End point timeframe:

Day 1 to end of study

End point values	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	128		
Units: Percentage of subjects				
number (confidence interval 95%)	25.2 (17.9 to 33.7)	32.8 (24.8 to 41.7)		

Statistical analyses

Statistical analysis title	CT-322 Arm vs Bevacizumab Arm
Comparison groups	Paclitaxel/Carboplatin/CT-322 v Paclitaxel/Carboplatin/Bevacizumab/Placebo
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.9
upper limit	4.4

Secondary: Number of Subjects With Serious Adverse Events (SAEs), Discontinuations Due to Adverse Events (AEs), Grade 3 to 4 AEs, and Who Died During Treatment Period

End point title	Number of Subjects With Serious Adverse Events (SAEs), Discontinuations Due to Adverse Events (AEs), Grade 3 to 4 AEs, and Who Died During Treatment Period

End point description:

AE was defined as any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that does not has a causal relationship with treatment. SAE was defined as a medical event that at any dose resulted in death, persistent or significant disability/incapacity, or drug dependency/abuse; was life-threatening, an important medical event, or a congenital anomaly/birth defect; or required or prolonged hospitalisation. Grade 3 to 4 AE were also reported. The analysis was performed on all treated subjects who received at least 1 dose of study therapy.

End point type	Secondary

End point timeframe:

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

End point values	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	128		
Units: Subjects				
SAEs (Any Grade)	51	48		
Drug-Related SAEs	28	24		
Grade 3/4 AEs	104	102		
Drug-Related Grade 3/4 AEs	87	83		
Deaths	55	57		
Deaths Within 30 Days of Last Study Dose	10	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Paclitaxel/Carboplatin/CT-322

Reporting group description:

Paclitaxel (200 mg/m2) and carboplatin (area under the plasma concentration versus time curve [AUC]=6) on Day 1 of a 21-day cycle, plus blinded CT-322 (2 mg/kg) weekly on Days 1, 8, and 15 of the 21-day cycle as an intravenous [IV] infusion.

Reporting group title	Paclitaxel/Carboplatin/Bevacizumab/Placebo

Reporting group description:

Paclitaxel (200 mg/m2) and carboplatin (AUC=6) on Day 1 of a 21-day cycle, plus blinded bevacizumab (15 mg/kg IV) on Day 1 and placebo (IV) on Day 8 and 15 of a 21-day cycle

Serious adverse events	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 127 (40.16%)	48 / 128 (37.50%)	
number of deaths (all causes)	10	10	
number of deaths resulting from adverse events	0	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	2 / 127 (1.57%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 127 (0.79%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 127 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	2 / 127 (1.57%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 127 (0.79%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 127 (0.79%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 127 (0.79%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 127 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 127 (1.57%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 127 (6.30%)	5 / 128 (3.91%)	
occurrences causally related to treatment / all	1 / 10	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	2 / 127 (1.57%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 127 (1.57%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 127 (0.79%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 127 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood amylase increased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersomnia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Monoparesis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	6 / 127 (4.72%)	6 / 128 (4.69%)	
occurrences causally related to treatment / all	7 / 7	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 127 (2.36%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 127 (2.36%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 127 (1.57%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal perforation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 127 (4.72%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 127 (4.72%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	3 / 127 (2.36%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecalith			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ileal perforation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			

subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 127 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 127 (1.57%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 127 (2.36%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	2 / 127 (1.57%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 127 (1.57%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 127 (2.36%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligodipsia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Paclitaxel/Carboplatin/CT-322	Paclitaxel/Carboplatin/Bevacizumab/Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 127 (99.21%)	125 / 128 (97.66%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	30 / 127 (23.62%)	30 / 128 (23.44%)	
occurrences (all)	47	40	
Hypotension			
subjects affected / exposed	6 / 127 (4.72%)	12 / 128 (9.38%)	
occurrences (all)	6	13	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	59 / 127 (46.46%)	54 / 128 (42.19%)	
occurrences (all)	126	153	
Asthenia			
subjects affected / exposed	13 / 127 (10.24%)	33 / 128 (25.78%)	
occurrences (all)	35	49	
Oedema peripheral			
subjects affected / exposed	30 / 127 (23.62%)	12 / 128 (9.38%)	
occurrences (all)	55	19	
Chest pain			
subjects affected / exposed	16 / 127 (12.60%)	22 / 128 (17.19%)	
occurrences (all)	31	35	
Pyrexia			
subjects affected / exposed	15 / 127 (11.81%)	18 / 128 (14.06%)	
occurrences (all)	18	28	
Pain			
subjects affected / exposed	10 / 127 (7.87%)	19 / 128 (14.84%)	
occurrences (all)	14	25	
Mucosal inflammation			
subjects affected / exposed	14 / 127 (11.02%)	15 / 128 (11.72%)	
occurrences (all)	15	21	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	35 / 127 (27.56%)	36 / 128 (28.13%)	
occurrences (all)	84	96	
Cough			
subjects affected / exposed	30 / 127 (23.62%)	36 / 128 (28.13%)	
occurrences (all)	60	72	
Dyspnoea			
subjects affected / exposed	25 / 127 (19.69%)	26 / 128 (20.31%)	
occurrences (all)	78	48	
Dysphonia			
subjects affected / exposed	6 / 127 (4.72%)	18 / 128 (14.06%)	
occurrences (all)	7	30	
Haemoptysis			
subjects affected / exposed	10 / 127 (7.87%)	10 / 128 (7.81%)	
occurrences (all)	18	13	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	24 / 127 (18.90%)	27 / 128 (21.09%)	
occurrences (all)	27	31	
Anxiety			
subjects affected / exposed	9 / 127 (7.09%)	16 / 128 (12.50%)	
occurrences (all)	9	18	
Confusional state			
subjects affected / exposed	2 / 127 (1.57%)	8 / 128 (6.25%)	
occurrences (all)	2	10	
Depression			
subjects affected / exposed	3 / 127 (2.36%)	8 / 128 (6.25%)	
occurrences (all)	4	9	
Investigations			
Weight decreased			
subjects affected / exposed	8 / 127 (6.30%)	20 / 128 (15.63%)	
occurrences (all)	15	21	
Platelet count decreased			
subjects affected / exposed	5 / 127 (3.94%)	8 / 128 (6.25%)	
occurrences (all)	13	15	
Neutrophil count decreased			

subjects affected / exposed	3 / 127 (2.36%)	8 / 128 (6.25%)	
occurrences (all)	4	17	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	20 / 127 (15.75%)	33 / 128 (25.78%)	
occurrences (all)	69	120	
Peripheral sensory neuropathy			
subjects affected / exposed	31 / 127 (24.41%)	23 / 128 (17.97%)	
occurrences (all)	106	72	
Headache			
subjects affected / exposed	17 / 127 (13.39%)	25 / 128 (19.53%)	
occurrences (all)	33	82	
Dizziness			
subjects affected / exposed	11 / 127 (8.66%)	22 / 128 (17.19%)	
occurrences (all)	24	39	
Dysgeusia			
subjects affected / exposed	14 / 127 (11.02%)	16 / 128 (12.50%)	
occurrences (all)	29	39	
Paraesthesia			
subjects affected / exposed	13 / 127 (10.24%)	17 / 128 (13.28%)	
occurrences (all)	25	62	
Hypoaesthesia			
subjects affected / exposed	4 / 127 (3.15%)	7 / 128 (5.47%)	
occurrences (all)	17	18	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	62 / 127 (48.82%)	69 / 128 (53.91%)	
occurrences (all)	198	256	
Anaemia			
subjects affected / exposed	28 / 127 (22.05%)	42 / 128 (32.81%)	
occurrences (all)	82	97	
Thrombocytopenia			
subjects affected / exposed	39 / 127 (30.71%)	31 / 128 (24.22%)	
occurrences (all)	122	65	
Leukopenia			

subjects affected / exposed	9 / 127 (7.09%)	21 / 128 (16.41%)	
occurrences (all)	37	98	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	54 / 127 (42.52%)	63 / 128 (49.22%)	
occurrences (all)	114	135	
Diarrhoea			
subjects affected / exposed	31 / 127 (24.41%)	36 / 128 (28.13%)	
occurrences (all)	45	58	
Constipation			
subjects affected / exposed	38 / 127 (29.92%)	32 / 128 (25.00%)	
occurrences (all)	54	55	
Vomiting			
subjects affected / exposed	29 / 127 (22.83%)	32 / 128 (25.00%)	
occurrences (all)	49	49	
Dyspepsia			
subjects affected / exposed	12 / 127 (9.45%)	21 / 128 (16.41%)	
occurrences (all)	16	27	
Abdominal pain			
subjects affected / exposed	9 / 127 (7.09%)	13 / 128 (10.16%)	
occurrences (all)	12	21	
Abdominal pain upper			
subjects affected / exposed	6 / 127 (4.72%)	7 / 128 (5.47%)	
occurrences (all)	7	14	
Stomatitis			
subjects affected / exposed	4 / 127 (3.15%)	8 / 128 (6.25%)	
occurrences (all)	10	20	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	50 / 127 (39.37%)	56 / 128 (43.75%)	
occurrences (all)	66	63	
Rash			
subjects affected / exposed	16 / 127 (12.60%)	16 / 128 (12.50%)	
occurrences (all)	22	24	
Pruritus			

subjects affected / exposed	9 / 127 (7.09%)	8 / 128 (6.25%)	
occurrences (all)	10	17	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	28 / 127 (22.05%)	17 / 128 (13.28%)	
occurrences (all)	57	34	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 127 (28.35%)	38 / 128 (29.69%)	
occurrences (all)	117	109	
Myalgia			
subjects affected / exposed	17 / 127 (13.39%)	26 / 128 (20.31%)	
occurrences (all)	47	82	
Pain in extremity			
subjects affected / exposed	14 / 127 (11.02%)	27 / 128 (21.09%)	
occurrences (all)	34	52	
Back pain			
subjects affected / exposed	14 / 127 (11.02%)	17 / 128 (13.28%)	
occurrences (all)	24	20	
Bone pain			
subjects affected / exposed	12 / 127 (9.45%)	11 / 128 (8.59%)	
occurrences (all)	15	14	
Musculoskeletal pain			
subjects affected / exposed	7 / 127 (5.51%)	14 / 128 (10.94%)	
occurrences (all)	10	14	
Muscle spasms			
subjects affected / exposed	2 / 127 (1.57%)	7 / 128 (5.47%)	
occurrences (all)	2	7	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 127 (8.66%)	16 / 128 (12.50%)	
occurrences (all)	15	21	
Upper respiratory tract infection			
subjects affected / exposed	13 / 127 (10.24%)	8 / 128 (6.25%)	
occurrences (all)	19	18	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	29 / 127 (22.83%)	30 / 128 (23.44%)	
occurrences (all)	39	44	
Dehydration			
subjects affected / exposed	11 / 127 (8.66%)	8 / 128 (6.25%)	
occurrences (all)	16	17	
Hypomagnesaemia			
subjects affected / exposed	11 / 127 (8.66%)	9 / 128 (7.03%)	
occurrences (all)	16	15	
Hypokalaemia			
subjects affected / exposed	6 / 127 (4.72%)	8 / 128 (6.25%)	
occurrences (all)	11	12	
Hyperglycaemia			
subjects affected / exposed	1 / 127 (0.79%)	9 / 128 (7.03%)	
occurrences (all)	1	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2009	• Allowed for the collection and storage of blood samples for use in future exploratory pharmacogenetic research studies.
06 August 2009	• Updated drug administration and dose modification guidelines. • Provided additional guidance on symptoms and management of Reversible Posterior Leukoencephalopathy Syndrome (RPLS). • Added N-terminal brain natriuretic peptide (NT-BNP) as a tool for cardiac safety assessment. • Increased the number of participating countries and sites.
25 August 2010	• Increase number of participating sites • Update Exclusion Criteria • Update Packaging and Labeling, provide additional guidance on study drug preparation, start of first dose, dose modification criteria and unblinding criteria • Reinforce requirement for premedication for all subjects prior to infusion of paclitaxel and subsequent doses of blinded investigational drug if needed and update monitoring requirements for infusion reaction • Simplify blood sample collection times for PK and PD Biomarkers • Update definition of PFS • Correct some inconsistencies within the protocol
03 November 2010	• Update Exclusion criterion to align with new bevacizumab SmPC • Removal of FDG-PET measurements as exploratory objective • Removal NT-BNP as an additional tool for cardiac safety assessment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: