Clinical trial results:
A Randomized, Double-Blind, Phase 3 Study Evaluating The Efficacy And Safety Of ABP 215 Compared With Bevacizumab In Subjects With Advanced Non-Small Cell Lung Cancer

Summary

EudraCT number	2013-000738-36
Trial protocol	HU CZ DE IT ES NL GR BG PL
Global end of trial date	23 July 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	20120265

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01966003
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	23 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to compare the efficacy of ABP 215 with bevacizumab.

Protection of trial subjects:

This study was conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312)), Declaration of Helsinki, and all applicable regulatory requirements.
This study was conducted in compliance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the US Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition this study adhered to all local regulatory requirements and requirements for data protection.
The investigator explained the benefits and risks of participation in the study to each subject or the subject’s legally acceptable representative and obtained written informed consent.
Written informed consent was required to be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of investigational product [IP]).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2013
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	Russian Federation: 113
Country: Number of subjects enrolled	Hungary: 78
Country: Number of subjects enrolled	Romania: 78
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Greece: 26
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	United States: 45

Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Australia: 50
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Germany: 76
Worldwide total number of subjects	642
EEA total number of subjects	416

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)	390
From 65 to 84 years	252
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 101 sites (14 sites in the US, 11 in Russia, 10 in Australia, 9 in Germany, 8 in Poland, 7 in Hungary, 7 in Romania, 6 in Italy, 6 in Spain, 5 in Bulgaria, 5 in Greece, 3 in the Czech Republic, 3 in Mexico, 3 in Taiwan, 2 in the Netherlands, 1 in Canada, and 1 in Hong Kong).

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio to receive ABP 215 or bevacizumab. Subjects were stratified by geographic region (Eastern Europe vs Western Europe vs Asia Pacific/Other vs North America), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), and sex.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ABP 215

Arm description:

Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.

Arm type	Experimental
Investigational medicinal product name	ABP 215
Investigational medicinal product code	ABP 215
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered 15 mg/kg Q3W by IV infusion

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

Dosage and administration details:

Administered at an area under the concentration-time curve (AUC) 6 by IV infusion Q3W

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

Dosage and administration details:

Administered 200 mg/m² IV Q3W

Arm title	Bevacizumab

Arm description:

Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more

than 6 cycles.

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

Dosage and administration details:

15 mg/kg Q3W by IV infusion

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

Dosage and administration details:

Administered 200 mg/m² IV Q3W

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

Dosage and administration details:

Administered at an area under the concentration-time curve (AUC) 6 by IV infusion Q3W

Number of subjects in period 1	ABP 215	Bevacizumab
Started	328	314
Received Study Drug	324	309
Completed	58	44
Not completed	270	270
Consent withdrawn by subject	29	19
Physician decision	12	13
Plan to receive commercial bevacizumab	44	67
Death	43	36
Other	1	1
Plan to receive non-study anticancer therapy	131	127
Lost to follow-up	4	3
Protocol deviation	6	4

Baseline characteristics

Reporting groups	
Reporting group title	ABP 215
Reporting group description:	
Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.	
Reporting group title	Bevacizumab
Reporting group description:	
Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.	

Reporting group values	ABP 215	Bevacizumab	Total
Number of subjects	328	314	642
Age Categorical Units: Subjects			
< 65 years	199	191	390
≥ 65 years	129	123	252
Age Continuous Units: years			
arithmetic mean	61.6	61.6	
standard deviation	± 9.09	± 8.88	-
Gender Categorical Units: Subjects			
Female	132	126	258
Male	196	188	384
Geographic Region Units: Subjects			
Eastern Europe	189	186	375
Western Europe	78	76	154
North America	31	26	57
Asia Pacific/Other	30	26	56
Eastern Cooperative Oncology Group (ECOG) Performance Status Units: Subjects			
Grade 0	127	117	244
Grade 1	201	197	398

End points

End points reporting groups

Reporting group title	ABP 215
Reporting group description:	
Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.	
Reporting group title	Bevacizumab
Reporting group description:	
Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.	

Primary: Percentage of Participants with an Objective Response

End point title	Percentage of Participants with an Objective Response
End point description:	
Tumor assessments were performed by central, independent, blinded radiologists according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest and abdomen. Objective response is defined as a best overall response of partial response (PR) or complete response (CR) as defined by RECIST v1.1. All participants who did not meet the criteria for CR or PR at the end of the study were considered non-responders. The primary analysis for ORR was based on the intent-to-treat (ITT) population (all randomized subjects).	
End point type	Primary
End point timeframe:	
Weeks 7, 13, 19, and approximately every 9 weeks thereafter. The mean (STD) actual follow-up time from randomization was 4.7 (3.04) and 5.0 (3.17) months for ABP 215 and bevacizumab, respectively.	

End point values	ABP 215	Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	314		
Units: percentage of participants				
number (not applicable)	39	41.7		

Statistical analyses

Statistical analysis title	Risk Ratio (ABP 215/Bevacizumab)
Statistical analysis description:	
The risk ratio and 90% confidence interval (CI) were estimated using a generalized linear model adjusted for the stratification factors (region, sex, and ECOG performance status).	
Comparison groups	ABP 215 v Bevacizumab

Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Risk ratio (RR)
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	1.09

Notes:

[1] - Clinical equivalence of the primary endpoint was demonstrated by comparing the 2-sided 90% CI of the risk ratio in ORR between ABP 215 and bevacizumab with an equivalence margin of (0.67, 1.5).

Statistical analysis title	Risk Difference (ABP 215 - Bevacizumab)

Statistical analysis description:

Risk difference and 90% CI were estimated using a generalized linear model adjusted for the randomization
stratification factors geographic region, ECOG performance status, and sex.

Comparison groups	ABP 215 v Bevacizumab
Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-2.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.26
upper limit	3.45

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR) was calculated as the time from the first objective response (PR or CR) to disease progression per RECIST v1.1 based on the central, independent, blinded radiologists' review. DOR was only calculated for participants with a response. For responders not meeting the criterion for progression by the end of the study, DOR was censored at the date of the last evaluable tumor assessment.

End point type	Secondary

End point timeframe:

Weeks 7, 13, 19, and approximately every 9 weeks thereafter. The mean (STD) actual follow-up time from randomization was 4.7 (3.04) and 5.0 (3.17) months for ABP 215 and bevacizumab, respectively.

End point values	ABP 215	Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	131		
Units: months				
median (confidence interval 95%)	5.8 (4.9 to 7.7)	5.6 (5.1 to 6.3)		

Statistical analyses

Statistical analysis title	Hazard Ratio for Duration of Response

Statistical analysis description:

The hazard ratio for ABP 215 relative to bevacizumab is based on a stratified Cox proportional hazards model. Stratification factors are geographic region, ECOG performance status, and sex.

Comparison groups	ABP 215 v Bevacizumab
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.51
upper limit	1.14

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) was defined as the time from the randomization date to the date of disease progression using RECIST v1.1 based on the central, independent, blinded radiologists' review, or death. Subjects who were alive and did not meet the criteria for progression by the end of the study were censored at their last evaluable disease assessment date. Subjects with no evaluable tumor assessments after randomization who did not die by the end of the study had their PFS times censored on the randomization date.

End point type	Secondary

End point timeframe:

Weeks 7, 13, 19, and approximately every 9 weeks thereafter. The mean (STD) actual follow-up time from randomization was 4.7 (3.04) and 5.0 (3.17) months for ABP 215 and bevacizumab, respectively.

End point values	ABP 215	Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	314		
Units: months				
median (confidence interval 95%)	6.6 (6.3 to 7.9)	7.9 (6.6 to 8.2)		

Statistical analyses

Statistical analysis title	Hazard Ratio for Progression-free Survival
Statistical analysis description:	
The hazard ratio for ABP 215 relative to bevacizumab was based on a stratified Cox proportional hazards model. Stratification factors are geographic region, ECOG performance status, and sex.	
Comparison groups	ABP 215 v Bevacizumab
Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.83
upper limit	1.29

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
19 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	ABP 215
Reporting group description:	
Participants received 15 mg/kg ABP 215 administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.	
Reporting group title	Bevacizumab
Reporting group description:	
Participants received bevacizumab 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles and carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles.	

Serious adverse events	ABP 215	Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 324 (26.23%)	71 / 309 (22.98%)	
number of deaths (all causes)	13	11	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Embolism arterial			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Prophylaxis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (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			
Death			
subjects affected / exposed	2 / 324 (0.62%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	2 / 324 (0.62%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	2 / 324 (0.62%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (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 / 324 (0.31%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial fistula			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	3 / 324 (0.93%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 324 (0.62%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 324 (0.93%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	0 / 3	5 / 6	
deaths causally related to treatment / all	0 / 2	1 / 2	
Pleural effusion			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 324 (0.62%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 324 (1.54%)	6 / 309 (1.94%)	
occurrences causally related to treatment / all	1 / 5	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 324 (0.62%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucinations, mixed			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar vertebral fracture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (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 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			

subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paroxysmal arrhythmia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	2 / 324 (0.62%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	2 / 324 (0.62%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	2 / 324 (0.62%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
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 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	2 / 324 (0.62%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 324 (0.93%)	6 / 309 (1.94%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	11 / 324 (3.40%)	8 / 309 (2.59%)	
occurrences causally related to treatment / all	0 / 14	2 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercoagulation			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			
subjects affected / exposed	6 / 324 (1.85%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 324 (0.62%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 324 (0.93%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
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	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery embolism			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	2 / 324 (0.62%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 324 (0.62%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 324 (0.62%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash generalised			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus hepatitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 324 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (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 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			

subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 324 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 324 (1.85%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	1 / 6	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomonas infection			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 324 (0.62%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 324 (0.31%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 324 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 324 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 309 (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 / 324 (0.31%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ABP 215	Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	286 / 324 (88.27%)	276 / 309 (89.32%)	
Investigations			
Weight decreased			
subjects affected / exposed	18 / 324 (5.56%)	16 / 309 (5.18%)	
occurrences (all)	19	16	
Vascular disorders			
Hypertension			
subjects affected / exposed	51 / 324 (15.74%)	41 / 309 (13.27%)	
occurrences (all)	66	70	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 324 (4.01%)	25 / 309 (8.09%)	
occurrences (all)	17	33	
Headache			
subjects affected / exposed	28 / 324 (8.64%)	24 / 309 (7.77%)	
occurrences (all)	30	32	
Neuropathy peripheral			
subjects affected / exposed	56 / 324 (17.28%)	38 / 309 (12.30%)	
occurrences (all)	86	60	
Paraesthesia			
subjects affected / exposed	28 / 324 (8.64%)	40 / 309 (12.94%)	
occurrences (all)	34	50	
Peripheral sensory neuropathy			
subjects affected / exposed	18 / 324 (5.56%)	16 / 309 (5.18%)	
occurrences (all)	23	34	
Polyneuropathy			
subjects affected / exposed	20 / 324 (6.17%)	22 / 309 (7.12%)	
occurrences (all)	26	28	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	65 / 324 (20.06%)	60 / 309 (19.42%)	
occurrences (all)	111	92	
Leukopenia			

subjects affected / exposed	23 / 324 (7.10%)	23 / 309 (7.44%)	
occurrences (all)	38	56	
Neutropenia			
subjects affected / exposed	55 / 324 (16.98%)	60 / 309 (19.42%)	
occurrences (all)	113	112	
Thrombocytopenia			
subjects affected / exposed	47 / 324 (14.51%)	43 / 309 (13.92%)	
occurrences (all)	83	79	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	49 / 324 (15.12%)	42 / 309 (13.59%)	
occurrences (all)	91	62	
Fatigue			
subjects affected / exposed	57 / 324 (17.59%)	59 / 309 (19.09%)	
occurrences (all)	70	84	
Pyrexia			
subjects affected / exposed	19 / 324 (5.86%)	20 / 309 (6.47%)	
occurrences (all)	22	27	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	36 / 324 (11.11%)	36 / 309 (11.65%)	
occurrences (all)	39	48	
Diarrhoea			
subjects affected / exposed	39 / 324 (12.04%)	55 / 309 (17.80%)	
occurrences (all)	51	79	
Gingival bleeding			
subjects affected / exposed	9 / 324 (2.78%)	19 / 309 (6.15%)	
occurrences (all)	9	22	
Nausea			
subjects affected / exposed	82 / 324 (25.31%)	95 / 309 (30.74%)	
occurrences (all)	124	159	
Stomatitis			
subjects affected / exposed	15 / 324 (4.63%)	18 / 309 (5.83%)	
occurrences (all)	17	26	
Vomiting			

subjects affected / exposed	37 / 324 (11.42%)	41 / 309 (13.27%)	
occurrences (all)	44	54	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 324 (8.02%)	21 / 309 (6.80%)	
occurrences (all)	30	21	
Dyspnoea			
subjects affected / exposed	24 / 324 (7.41%)	24 / 309 (7.77%)	
occurrences (all)	26	28	
Epistaxis			
subjects affected / exposed	44 / 324 (13.58%)	39 / 309 (12.62%)	
occurrences (all)	48	60	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	140 / 324 (43.21%)	127 / 309 (41.10%)	
occurrences (all)	167	159	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	26 / 324 (8.02%)	19 / 309 (6.15%)	
occurrences (all)	39	25	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 324 (7.10%)	29 / 309 (9.39%)	
occurrences (all)	25	48	
Back pain			
subjects affected / exposed	14 / 324 (4.32%)	19 / 309 (6.15%)	
occurrences (all)	15	22	
Bone pain			
subjects affected / exposed	20 / 324 (6.17%)	25 / 309 (8.09%)	
occurrences (all)	24	33	
Myalgia			
subjects affected / exposed	39 / 324 (12.04%)	44 / 309 (14.24%)	
occurrences (all)	78	76	
Pain in extremity			
subjects affected / exposed	24 / 324 (7.41%)	20 / 309 (6.47%)	
occurrences (all)	28	20	

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 54 / 324 (16.67%) 65	 42 / 309 (13.59%) 52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2013	The primary purposes of Amendment 1 were the following: • Modify the restrictions on chemotherapy pretreatment regimens and treatment regimens for chemotherapy-associated toxicities to accommodate differing international standards • Clarify that the scheduling of tumor assessments should be independent of treatment delays • Add an ADA sample to be collected approximately 6 months after the end of treatment visit for subjects still on study • Clarify that screening radiologic assessment must be MRI or CT and must include both the chest and abdomen • Clarify that abstinence must be true abstinence to be an acceptable method of birth control • Clarify that the study duration was approximately 25 weeks „h Specify that if chemotherapy was delayed due to toxicity, IP should be given according to the original schedule (ie, Q3W) • Clarify that the treatment period ends 21 days after the last dose of study medication or study-specified chemotherapy.
24 March 2014	The primary purposes of Amendment 2 were the following: • Clarify the entry criteria to o more clearly specify the exclusionary periods for certain medical histories o specify that subjects with low dose anti-coagulation therapy for peripheral port patency were permitted • Revised the primary analysis to be based on the ITT analysis set and updated power calculations. • Clarify the definition of end of the clinical study as 21 days after the last subject on study receives the last dose of IP and/or chemotherapy • Clarify and update the recommended dose adjustments • Update the definition of DOR to reflect that response confirmation is not required and to specify that response and progression were defined by modified RECIST v1.1 • Specify that CT or MRI performed as routine standard of care, prior to the subject signing informed consent, could be used for screening purposes, as long as the assessments were performed within 28 days before randomization, and that baseline assessment (physical examination, vital signs, and clinical laboratory assessments) could be performed 1 day before treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported