Clinical trial results:
A Phase III, Randomised, Parallel Group, Multi-Centre Study in Recurrent Glioblastoma Patients to Compare the Efficacy of Cediranib (AZD2171) Monotherapy and the Combination of Cediranib with Lomustine to the Efficacy of Lomustine Alone

Summary

EudraCT number	2007-000383-24
Trial protocol	DE FR NL BE CZ AT GB
Global end of trial date	26 September 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	D8480C00055

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	132 Hills Road, Cambridge, United Kingdom, CB2 1PG
Public contact	Tsveta Milenkova, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
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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	25 April 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2010
Global end of trial reached?	Yes
Global end of trial date	26 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine the relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of PFS as assessed by independent radiographic review.

Protection of trial subjects:

Due to delayed bone marrow suppression, blood counts were monitored weekly for at least 6 weeks after a dose. Doses subsequent to the initial dose were adjusted according to the haematologic response of the subject to the preceding dose.A repeat course of lomustine would not be given until circulating blood elements have returned to acceptable levels. This usually occurs within 6 weeks. Lomustine could've been dose reduced a maximum of 2 times.

Administration of antiemetics was recommended to treat and prevent nausea and vomiting according to standard of care. Additionally, the dose of lomustine could be split over 3 days if necessary.

For AZD2171 dose interruptions should have been used as the first approach to managing toxicity and dose reduction could be considered. A management plan was provided to offer guidance on how to make toxicity. Two dose reductions for AZD2171 was permitted during the study. No re-escalation of dose was permitted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2008
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: 34
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 41
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Netherlands: 44
Country: Number of subjects enrolled	United Kingdom: 61
Country: Number of subjects enrolled	United States: 135
Worldwide total number of subjects	423
EEA total number of subjects	228

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)	342
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 423 patients from 71 centres in 10 countries (Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Netherlands, UK, and US) were enrolled into this study. The first patient was enrolled on 8 October 2008 and the last patient was enrolled on 2 September 2009.

Pre-assignment

Screening details:

Of the 423 patients enrolled, 325 were randomised, and 315 of those randomised received at least 1 dose of study treatment. Of the 10 patients who were randomised but did not receive study treatment, all had discontinued the study before 25 April 2010.

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	Investigator, Subject

Blinding implementation details:

The treatment groups are double blind for the lomustine containing arms and the 30 mg alone arm is unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cediranib 30 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cediranib
Investigational medicinal product code	AZD2171
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the monotherapy arm received 1 x 30 mg tablet orally, once daily

Arm title	Cediranib 20 mg + lomustine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cediranib and lomustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients took 1 x 20 mg cediranib tablet once daily.

Lomustine was administered orally at baseline and every 6 weeks thereafter at a dose of 110 mg/m2. The 110 mg/m2 dose was the starting dose, but lomustine was capped at a total maximum dose of 240 mg

Arm title	Placebo + lomustine

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo and lomustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients took 1 x 20 mg matched cediranib placebo tablet orally, once daily.

Lomustine was administered orally at baseline and every 6 weeks thereafter at a dose of 110 mg/m2. The 110 mg/m2 dose was the starting dose, but lomustine was capped at a total maximum dose of 240 mg

Number of subjects in period 1[1]	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine
Started	131	129	65
Completed	13	18	7
Not completed	118	111	58
Other	2	1	-
Condition under investigation worsened	89	78	44
Adverse event	19	22	10
Voluntary discontinuation by subject	8	6	4
Protocol deviation	-	4	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 423 patients enrolled, 325 were randomised,whereas out of these patients enrolled 98 failed screening and didn’t actually enter the study. Therefore only 325 patients were randomised to a treatment and thus “started” treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Cediranib 30 mg
Reporting group description: -	
Reporting group title	Cediranib 20 mg + lomustine
Reporting group description: -	
Reporting group title	Placebo + lomustine
Reporting group description: -	

Reporting group values	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine
Number of subjects	131	129	65
Age Categorical Units: Subjects			
≥18 to <65 years	109	108	55
≥65 to <75 years	18	20	8
≥75 years	4	1	2
Age Continuous Units: years			
arithmetic mean	53.4	53.7	52
standard deviation	± 11.8	± 10.8	± 13.1
Gender Categorical Units: Subjects			
Female	46	44	24
Male	85	85	41
Race Units: Subjects			
White	127	123	63
Black or African American	3	1	1
Asian	0	3	0
American Indian or Alaska Native	1	1	0
Other	0	1	1
Karnofsky Performance Status Units: Subjects			
KPS 30	0	1	0
KPS 60	0	0	1
KPS 70	33	27	10
KPS 80	32	35	13
KPS 90	38	44	27
KPS 100	27	22	13
Missing	1	0	1
Resection for recurrent disease Units: Subjects			
Resection	50	49	24
No resection	81	80	41
Baseline steroid use Units: Subjects			
Steroid use	64	71	26

No steroid use	67	58	39
Baseline LDH Units: Subjects			
≤1.5 x ULN	122	125	63
>1.5 x ULN	2	0	0
Missing	7	4	2
Baseline VEGF-A Units: Subjects			
≥98 pg/mL	45	44	13
<98 pg/mL	65	62	45
Missing	21	23	7
Time from last radiotherapy to randomisation Units: Subjects			
0 to ≤3 months	2	4	0
3 months to ≤6 months	32	29	16
6 months to ≤12 months	52	42	27
>12 months	45	54	22
Weight Units: Kg			
arithmetic mean	81.5	81.2	79.8
standard deviation	± 16.9	± 15.3	± 15.3
BMI Units: Kg/m^2			
arithmetic mean	26.8	26.9	26.8
standard deviation	± 5	± 4.2	± 4.2

Reporting group values	Total		
Number of subjects	325		
Age Categorical Units: Subjects			
≥18 to <65 years	272		
≥65 to <75 years	46		
≥75 years	7		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	114		
Male	211		
Race Units: Subjects			
White	313		
Black or African American	5		
Asian	3		
American Indian or Alaska Native	2		
Other	2		
Karnofsky Performance Status Units: Subjects			

KPS 30	1		
KPS 60	1		
KPS 70	70		
KPS 80	80		
KPS 90	109		
KPS 100	62		
Missing	2		
Resection for recurrent disease Units: Subjects			
Resection	123		
No resection	202		
Baseline steroid use Units: Subjects			
Steroid use	161		
No steroid use	164		
Baseline LDH Units: Subjects			
≤1.5 x ULN	310		
>1.5 x ULN	2		
Missing	13		
Baseline VEGF-A Units: Subjects			
≥98 pg/mL	102		
<98 pg/mL	172		
Missing	51		
Time from last radiotherapy to randomisation Units: Subjects			
0 to ≤3 months	6		
3 months to ≤6 months	77		
6 months to ≤12 months	121		
>12 months	121		
Weight Units: Kg arithmetic mean standard deviation	- -		
BMI Units: Kg/m^2 arithmetic mean standard deviation	- -		

End points

End points reporting groups	
Reporting group title	Cediranib 30 mg
Reporting group description: -	
Reporting group title	Cediranib 20 mg + lomustine
Reporting group description: -	
Reporting group title	Placebo + lomustine
Reporting group description: -	

Primary: Progression-free survival	
End point title	Progression-free survival
End point description:	
Primary assessment of PFS will be made on the basis of axial T1-weighted contrast enhanced MRI from independent radiographic review. Supportive assessment of PFS will be made on the basis of axial T1-weighted contrast enhanced MRI from site review (ie, investigator review) and on the basis of combination of axial T1-weighted contrast enhanced MRI and T2-weighted/fluid attenuated inversion recovery (FLAIR) MRI from independent radiographic review	
End point type	Primary
End point timeframe:	
The primary analysis is scheduled to occur after 230 PFS events. The data cut off was 25 April 2010.	

End point values	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131	129	65	
Units: Days				
median (inter-quartile range (Q1-Q3))	92 (80 to 128)	125 (83 to 201)	82 (42 to 168)	

Statistical analyses

Statistical analysis title	PFS based on central review T1
Statistical analysis description:	
Cediranib 30mg compared to placebo + lomustine	
Comparison groups	Placebo + lomustine v Cediranib 30 mg
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.8992 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.5

Notes:

[1] - Hazard Ratio and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Hazard Ratio <1 favours cediranib.
[2] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65)

Statistical analysis title	PFS based on central review T1

Statistical analysis description:

Cediranib 20mg and lomustine compared to placebo and lomustine

Comparison groups	Cediranib 20 mg + lomustine v Placebo + lomustine
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.1624 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.08

Notes:

[3] - Hazard Ratio and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Hazard Ratio <1 favours cediranib.
[4] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65)

Statistical analysis title	Sensitivity of PFS

Statistical analysis description:

PFS based on the earlier of site and central review, T1.

Cediranib 30mg compared to Placebo and lomustine

Comparison groups	Cediranib 30 mg v Placebo + lomustine
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.538 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.34

Notes:

[5] - Hazard Ratio and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Hazard Ratio <1 favours cediranib.

[6] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65)

Statistical analysis title	Sensitivity of PFS

Statistical analysis description:

PFS based on the earlier of site and central review, T1.

Cediranib 20mg and lomustine compared to Placebo and lomustine

Comparison groups	Cediranib 20 mg + lomustine v Placebo + lomustine
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.03 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.99

Notes:

[7] - Hazard Ratio and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Hazard Ratio <1 favours cediranib.

[8] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65)

Secondary: Overall survival

End point title	Overall survival

End point description:

The final OS was scheduled to take place after 270 deaths. At the time of the primary there was already a high maturity of the data (197 death events). Based on predictive power calculations there was a 0.01% chance of a positive outcome at the final analysis it was decided to not do the final OS analysis.

The OS will be calculated as the interval from the date of randomization to the date of patient death (any cause). Patients who have not died at the time of the analysis, who are lost to follow-up or who withdraw consent will be censored at the last date the patient was known to be alive.

End point type	Secondary

End point timeframe:

The OS was analysed at the same time as the primary objective (PFS).

End point values	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131	129	65[9]	
Units: Months				
median (inter-quartile range (Q1-Q3))	8 (4.1 to 14.5)	9.4 (6.2 to 14.5)	9.8 (4.9 to 9999)	

Notes:

[9] - Median 9.8 with Inter-Quartile Range of 4.9 to NC.

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description:	
Cediranib 30mg compared to placebo and lomustine	
Comparison groups	Cediranib 30 mg v Placebo + lomustine
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.1002 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	2.13

Notes:

[10] - Hazard Ratio and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Hazard Ratio <1 favours cediranib.

[11] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65)

Statistical analysis title	Overall survival
Statistical analysis description:	
Cediranib 20mg and lomustine compared to placebo and lomustine	
Comparison groups	Cediranib 20 mg + lomustine v Placebo + lomustine
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.4985 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.72

Notes:

[12] - Hazard Ratio and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Hazard Ratio <1 favours cediranib.

[13] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65)

Secondary: Best objective response

End point title	Best objective response

End point description:

An individual visit response of PR is defined as a greater than or equal to 50% reduction in the sum of the products of the largest perpendicular diameters of contrast enhancement for all lesions compared to baseline as long as the steroid dose has not been increased within the previous 10 days and no new lesions are present.

An individual visit response of CR is defined as the complete disappearance of all tumor on MRI scan.

End point type	Secondary

End point timeframe:

Analysis performed at the same time as the primary analysis.

End point values	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118[14]	122[15]	56[16]	
Units: Patients				
Complete response	1	2	0	
Partial response	17	19	5	
Stable disease	44	57	21	
Unconfirmed confirmed response	0	1	0	
Unconfirmed partial response	32	9	2	
Progressive disease	10	19	23	
Non-evaluable	14	14	5	

Notes:

[14] - Patients with measurable disease at baseline

[15] - Patients with measurable disease at baseline

[16] - Patients with measurable disease at baseline

Statistical analyses

Statistical analysis title	Best objective response

Statistical analysis description:

Analysis of best objective response based on central review T1.

Cediranib 30mg compared to placebo and lomustine

Comparison groups	Cediranib 30 mg v Placebo + lomustine

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.2486 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	5.9

Notes:

[17] - A responder is a patient with best confirmed PR or CR.

Odds ratio, p-value, and CI estimated from logistic regression model with factors for treatment, surgical resection (yes/no prior to enrolment), and age (≤65 vs. >65 years).

Odds ratio >1 favours cediranib.

[18] - P-value estimated from logistic regression model with factors for treatment, surgical resection (yes/no prior to enrolment), and age (≤65 vs. >65 years)

Statistical analysis title	Best objective response

Statistical analysis description:

Analysis of best objective response based on central review T1.

Cediranib 20mg and lomustine compared to placebo and lomustine

Comparison groups	Cediranib 20 mg + lomustine v Placebo + lomustine
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.1522 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	6.7

Notes:

[19] - A responder is a patient with best confirmed PR or CR.

Odds ratio, p-value, and CI estimated from logistic regression model with factors for treatment, surgical resection (yes/no prior to enrolment), and age (≤65 vs. >65 years).

Odds ratio >1 favours cediranib

[20] - P-value estimated from logistic regression model with factors for treatment, surgical resection (yes/no prior to enrolment), and age (≤65 vs. >65 years).

Secondary: Alive and progression-free at 6 months

End point title	Alive and progression-free at 6 months

End point description:

A patient will be defined as having progressed by 6 months, defined as 24 weeks (±10 days), if he/she has a progression event within 6 months of randomization, as assessed by independent review on axial T1-weighted contrast enhanced MRI only.

End point type	Secondary

End point timeframe:

Analysis performed at the same time as the primary analysis.

End point values	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131	129	65	
Units: Alive + progression-free at 6 months (%)				
number (not applicable)	16.23	34.53	24.51	

Statistical analyses

Statistical analysis title	APF6

Statistical analysis description:

HR, CI, and p-value estimated from the methods of Hosmer and Lemeshow 1999 and Whitehead 1989. APF6 Alive and progression-free at 6 months (defined as 24 weeks after randomisation).

Comparison groups	Cediranib 30 mg v Placebo + lomustine
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.272 [22]
Method	Hosmer and Lemeshow 1999
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.92

Notes:

[21] - Cediranib 30mg compared to Placebo and lomustine

[22] - P-value estimated from the methods of Hosmer and Lemeshow 1999 and Whitehead 1989. APF6 Alive and progression-free at 6 months (defined as 24 weeks after randomisation).

Statistical analysis title	APF6

Statistical analysis description:

HR, CI, and p-value estimated from the methods of Hosmer and Lemeshow 1999 and Whitehead 1989. APF6 Alive and progression-free at 6 months (defined as 24 weeks after randomisation).

Comparison groups	Cediranib 20 mg + lomustine v Placebo + lomustine
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.107 [24]
Method	Hosmer and Lemeshow 1999
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.08

Notes:

[23] - Cediranib 20mg and lomustine compared to placebo and lomustine

[24] - P-value estimated from the methods of Hosmer and Lemeshow 1999 and Whitehead 1989. APF6 Alive and progression-free at 6 months (defined as 24 weeks after randomisation).

Secondary: Average daily steroid dosage change from baseline until progression

End point title	Average daily steroid dosage change from baseline until progression

End point description:

Percent change in average daily steroid dosage from baseline will be derived for patients who were receiving steroids at baseline. The mean steroid dosage prior to treatment will be considered as the patient's baseline.

The percent change in average daily steroid dosage from baseline is calculated by following formula: PC = (md – bm)/bm*100; where PC is the percent change in average daily steroid dosage from baseline; md the mean daily steroid dosage recorded from the first day of therapy to progression; and bm the baseline mean.

The mean will be calculated from all non-missing values. The number of steroid-free days is calculated as the number of steroid-free days from baseline to progression.

End point type	Secondary

End point timeframe:

At the time of the primary analysis.

End point values	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131	129	65	
Units: Number of steroid-free days				
arithmetic mean (standard deviation)				
Use of steroids at baseline	15.9 (± 34.71)	21.5 (± 44.43)	18 (± 52.64)	
No use of steroids at baseline	130.3 (± 126.08)	140.7 (± 92.5)	143.1 (± 130.08)	

Statistical analyses

Statistical analysis title	% change from baseline in mean daily steroid dose

Statistical analysis description:

Analysis using baseline-scaled ratio: post-baseline value/baseline value. This ratio was log-transformed prior to analysis and then exponentiated after analysis.

Comparison groups	Cediranib 30 mg v Placebo + lomustine

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.006
Method	Mixed models analysis
Parameter estimate	Ratio of glsmeans
Point estimate	-30.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.73
upper limit	-10.08

Notes:

[25] - Cediranib 30mg compared to placebo and lomustine

% change in mean daily steroid dose from baseline to progression (based on central review T1, or death) or study discontinuation (whichever was earlier).

Statistical analysis title	% change from baseline in mean daily steroid dose

Statistical analysis description:

Analysis using baseline-scaled ratio: post-baseline value/baseline value. This ratio was log-transformed prior to analysis and then exponentiated after analysis.

Comparison groups	Cediranib 20 mg + lomustine v Placebo + lomustine
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	< 0.012
Method	Mixed models analysis
Parameter estimate	Ratio of glsmeans
Point estimate	-27.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.54
upper limit	-0.73

Notes:

[26] - Cediranib 20mg and lomustine compared to placebo and lomustine.

% change in mean daily steroid dose from baseline to progression (based on central review T1, or death) or study discontinuation (whichever was earlier).

Secondary: Time to deterioration of the neurological status of patients

End point title	Time to deterioration of the neurological status of patients

End point description:

End point type	Secondary

End point timeframe:

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End point values	Cediranib 30 mg	Cediranib 20 mg + lomustine	Placebo + lomustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131	129	65[27]	
Units: Days				
median (inter-quartile range (Q1-Q3))	126 (77 to 224)	170 (84 to 336)	111 (44 to 999999)	

Notes:

[27] - Median 111 with Inter-Quartile Range of 44 to NC.

Statistical analyses

Statistical analysis title	Time to deterioration of neurological status

Statistical analysis description:

HR and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Comparison groups	Cediranib 30 mg v Placebo + lomustine
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.5731 [29]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.22

Notes:

[28] - Radiological progression not considered an event (censored). Hazard Ratio <1 favours cediranib.

Cediranib 30mg compared to placebo and lomustine

[29] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years)

Statistical analysis title	Time to deterioration of neurological status

Statistical analysis description:

HR and confidence interval estimated from a Cox-Proportional Hazards model including the factors surgical resection (yes/no prior to enrolment) and age (≤65 vs. >65 years).

Comparison groups	Cediranib 20 mg + lomustine v Placebo + lomustine
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	< 0.0091 [31]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.95

Notes:

[30] - Radiological progression not considered an event (censored). Hazard Ratio <1 favours cediranib.

[31] - P-value estimated from Log-Rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs.
>65 years).

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study drug until last study visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17
Reporting groups	
Reporting group title	ced 20 mg +lom 110 mg/m2
Reporting group description: ced 20 mg +lom 110 mg/m2	
Reporting group title	pla 20 mg +lom 110 mg/m2
Reporting group description: pla 20 mg +lom 110 mg/m2	
Reporting group title	cediranib 30 mg
Reporting group description: cediranib 30 mg	

Serious adverse events	ced 20 mg +lom 110 mg/m2	pla 20 mg +lom 110 mg/m2	cediranib 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 123 (36.59%)	26 / 64 (40.63%)	55 / 128 (42.97%)
number of deaths (all causes)	73	33	85
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Vascular disorders			
DEEP VEIN THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 123 (3.25%)	1 / 64 (1.56%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	2 / 4	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOMA			
alternative dictionary used:			

MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHLEBITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DEATH			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
FATIGUE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GAIT DISTURBANCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
HYPERSENSITIVITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
MENORRHAGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA EXERTIONAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	6 / 123 (4.88%)	3 / 64 (4.69%)	4 / 128 (3.13%)
occurrences causally related to treatment / all	1 / 6	2 / 3	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
AGGRESSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANXIETY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 123 (1.63%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENTAL STATUS CHANGES			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERSONALITY CHANGE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
CONCUSSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEEDING TUBE COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAD INJURY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT DISLOCATION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TACHYCARDIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
APHASIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATAXIA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL CYST			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL HAEMATOMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	2 / 64 (3.13%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL VENOUS THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLEX PARTIAL SEIZURES			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONVULSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 123 (2.44%)	2 / 64 (3.13%)	11 / 128 (8.59%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ENCEPHALOPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GRAND MAL CONVULSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	1 / 64 (1.56%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDROCEPHALUS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 123 (1.63%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTRACRANIAL PRESSURE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC CEREBRAL INFARCTION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROLOGICAL DECOMPENSATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROLOGICAL SYMPTOM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	2 / 64 (3.13%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARTIAL SEIZURES			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	2 / 64 (3.13%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUS HEADACHE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SOMNOLENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPEECH DISORDER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 123 (2.44%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 123 (1.63%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	5 / 123 (4.07%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	8 / 123 (6.50%)	2 / 64 (3.13%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	8 / 8	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 123 (1.63%)	1 / 64 (1.56%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	1 / 2	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	2 / 123 (1.63%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL PERFORATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 123 (1.63%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC STEATOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
RASH			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN DISORDER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
ADDISON'S DISEASE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTHYROIDISM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	1 / 64 (1.56%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MOBILITY DECREASED			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCLE HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULAR WEAKNESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOPOROSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BRONCHITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 123 (1.63%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CELLULITIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER OPHTHALMIC			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 123 (2.44%)	0 / 64 (0.00%)	4 / 128 (3.13%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	1 / 64 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

WOUND INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	2 / 64 (3.13%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	0 / 64 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
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	ced 20 mg +lom 110 mg/m2	pla 20 mg +lom 110 mg/m2	cediranib 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 123 (97.56%)	61 / 64 (95.31%)	124 / 128 (96.88%)
Vascular disorders			
HYPERTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	57 / 123 (46.34%)	4 / 64 (6.25%)	64 / 128 (50.00%)
occurrences (all)	74	4	85
General disorders and administration site conditions			

ASTHENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	12 / 123 (9.76%)	5 / 64 (7.81%)	5 / 128 (3.91%)
occurrences (all)	12	7	5
FATIGUE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	72 / 123 (58.54%)	30 / 64 (46.88%)	65 / 128 (50.78%)
occurrences (all)	89	44	86
OEDEMA PERIPHERAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	16 / 123 (13.01%)	8 / 64 (12.50%)	17 / 128 (13.28%)
occurrences (all)	18	10	20
Respiratory, thoracic and mediastinal disorders			
COUGH			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	16 / 123 (13.01%)	5 / 64 (7.81%)	13 / 128 (10.16%)
occurrences (all)	17	6	16
DYSPHONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	36 / 123 (29.27%)	6 / 64 (9.38%)	39 / 128 (30.47%)
occurrences (all)	37	7	41
DYSPNOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 123 (8.13%)	1 / 64 (1.56%)	7 / 128 (5.47%)
occurrences (all)	10	2	10
EPISTAXIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	11 / 123 (8.94%)	2 / 64 (3.13%)	3 / 128 (2.34%)
occurrences (all)	18	2	4
Psychiatric disorders			
AGITATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	2 / 64 (3.13%)	8 / 128 (6.25%)
occurrences (all)	1	2	8
ANXIETY			

alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 123 (7.32%)	3 / 64 (4.69%)	5 / 128 (3.91%)
occurrences (all)	9	3	5
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	6 / 123 (4.88%)	1 / 64 (1.56%)	10 / 128 (7.81%)
occurrences (all)	6	1	11
DEPRESSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 123 (8.13%)	3 / 64 (4.69%)	7 / 128 (5.47%)
occurrences (all)	11	3	7
INSOMNIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 123 (7.32%)	8 / 64 (12.50%)	9 / 128 (7.03%)
occurrences (all)	9	9	10
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	13 / 123 (10.57%)	2 / 64 (3.13%)	4 / 128 (3.13%)
occurrences (all)	17	2	4
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 123 (7.32%)	1 / 64 (1.56%)	2 / 128 (1.56%)
occurrences (all)	11	1	2
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	13 / 123 (10.57%)	2 / 64 (3.13%)	2 / 128 (1.56%)
occurrences (all)	16	2	2
PLATELET COUNT DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	21 / 123 (17.07%)	9 / 64 (14.06%)	3 / 128 (2.34%)
occurrences (all)	25	12	3
WEIGHT DECREASED			

alternative dictionary used: MedDRA 17			
subjects affected / exposed	14 / 123 (11.38%)	0 / 64 (0.00%)	6 / 128 (4.69%)
occurrences (all)	15	0	7
WHITE BLOOD CELL COUNT DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	15 / 123 (12.20%)	7 / 64 (10.94%)	0 / 128 (0.00%)
occurrences (all)	23	7	0
Injury, poisoning and procedural complications			
CONTUSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 123 (8.13%)	2 / 64 (3.13%)	7 / 128 (5.47%)
occurrences (all)	12	3	8
FALL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	6 / 123 (4.88%)	5 / 64 (7.81%)	5 / 128 (3.91%)
occurrences (all)	7	10	5
Nervous system disorders			
APHASIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 123 (3.25%)	3 / 64 (4.69%)	12 / 128 (9.38%)
occurrences (all)	4	4	14
CONVULSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 123 (7.32%)	7 / 64 (10.94%)	17 / 128 (13.28%)
occurrences (all)	10	9	21
DIZZINESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 123 (5.69%)	4 / 64 (6.25%)	13 / 128 (10.16%)
occurrences (all)	8	4	14
HEADACHE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	40 / 123 (32.52%)	24 / 64 (37.50%)	35 / 128 (27.34%)
occurrences (all)	65	30	47
HEMIPARESIS			

alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 123 (3.25%)	5 / 64 (7.81%)	4 / 128 (3.13%)
occurrences (all)	4	5	4
LETHARGY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 123 (5.69%)	3 / 64 (4.69%)	5 / 128 (3.91%)
occurrences (all)	9	4	6
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 123 (8.13%)	1 / 64 (1.56%)	1 / 128 (0.78%)
occurrences (all)	18	1	1
LEUKOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	25 / 123 (20.33%)	11 / 64 (17.19%)	2 / 128 (1.56%)
occurrences (all)	47	14	2
LYMPHOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	8 / 123 (6.50%)	8 / 64 (12.50%)	6 / 128 (4.69%)
occurrences (all)	11	9	7
NEUTROPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	28 / 123 (22.76%)	8 / 64 (12.50%)	2 / 128 (1.56%)
occurrences (all)	44	10	2
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	69 / 123 (56.10%)	28 / 64 (43.75%)	6 / 128 (4.69%)
occurrences (all)	123	35	6
Eye disorders			
VISION BLURRED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	6 / 123 (4.88%)	4 / 64 (6.25%)	5 / 128 (3.91%)
occurrences (all)	6	5	5
Gastrointestinal disorders			

ABDOMINAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	11 / 123 (8.94%)	2 / 64 (3.13%)	7 / 128 (5.47%)
occurrences (all)	11	2	7
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 123 (5.69%)	4 / 64 (6.25%)	5 / 128 (3.91%)
occurrences (all)	8	4	7
CONSTIPATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	26 / 123 (21.14%)	16 / 64 (25.00%)	26 / 128 (20.31%)
occurrences (all)	30	17	42
DIARRHOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	87 / 123 (70.73%)	11 / 64 (17.19%)	91 / 128 (71.09%)
occurrences (all)	253	18	219
DRY MOUTH			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 123 (5.69%)	1 / 64 (1.56%)	5 / 128 (3.91%)
occurrences (all)	7	1	5
FAECAL INCONTINENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 123 (0.00%)	0 / 64 (0.00%)	7 / 128 (5.47%)
occurrences (all)	0	0	7
NAUSEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	36 / 123 (29.27%)	22 / 64 (34.38%)	26 / 128 (20.31%)
occurrences (all)	65	31	39
ORAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	5 / 123 (4.07%)	4 / 64 (6.25%)	8 / 128 (6.25%)
occurrences (all)	12	6	14
STOMATITIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	3 / 123 (2.44%)	2 / 64 (3.13%)	14 / 128 (10.94%)
occurrences (all)	3	2	17
VOMITING			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	25 / 123 (20.33%)	7 / 64 (10.94%)	10 / 128 (7.81%)
occurrences (all)	36	10	17
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 123 (7.32%)	2 / 64 (3.13%)	11 / 128 (8.59%)
occurrences (all)	9	2	15
DRY SKIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	6 / 123 (4.88%)	3 / 64 (4.69%)	7 / 128 (5.47%)
occurrences (all)	6	3	8
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 123 (0.81%)	2 / 64 (3.13%)	9 / 128 (7.03%)
occurrences (all)	1	2	9
PETECHIAE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 123 (5.69%)	0 / 64 (0.00%)	4 / 128 (3.13%)
occurrences (all)	9	0	4
PRURITUS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	5 / 123 (4.07%)	4 / 64 (6.25%)	5 / 128 (3.91%)
occurrences (all)	6	4	5
RASH			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 123 (8.13%)	1 / 64 (1.56%)	13 / 128 (10.16%)
occurrences (all)	15	1	14
Renal and urinary disorders			
POLYURIA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 123 (0.00%)	4 / 64 (6.25%)	1 / 128 (0.78%)
occurrences (all)	0	4	1
URINARY INCONTINENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 123 (3.25%)	1 / 64 (1.56%)	10 / 128 (7.81%)
occurrences (all)	5	1	13
Endocrine disorders			
HYPOTHYROIDISM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 123 (8.13%)	0 / 64 (0.00%)	24 / 128 (18.75%)
occurrences (all)	11	0	24
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	8 / 123 (6.50%)	1 / 64 (1.56%)	8 / 128 (6.25%)
occurrences (all)	10	1	10
BACK PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 123 (8.13%)	7 / 64 (10.94%)	7 / 128 (5.47%)
occurrences (all)	13	7	7
MUSCLE SPASMS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 123 (5.69%)	3 / 64 (4.69%)	2 / 128 (1.56%)
occurrences (all)	8	3	2
MUSCULAR WEAKNESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	8 / 123 (6.50%)	6 / 64 (9.38%)	10 / 128 (7.81%)
occurrences (all)	8	6	11
PAIN IN EXTREMITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	12 / 123 (9.76%)	4 / 64 (6.25%)	4 / 128 (3.13%)
occurrences (all)	14	4	4
Infections and infestations			

UPPER RESPIRATORY TRACT INFECTION alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 123 (7.32%)	3 / 64 (4.69%)	6 / 128 (4.69%)
occurrences (all)	9	3	6
URINARY TRACT INFECTION alternative dictionary used: MedDRA 17			
subjects affected / exposed	8 / 123 (6.50%)	2 / 64 (3.13%)	5 / 128 (3.91%)
occurrences (all)	9	2	5
Metabolism and nutrition disorders DECREASED APPETITE alternative dictionary used: MedDRA 17			
subjects affected / exposed	28 / 123 (22.76%)	4 / 64 (6.25%)	16 / 128 (12.50%)
occurrences (all)	33	4	19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2010	Following the primary analysis of PFS and analysis of the secondary endpoints, the following changes were implemented: On approval of this amendment, treatment was unblinded, and patients who were still receiving cediranib were given the option, in consultation with their physician, to continue on treatment while deriving clinical benefit. Follow-up for OS ceased. Patients who had discontinued study treatment and were being followed for OS were to be discontinued from the study. End of study definition was changed to the last visit of the last patient for any protocol-related activity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported