Clinical trial results:
Multi-centre, randomised, double-blind phase II study comparing cediranib (AZD2171) plus gefitinib (Iressa, ZD1839) with cediranib plus placebo in subjects with recurrent/progressive glioblastoma (DORIC Trial)

Summary

EudraCT number	2010-021531-13
Trial protocol	GB
Global end of trial date	26 February 2014

Results information

Result version number	v1 (current)
This version publication date	09 November 2016
First version publication date	09 November 2016

Trial information

Trial identification

Sponsor protocol code	UCL/10/0035

Additional study identifiers

ISRCTN number	ISRCTN00549973
ClinicalTrials.gov id (NCT number)	NCT01310855
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E6BT
Public contact	public contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Treatment options for patients with glioblastoma are limited. It accounts for about 60% of brain tumours and life expectancy is limited. Novel treatment options for patients with GBM represents an unmet need. The main objective was to compare the efficacy of cediranib in combination with oral gefitinib with cediranib alone. The primary outcome variable was progression free survival as defined as the date from randomisation to the date of first progression or death due to any cause, whichever one came first.

Protection of trial subjects:

Patients were closely monitored for side effects while on treatment. Patients were monitored closely for haemorrhagic events and there were clear guidelines in the protocol for the prevention and management of these side effects, including dose adjustment schedules, and daily blood pressure monitoring. Patients also underwent ECGs during the trial.
The protocol listed drugs that were not permitted to be used concomitantly with study medication including the need to switch enzyme-inducing anti-epileptic drugs to non-enzyme inducing anti-epileptic drugs.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	24 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	30
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial opened in England sites only.
Date first site open: 16/05/2011
Date first patient entered: 24/05/2011
Date final patient entered: 06/08/2012
38 patients were recruited across 10 sites in the UK
The study closed to recruitment early due to AstraZeneca withdrawing the development of cediranib further

Pre-assignment

Screening details:

All eligibility criteria were based on routine tests and investigations. Patients must also have completed standard first-line treatment for glioblastoma including surgery.

Period 1

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

Blinding implementation details:

The randomisation schedule that provided details of individual patient treatment were produced by computer software that incorporated a standard procedure for generating random numbers. All study personnel were unaware of the randomised treatment until all decisions regarding the integrity and evaluability of the data from all patients had been made and documented.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cediranib and Gefitinib-matched Placebo

Arm description:

Patients enrolled to the placebo arm received 30mg od orally plus placebo od orally. Each cycle of treatment lasted 6 weeks.

Arm type	Placebo
Investigational medicinal product name	Cediranib
Investigational medicinal product code	AZD2171
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient received 30mg od orally. Treatment continued until confirmation of progression, patient decision or the development of unacceptable toxicity.

Cediranib was supplied as 35 x film-coated tablets per bottle, containing 30mg cediranib maleate/tablet (20mg and 15mg tablets also available where dose reductions were necessary). Other ingredients are mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate and magnesium stearate with a film coat containing hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide and titanium dioxide

Investigational medicinal product name	Gefitinib-matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patient received gefitinib-matched placebo, 500mg od orally

Drug distributed to patient as 100 x 250mg film-coated tablets identical to Gefitinib per bottle. The tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulphate and magnesium stearate with a film coat containing hypromellose, macrogol 300, red iron oxide, yellow iron oxide and titanium dioxide.

Arm title	Cediranib and Gefitinib

Arm description:

Patients enrolled in the experimental arm received cediranib 30mg od orally and gefitinib 500mg od orally

Arm type	Experimental
Investigational medicinal product name	Gefitinib
Investigational medicinal product code	ZD1839
Other name	IRESSA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

gefitinib 500mg od orally. Gefitinib was distributed to patient as 100 x film-coated tablets per bottle, containing 250mg of gefitinib/tablet.

Other ingredients are lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium, povidone (K29-32) (E1201), sodium laurilsulfate, magnesium stearate, hypromellose (E464), macrogol 300, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172).

Investigational medicinal product name	Cediranib
Investigational medicinal product code	AZD2171
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient received 30mg od orally. Treatment continued until confirmation of progression, patient decision or the development of unacceptable toxicity.

Cediranib was supplied as 35 x film-coated tablets per bottle, containing 30mg cediranib maleate/tablet (20mg and 15mg tablets also available where dose reductions were necessary). Other ingredients are mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate and magnesium stearate with a film coat containing hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide and titanium dioxide

Number of subjects in period 1	Cediranib and Gefitinib-matched Placebo	Cediranib and Gefitinib
Started	19	19
Completed	19	19

Baseline characteristics

Reporting groups	
Reporting group title	Cediranib and Gefitinib-matched Placebo
Reporting group description:	
Patients enrolled to the placebo arm received 30mg od orally plus placebo od orally. Each cycle of treatment lasted 6 weeks.	
Reporting group title	Cediranib and Gefitinib
Reporting group description:	
Patients enrolled in the experimental arm received cediranib 30mg od orally and gefitinib 500mg od orally	

Reporting group values	Cediranib and Gefitinib-matched Placebo	Cediranib and Gefitinib	Total
Number of subjects	19	19	38
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	15	30
From 65-84 years	4	4	8
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	6	11
Male	14	13	27

End points

End points reporting groups

Reporting group title	Cediranib and Gefitinib-matched Placebo
Reporting group description:	
Patients enrolled to the placebo arm received 30mg od orally plus placebo od orally. Each cycle of treatment lasted 6 weeks.	
Reporting group title	Cediranib and Gefitinib
Reporting group description:	
Patients enrolled in the experimental arm received cediranib 30mg od orally and gefitinib 500mg od orally	

Primary: Median Progression free survival (PFS)

End point title	Median Progression free survival (PFS)
End point description:	
Cediranib + Gefitinib: While 19 patients were randomised to this arm, one patient in this arm did not complete their patient diary so it was not possible to confirm that they took any of the randomized medication. Excluding this patient had no material effect on the hazard ratio (0.67, 90% CI 0.38 to 1.18), so they were included in the progression free survival analysis. This patient however was excluded from safety reporting.	
End point type	Primary
End point timeframe:	
Progression free survival (PFS) defined as the time from the date of randomisation to the date of first progression or death due to any cause, whichever one comes first.	

End point values	Cediranib and Gefitinib-matched Placebo	Cediranib and Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: month				
number (not applicable)	2.8	3.6		

Statistical analyses

Statistical analysis title	Progression-free survival
Statistical analysis description:	
Progression free survival (PFS) defined as the time from the date of randomisation to the date of first progression or death due to any cause, whichever one comes first.	
Comparison groups	Cediranib and Gefitinib-matched Placebo v Cediranib and Gefitinib

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.17
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.41
upper limit	1.26

Notes:

[1] - Survival times were presented in the form of summary statistics

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred between informed consent and 30 days post last trial treatment administration had to be reported.

Adverse event reporting additional description:

SAEs are listed in full. Non-serious adverse events includes all events (including SAEs) of grade 3 or higher with a 5% threshold frequency.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Cediranib + Gefitinib

Reporting group description:

Cediranib + Gefitinib. While 19 patients were randomised to this arm, one patient in this arm did not complete their patient diary so it was not possible to confirm that they took any of the randomized medication. Excluding this patient had no material effect on the hazard ratio (0.67, 90% CI 0.38 to 1.18), so they were included in progression free survival analysis. This patient however was excluded from safety reporting.

Reporting group title	Cediranib + Placebo

Reporting group description:

Cediranib + Placebo

Serious adverse events	Cediranib + Gefitinib	Cediranib + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	7 / 19 (36.84%)	
number of deaths (all causes)	18	19	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Pulmonary embolism			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive Disturbance			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphasia			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement involuntary			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other, hemispatial neglect of right arm			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other- Right Arm numbness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other- Right homonymous heminopia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
other-reduced mobility			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 18 (11.11%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other-weakness in right arm			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Cushingoid			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cediranib + Gefitinib	Cediranib + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)	12 / 19 (63.16%)	
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 18 (27.78%)	1 / 19 (5.26%)	
occurrences (all)	5	1	
Thromboembolic event			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
General disorders and administration site conditions			

Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 18 (22.22%)	6 / 19 (31.58%)	
occurrences (all)	4	6	
Psychiatric disorders			
Cognitive Disturbance			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
confusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Investigations			
Lymphopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 18 (16.67%)	2 / 19 (10.53%)	
occurrences (all)	3	2	
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
cholesterol high			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hypertrigylceridomia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
GGT increased			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Nervous system disorders			
Dysphasia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Seizure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
other			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
movements involuntary			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Paresthesia			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Eye disorders			
Eye disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
blurred vision			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Mucositis oral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
skin ulceration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			

Cushingoid			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle weakness right-sided			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
generalised muscle weakness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Rash Pustular			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 18 (11.11%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Anorexia			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 18 (5.56%)	3 / 19 (15.79%)	
occurrences (all)	1	3	
Hyperglycemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2011	ZD1839 was misspelt as AZD1839 on the original labels submitted with the CTA application. Trial procedures for dose reductions of Iressa(ZD1839) or Placebo have been changed so that a new patient diary will be issued in the event of a dose reduction, with the new number of tablets to take per day written at the top of the diary. This change has been made in order to reduce drug wastage and unnecessary patient trips to the pharmacy in order to dispense a new bottle of IMP (with a new label), as would have previously been necessary for a midcycle dose reduction from 2 tablets per day to 1 tablet per day.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 August 2012	AstraZenica discontinued development of cediranib during recruitment to the trial. Recruitment to the trial was thus terminated prematurely in 06/08/2012	-

Notes:

Limitations and caveats

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

-non-serious AEs: 'occurrences all number' cannot be provided as only highest grade experienced by patient collected on CRF; subjects affected number is entered instead
-serious AEs & non-serious AEs are listed under non-serious adverse event.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27232884