



Clinical trial results:

A Phase 3 Randomized, Double-Blind Study of PF-06439535 Plus Paclitaxel-Carboplatin and Bevacizumab Plus Paclitaxel-Carboplatin for the First-Line Treatment of Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer

Summary

EudraCT number	2014-003878-16
Trial protocol	SK NL CZ DE ES PL HU GR HR IT
Global end of trial date	22 December 2017

Results information

Result version number	v2 (current)
This version publication date	20 December 2018
First version publication date	23 May 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	B7391003
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	01 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2017
Global end of trial reached?	Yes
Global end of trial date	22 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the confirmed objective response rate (ORR) by Week 19 following treatment with PF-06439535 in combination with paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel and carboplatin in subjects who had not received previous treatment for advanced non-small cell lung cancer (NSCLC).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2015
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	Australia: 6
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Chile: 10
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Greece: 18
Country: Number of subjects enrolled	Hungary: 52
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Poland: 40

Country: Number of subjects enrolled	Romania: 62
Country: Number of subjects enrolled	Russian Federation: 176
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Turkey: 32
Country: Number of subjects enrolled	Ukraine: 152
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	719
EEA total number of subjects	240

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)	456
From 65 to 84 years	261
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 719 subjects were enrolled in this study, and 5 of them did not receive any therapy. One (1) additional subject received only chemotherapy, and did not receive blinded bevacizumab.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-06439535

Arm description:

Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.

Arm type	Experimental
Investigational medicinal product name	PF-06439535
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PF-06439535 was administered on Day 1 of each 21-day cycle. The initial dose was 15 mg/kg delivered over 90 minutes as an intravenous infusion. The length of infusion could be adjusted based on subject's tolerability.

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 was administered by intravenous infusion over a minimum of 15 minutes, and could be administered immediately after the paclitaxel infusion had completed. Subjects were administered carboplatin for at least 4 cycles and no more than 6 cycles. Dose reduction was allowed based on occurrence of toxicity. The initial dose was AUC 6, based on subject's pre-existing renal function or renal function and desired platelet nadir.

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

Dosage and administration details:

Paclitaxel was administered at a dose of 200 mg/m² by intravenous infusion over 3 hours on Day 1 of

each 21-day cycle. In the absence of progressive disease, subjects received paclitaxel treatment for at least 4 cycles but no more than 6 cycles. Dose reduction was allowed based on occurrence of toxicity. Paclitaxel was administered as the first drug when chemotherapy was administered.

Arm title	Bevacizumab-EU
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Arm description:

Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.

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

Dosage and administration details:

Bevacizumab-EU was administered on Day 1 of each 21-day cycle. The initial dose was 15 mg/kg delivered over 90 minutes as an intravenous infusion. The length of infusion could be adjusted based on subject's tolerability.

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

Dosage and administration details:

Paclitaxel was administered at a dose of 200 mg/m² by intravenous infusion over 3 hours on Day 1 of each 21-day cycle. In the absence of progressive disease, subjects received paclitaxel treatment for at least 4 cycles but no more than 6 cycles. Dose reduction was allowed based on occurrence of toxicity. Paclitaxel was administered as the first drug when chemotherapy was administered.

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 was administered by intravenous infusion over a minimum of 15 minutes, and could be administered immediately after the paclitaxel infusion had completed. Subjects were administered carboplatin for at least 4 cycles and no more than 6 cycles. Dose reduction was allowed based on occurrence of toxicity. The initial dose was AUC 6, based on subject's pre-existing renal function or renal function and desired platelet nadir.

Number of subjects in period 1	PF-06439535	Bevacizumab-EU
Started	358	361
Received treatment	356	358
Completed	193	188
Not completed	165	173
Adverse event, serious fatal	136	138
Consent withdrawn by subject	14	14
Randomized but did not receive treatment	2	3
Unspecified	-	1
Lost to follow-up	10	15
Protocol deviation	3	2

Baseline characteristics

Reporting groups

Reporting group title	PF-06439535
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Reporting group description:

Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.

Reporting group title	Bevacizumab-EU
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Reporting group description:

Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.

Reporting group values	PF-06439535	Bevacizumab-EU	Total
Number of subjects	358	361	719
Age, Customized			
Units: Subjects			
18-44 years	19	17	36
45-64 years	198	222	420
>= 65 years	141	122	263
Age Continuous			
Units: years			
arithmetic mean	61.7	60.9	
standard deviation	± 9.5	± 8.9	-
Sex/Gender, Customized			
Units: Subjects			
Female	121	131	252
Male	237	230	467
Race/Ethnicity, Customized			
Units: Subjects			
WHITE	319	319	638
BLACK	3	1	4
ASIAN	36	40	76
OTHER	0	1	1

End points

End points reporting groups

Reporting group title	PF-06439535
Reporting group description:	
Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m ²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.	
Reporting group title	Bevacizumab-EU
Reporting group description:	
Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m ²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.	

Primary: Objective Response Rate (ORR) by Week 19

End point title	Objective Response Rate (ORR) by Week 19
End point description:	
ORR: percentage of subjects who achieved complete response (CR) or partial response (PR) by Week 19 based on Response Evaluation Criteria in Solid Tumors v 1.1 which was confirmed by Week 25. A subject achieved CR if both target and non-target lesions achieved CR, no new lesions; achieved PR if target lesions achieved CR or PR, non-target lesions were assessed as non-CR/non-PD (progressive disease), indeterminate or missing, and no new lesions. For target lesions, CR: complete disappearance of all target lesions except nodal disease (target nodes decreased to normal size); PR: $\geq 30\%$ decrease under baseline of the sum of diameters of all target measurable lesions. For non-target lesions, CR: disappearance of all non-target lesions and normalization of tumor marker levels and all lymph nodes were normal in size; non-CR/non-PD: persistence of any non-target lesions and/or tumor marker level above the normal limits. The analysis population included all randomized subjects.	
End point type	Primary
End point timeframe:	
25 weeks	

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	361		
Units: percentage of subjects				
number (confidence interval 95%)	45.3 (40.01 to 50.57)	44.6 (39.40 to 49.89)		

Statistical analyses

Statistical analysis title	Risk difference analysis with 95% CI
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	equivalence ^[1]
Parameter estimate	Risk difference (RD)
Point estimate	0.6531
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.608
upper limit	7.9082

Notes:

[1] - Calculated based on 2-sided Miettinen and Nurminen method without strata for risk difference for confirmed response. EU equivalence margins (95% CI in -13% to 13%).

Statistical analysis title	Risk ratio analysis with 90% CI
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	equivalence ^[2]
Parameter estimate	Risk ratio (RR)
Point estimate	1.0146
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8856
upper limit	1.1625

Notes:

[2] - Calculated based on 2-sided Miettinen and Nurminen method without strata for risk ratio for confirmed response. US equivalence margins (90% CI in 0.73 to 1.37).

Statistical analysis title	Risk ratio analysis with 95% CI
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	equivalence ^[3]
Parameter estimate	Risk ratio (RR)
Point estimate	1.0146
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8628
upper limit	1.1933

Notes:

[3] - Calculated based on 2-sided Miettinen and Nurminen method without strata for risk ratio for confirmed response. Japan equivalence margins (95% CI in 0.729 to 1.371).

Secondary: Number of Subjects with Treatment-Emergent Adverse Events

End point title	Number of Subjects with Treatment-Emergent Adverse Events
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End point description:

AE: any untoward medical occurrence in a clinical investigation subject, without regard to causality.
TEAEs: AEs that occurred for the first time during treatment or AEs that increased in severity during

treatment. Serious AEs (SAEs) were any untoward medical occurrence at any dose that resulted in death; was life-threatening; required inpatient hospitalization or caused prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect. AEs included SAEs and non-serious AEs. Causality to study treatment was determined by the investigator. Severity was graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. The analysis population included all subjects who were randomized and received at least 1 dose of study treatment.

End point type	Secondary
End point timeframe:	
55 weeks	

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	358		
Units: subjects				
All-causality AE	344	347		
All-causality SAE	81	80		
Bevacizumab-related AE	190	199		
Bevacizumab-related SAE	23	17		
Grade 1 all-causality AE	32	41		
Grade 2 all-causality AE	141	134		
Grade 3 all-causality AE	125	104		
Grade 4 all-causality AE	25	44		
Grade 5 all-causality AE	21	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Laboratory Abnormalities (Without Regard to Baseline Abnormality)

End point title	Number of Subjects with Laboratory Abnormalities (Without Regard to Baseline Abnormality)
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End point description:

Laboratory evaluation included hematology (hemoglobin, white blood cells, platelets and absolute neutrophil count), blood chemistry (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, serum or plasma creatinine, sodium, potassium, total calcium, magnesium, blood urea nitrogen or urea, and albumin), coagulation (international normalized ratio for prothrombin time and activated partial thromboplastin time) and urinalysis (dipstick followed by a quantitative urine protein analysis for results of 2+ or greater). The analysis population included all subjects who were randomized and received at least 1 dose of study treatment, and had laboratory evaluation done.

End point type	Secondary
End point timeframe:	
55 weeks	

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	348		
Units: subjects	303	304		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
End point description:	
DOR was defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD or to death due to any cause in the absence of documented PD. DOR was based on the Brookmeyer and Crowley method. The analysis population included all randomized subjects who had a confirmed objective response achieved by Week 19.	
End point type	Secondary
End point timeframe:	
55 weeks	

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	161		
Units: weeks				
median (confidence interval 95%)	36.3 (31.6 to 43.6)	28.7 (27.0 to 36.3)		

Statistical analyses

Statistical analysis title	Hazard ratio analysis
Statistical analysis description:	
A hazard ratio =1 indicated no difference in progressive disease(PD)/death between 2 reporting groups; >1 indicated an increase in PD/death in PF-06439535; <1 indicated an increase in PD/death in bevacizumab-EU.	
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.1077
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	1.051

Notes:

[4] - Hazard ratio of PF-06439535 versus Bevacizumab-EU

Secondary: Progression Free Survival Rate at 55 Weeks

End point title	Progression Free Survival Rate at 55 Weeks
End point description:	
This outcome measure refers to the possibility of being progression free at 55 weeks since start of study treatment, estimated from the Kaplan-Meier curve using the product-limit method. The analysis population included all randomized subjects.	
End point type	Secondary
End point timeframe:	
55 weeks	

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	361		
Units: percentage of subjects				
number (confidence interval 95%)	32.3 (26.9 to 37.8)	30.5 (25.3 to 35.8)		

Statistical analyses

Statistical analysis title	Hazard ratio analysis
Statistical analysis description:	
A hazard ratio =1 indicated no difference in progressive disease(PD)/death between 2 reporting groups; >1 indicated an increase in PD/death in PF-06439535; <1 indicated an increase in PD/death in bevacizumab-EU.	
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.4492
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.931
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.777
upper limit	1.116

Notes:

[5] - Hazard ratio of PF-06439535 versus Bevacizumab-EU

Secondary: Survival Rate at 55 Weeks

End point title	Survival Rate at 55 Weeks
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End point description:

This outcome measure refers to the possibility of being alive at 55 weeks since start of study treatment, estimated from the Kaplan-Meier curve using the product-limit method. The analysis population included all randomized subjects.

End point type	Secondary
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End point timeframe:

55 weeks

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	361		
Units: percentage of subjects				
number (confidence interval 95%)	65.8 (60.5 to 70.6)	64.1 (58.6 to 69.0)		

Statistical analyses

Statistical analysis title	Hazard ratio analysis
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Statistical analysis description:

A hazard ratio =1 indicated no difference in progressive disease(PD)/death between 2 reporting groups; >1 indicated an increase in PD/death in PF-06439535; <1 indicated an increase in PD/death in bevacizumab-EU.

Comparison groups	PF-06439535 v Bevacizumab-EU
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Number of subjects included in analysis	719
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Analysis specification	Pre-specified
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Analysis type	other ^[6]
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P-value	= 0.4726
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Method	Logrank
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Parameter estimate	Hazard ratio (HR)
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Point estimate	0.918
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.729
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upper limit	1.157
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Notes:

[6] - Hazard ratio of PF-06439535 versus Bevacizumab-EU

Secondary: Serum Concentration of Bevacizumab up to 1 Year

End point title	Serum Concentration of Bevacizumab up to 1 Year
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End point description:

The analysis population included all subjects who were randomized and received study treatment as planned and had no major protocol deviations, and had at least 1 drug concentration measurement after administration of study treatment. Not all subjects had measurements at each time point.

End point type	Secondary
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End point timeframe:

Pre-dose from Cycle 1 to Cycle 17, 2.5 hours post-dose in Cycle 1, and 1.5 hours post-dose in Cycle 5

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	354		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose in Cycle 1	68.08 (± 705.53)	116.4 (± 1032.1)		
2.5 hours post-dose in Cycle 1	280000 (± 103260)	302200 (± 100360)		
Pre-dose in Cycle 2	54350 (± 44479)	58930 (± 49452)		
Pre-dose in Cycle 3	81090 (± 48671)	83350 (± 32384)		
Pre-dose in Cycle 4	100900 (± 54979)	99750 (± 50531)		
Pre-dose in Cycle 5	105300 (± 48469)	110000 (± 65416)		
1.5 hours post-dose in Cycle 5	360700 (± 131170)	377200 (± 142250)		
Pre-dose in Cycle 6	112000 (± 40825)	116700 (± 53844)		
Pre-dose in Cycle 7	117300 (± 53844)	122100 (± 47793)		
Pre-dose in Cycle 8	123600 (± 48893)	126400 (± 52985)		
Pre-dose in Cycle 9	127200 (± 46200)	140900 (± 62548)		
Pre-dose in Cycle 10	125700 (± 50769)	135900 (± 53975)		
Pre-dose in Cycle 11	129500 (± 61329)	135600 (± 54531)		
Pre-dose in Cycle 12	135200 (± 64560)	136300 (± 51312)		
Pre-dose in Cycle 13	130900 (± 58093)	139700 (± 53750)		
Pre-dose in Cycle 14	128000 (± 50840)	136200 (± 53439)		
Pre-dose in Cycle 15	134000 (± 55933)	134000 (± 49663)		
Pre-dose in Cycle 16	137000 (± 54813)	128600 (± 49742)		
Pre-dose in Cycle 17	134800 (± 86847)	127500 (± 52784)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Anti-Drug Antibody (ADA)

End point title	Number of Subjects with Anti-Drug Antibody (ADA)
End point description: ADA assay was performed using a sensitive, specific, and semi-quantitative electrochemiluminescent (ECL) method, which used biotinylated- and ruthenium-labeled PF-06439535 as reagents. Samples with ADA titer greater than or equal to (\geq) 2.29 were considered positive. The analysis population included all subjects who were randomized and received at least 1 dose of study treatment.	
End point type	Secondary
End point timeframe: 55 weeks	

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	358		
Units: subjects				
Cycle 1 pre-dose	1	3		
Overall (post-treatment)	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Neutralizing Antibody (NAb)

End point title	Number of Subjects with Neutralizing Antibody (NAb)
End point description: Only samples that were confirmed positive for ADA were further tested for NAb. The NAb analysis was conducted using a single validated quasi-quantitative enzyme-linked immunosorbent assay (ELISA) that utilized PF-06439535 as a reagent. Samples with NAb titer ≥ 1.70 were considered positive.	
End point type	Secondary
End point timeframe: 55 weeks	

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: number of subjects				
Cycle 1 pre-dose	1	0		
Overall (post-treatment)	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

55 weeks

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	PF-06439535
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Reporting group description:

Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.

Reporting group title	Total
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Reporting group description:

This reporting group include all subjects who received at least 1 dose of study treatment from PF-06439535 and Bevacizumab-EU groups.

Reporting group title	Bevacizumab-EU
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Reporting group description:

Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m²) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed for paclitaxel and carboplatin in response to toxicity. Paclitaxel was administered before carboplatin.

Serious adverse events	PF-06439535	Total	Bevacizumab-EU
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 356 (22.75%)	161 / 714 (22.55%)	80 / 358 (22.35%)
number of deaths (all causes)	144	293	149
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone cancer metastatic			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neoplasm progression			
subjects affected / exposed	2 / 356 (0.56%)	4 / 714 (0.56%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 4	0 / 2
Tumour necrosis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Vascular disorders			
Brachiocephalic vein thrombosis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism arterial			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Haemorrhage			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Subgaleal haematoma			

subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 356 (1.12%)	5 / 714 (0.70%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	3 / 5	3 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 356 (0.56%)	5 / 714 (0.70%)	3 / 358 (0.84%)
occurrences causally related to treatment / all	1 / 2	1 / 5	0 / 3
deaths causally related to treatment / all	1 / 2	1 / 5	0 / 3
Disease progression			
subjects affected / exposed	4 / 356 (1.12%)	9 / 714 (1.26%)	5 / 358 (1.40%)
occurrences causally related to treatment / all	0 / 4	0 / 9	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 6	0 / 4
General physical health deterioration			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 356 (0.56%)	3 / 714 (0.42%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 356 (0.56%)	4 / 714 (0.56%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	1 / 2	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	2 / 356 (0.56%)	3 / 714 (0.42%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	2 / 2	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 356 (0.56%)	4 / 714 (0.56%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	2 / 2	2 / 5	0 / 3
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 356 (0.56%)	3 / 714 (0.42%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	7 / 356 (1.97%)	9 / 714 (1.26%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	2 / 7	4 / 9	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	3 / 356 (0.84%)	6 / 714 (0.84%)	3 / 358 (0.84%)
occurrences causally related to treatment / all	1 / 3	2 / 6	1 / 3
deaths causally related to treatment / all	1 / 2	2 / 5	1 / 3
Pulmonary oedema			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Acute myocardial infarction			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 2	0 / 1
Angina unstable			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Cardiovascular insufficiency			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Myocardial infarction			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Headache			

subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 356 (0.00%)	3 / 714 (0.42%)	3 / 358 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Mononeuropathy			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 356 (0.56%)	7 / 714 (0.98%)	5 / 358 (1.40%)
occurrences causally related to treatment / all	2 / 4	3 / 10	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	5 / 356 (1.40%)	12 / 714 (1.68%)	7 / 358 (1.96%)
occurrences causally related to treatment / all	2 / 7	3 / 14	1 / 7
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Leukopenia			
subjects affected / exposed	2 / 356 (0.56%)	2 / 714 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 356 (1.12%)	10 / 714 (1.40%)	6 / 358 (1.68%)
occurrences causally related to treatment / all	1 / 5	6 / 13	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 356 (0.84%)	6 / 714 (0.84%)	3 / 358 (0.84%)
occurrences causally related to treatment / all	2 / 5	4 / 8	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 356 (0.56%)	4 / 714 (0.56%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			

subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	2 / 356 (0.56%)	2 / 714 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal infection			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated tuberculosis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Febrile infection			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	4 / 356 (1.12%)	4 / 714 (0.56%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 356 (0.28%)	3 / 714 (0.42%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral fungal infection			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			

subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	8 / 356 (2.25%)	14 / 714 (1.96%)	6 / 358 (1.68%)
occurrences causally related to treatment / all	3 / 11	3 / 17	0 / 6
deaths causally related to treatment / all	1 / 2	1 / 2	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 356 (0.56%)	2 / 714 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 356 (0.28%)	3 / 714 (0.42%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	1 / 1	1 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	4 / 356 (1.12%)	4 / 714 (0.56%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	3 / 5	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PF-06439535	Total	Bevacizumab-EU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	328 / 356 (92.13%)	661 / 714 (92.58%)	333 / 358 (93.02%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	49 / 356 (13.76%)	88 / 714 (12.32%)	39 / 358 (10.89%)
occurrences (all)	95	148	53
Aspartate aminotransferase increased			
subjects affected / exposed	44 / 356 (12.36%)	81 / 714 (11.34%)	37 / 358 (10.34%)
occurrences (all)	94	153	59
Blood alkaline phosphatase increased			

subjects affected / exposed occurrences (all)	29 / 356 (8.15%) 46	61 / 714 (8.54%) 94	32 / 358 (8.94%) 48
Blood creatinine increased subjects affected / exposed occurrences (all)	16 / 356 (4.49%) 28	37 / 714 (5.18%) 61	21 / 358 (5.87%) 33
Platelet count decreased subjects affected / exposed occurrences (all)	23 / 356 (6.46%) 31	42 / 714 (5.88%) 69	19 / 358 (5.31%) 38
Weight decreased subjects affected / exposed occurrences (all)	36 / 356 (10.11%) 43	65 / 714 (9.10%) 83	29 / 358 (8.10%) 40
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	19 / 356 (5.34%) 26	41 / 714 (5.74%) 52	22 / 358 (6.15%) 26
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	60 / 356 (16.85%) 83	122 / 714 (17.09%) 193	62 / 358 (17.32%) 110
Nervous system disorders Headache subjects affected / exposed occurrences (all)	30 / 356 (8.43%) 35	67 / 714 (9.38%) 80	37 / 358 (10.34%) 45
Neuropathy peripheral subjects affected / exposed occurrences (all)	53 / 356 (14.89%) 67	118 / 714 (16.53%) 153	65 / 358 (18.16%) 86
Paraesthesia subjects affected / exposed occurrences (all)	40 / 356 (11.24%) 64	71 / 714 (9.94%) 100	31 / 358 (8.66%) 36
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	34 / 356 (9.55%) 45	80 / 714 (11.20%) 115	46 / 358 (12.85%) 70
Polyneuropathy subjects affected / exposed occurrences (all)	23 / 356 (6.46%) 34	42 / 714 (5.88%) 56	19 / 358 (5.31%) 22
Blood and lymphatic system disorders			

Leukopenia			
subjects affected / exposed	26 / 356 (7.30%)	56 / 714 (7.84%)	30 / 358 (8.38%)
occurrences (all)	44	100	56
Neutropenia			
subjects affected / exposed	59 / 356 (16.57%)	125 / 714 (17.51%)	66 / 358 (18.44%)
occurrences (all)	130	274	144
Thrombocytopenia			
subjects affected / exposed	55 / 356 (15.45%)	121 / 714 (16.95%)	66 / 358 (18.44%)
occurrences (all)	122	247	125
Anaemia			
subjects affected / exposed	102 / 356 (28.65%)	208 / 714 (29.13%)	106 / 358 (29.61%)
occurrences (all)	196	396	200
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 356 (12.92%)	89 / 714 (12.46%)	43 / 358 (12.01%)
occurrences (all)	78	143	65
Fatigue			
subjects affected / exposed	73 / 356 (20.51%)	144 / 714 (20.17%)	71 / 358 (19.83%)
occurrences (all)	110	197	87
Pyrexia			
subjects affected / exposed	24 / 356 (6.74%)	47 / 714 (6.58%)	23 / 358 (6.42%)
occurrences (all)	31	72	41
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	39 / 356 (10.96%)	66 / 714 (9.24%)	27 / 358 (7.54%)
occurrences (all)	45	81	36
Diarrhoea			
subjects affected / exposed	46 / 356 (12.92%)	94 / 714 (13.17%)	48 / 358 (13.41%)
occurrences (all)	59	125	66
Nausea			
subjects affected / exposed	71 / 356 (19.94%)	140 / 714 (19.61%)	69 / 358 (19.27%)
occurrences (all)	111	223	112
Vomiting			
subjects affected / exposed	41 / 356 (11.52%)	74 / 714 (10.36%)	33 / 358 (9.22%)
occurrences (all)	52	94	42
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	41 / 356 (11.52%) 53	88 / 714 (12.32%) 111	47 / 358 (13.13%) 58
Dyspnoea subjects affected / exposed occurrences (all)	32 / 356 (8.99%) 38	67 / 714 (9.38%) 79	35 / 358 (9.78%) 41
Epistaxis subjects affected / exposed occurrences (all)	40 / 356 (11.24%) 51	72 / 714 (10.08%) 99	32 / 358 (8.94%) 48
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	166 / 356 (46.63%) 216	331 / 714 (46.36%) 448	165 / 358 (46.09%) 232
Rash subjects affected / exposed occurrences (all)	9 / 356 (2.53%) 10	30 / 714 (4.20%) 39	21 / 358 (5.87%) 29
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	28 / 356 (7.87%) 50	62 / 714 (8.68%) 126	34 / 358 (9.50%) 76
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	40 / 356 (11.24%) 82	83 / 714 (11.62%) 153	43 / 358 (12.01%) 71
Bone pain subjects affected / exposed occurrences (all)	25 / 356 (7.02%) 58	48 / 714 (6.72%) 105	23 / 358 (6.42%) 47
Myalgia subjects affected / exposed occurrences (all)	54 / 356 (15.17%) 131	103 / 714 (14.43%) 240	49 / 358 (13.69%) 109
Pain in extremity subjects affected / exposed occurrences (all)	16 / 356 (4.49%) 23	39 / 714 (5.46%) 52	23 / 358 (6.42%) 29
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	48 / 356 (13.48%)	94 / 714 (13.17%)	46 / 358 (12.85%)
occurrences (all)	76	141	65

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2015	Protocol was amended to incorporate feedback from investigators, regulatory agencies, and protocol template updates.
10 June 2016	For EU, primary analysis was changed to risk difference; inclusion and exclusion criteria were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported