



Clinical trial results:

CIRCCa(Cediranib In Recurrent Cervical Cancer)

A Randomised Double Blind Phase II trial of carboplatin-paclitaxel plus cediranib versus carboplatin-paclitaxel plus placebo in metastatic/recurrent cervical cancer

Summary

EudraCT number	2009-011542-25
Trial protocol	GB
Global end of trial date	30 April 2015

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	11 May 2016

Trial information

Trial identification

Sponsor protocol code	C-2009-01
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Additional study identifiers

ISRCTN number	ISRCTN23516549
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	West Glasgow Ambulatory Care Hospital, Dalnair Street, Glasgow, United Kingdom, G3 8SW
Public contact	Karen Carty, Cancer Research UK Clinical Trials Unit, 0044 141 301 7191, karen.carty@glasgow.ac.uk
Scientific contact	Jim Paul, Cancer Research UK Clinical Trials Unit, 0044 141 301 7188, james.paul@glasgow.ac.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, Glasgow, United Kingdom, G12 8QQ
Public contact	Karen Carty, Cancer Research UK Clinical Trials Unit, 0044 141 301 7197, karen.carty@glasgow.ac.uk
Scientific contact	James Paul, Cancer Research UK Clinical Trials Unit, 0044 141 301 7188, james.paul@glasgow.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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to provide preliminary evidence regarding whether the addition of cediranib to a combination of carboplatin and paclitaxel will increase progression free survival by 50% in patients with metastatic recurrent cervical cancer.

Protection of trial subjects:

As part of the study patients required to attend for additional clinic visits and investigations which would be above those considered to be standard care. The visit schedule and the number and type of investigations were fully explained to patients verbally and in writing via the patient information sheet to ensure patients were fully aware what was entailed in participating in the trial prior to them consenting to the study.

The patient information sheet also fully explained the design of the study (randomised, double blind trial) that half of patients would receive study treatment (Cediranib) in addition to their chemotherapy with the other half receiving placebo in addition to their chemotherapy.

The side effects of chemotherapy Carboplatin and Paclitaxel were explained in patient information sheet, as were the expected side effects for the investigational medicinal product Cediranib. All patients were closely monitored throughout the course of the study for adverse events and were advised to report adverse events to their study team as they arose.

Specific measures were included in the protocol for management of adverse events related to Cediranib.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2010
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: 69
Worldwide total number of subjects	69
EEA total number of subjects	69

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)	65
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study opened to recruitment on 03rd June 2010 and closed to recruitment on 31st July 2012. This study was opened to recruitment in the United Kingdom

Pre-assignment

Screening details:

The screening period for the study was up to 28 days prior to randomisation. Prior to screening investigations commencing patient must have provided informed consent to participate in the study. Patients treated with potent inhibitors of CYP3A4 and 2C8 were excluded from the trial if they had received these within 2 wks of 1st planned dose.

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Matched placebo provided for oral drug

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received either treatment drug [Cediranib] 20 mg daily or placebo daily throughout 6 cycles of chemotherapy treatment (Approx 18 weeks of chemotherapy) following completion of chemotherapy patients continued to receive either treatment drug or placebo daily until disease progression.

Arm title	Experimental
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Arm description:

Cediranib

Arm type	Experimental
Investigational medicinal product name	Cediranib (AZD2171)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received either treatment drug (20mg) of placebo daily throughout 6 cycles of chemotherapy treatment (approx. 18 weeks of chemotherapy) following completion of chemotherapy patients continued to receive either treatment drug or placebo daily until disease progression

Number of subjects in period 1	Control	Experimental
Started	35	34
Completed	31	30
Not completed	4	4
Consent withdrawn by subject	2	2
No post-baseline data	-	2
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Control
Reporting group description: Placebo	
Reporting group title	Experimental
Reporting group description: Cediranib	

Reporting group values	Control	Experimental	Total
Number of subjects	35	34	69
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)	35	30	65
From 65-84 years	0	4	4
85 years and over	0	0	0
Age continuous Units: years			
median	44	43.5	
inter-quartile range (Q1-Q3)	34 to 53	37 to 60	-
Gender categorical Units: Subjects			
Female	35	34	69
Male	0	0	0
ECOG Performance Status at Randomisation			
Minimisation factor: ECOG Performance Status at Randomisation			
Units: Subjects			
ECOG 0	14	17	31
ECOG 1	21	17	38
Number of lines of previous treatment			
Minimisation factor: Number of lines of previous treatment			
Units: Subjects			
0 lines	6	6	12
1 line	29	28	57
Disease site			
Minimisation factor: Disease site			
Units: Subjects			
Local relapse only	3	6	9
Extra pelvic metastases only	12	9	21

Local relapse and extra pelvic metastases	20	19	39
Disease-free survival after primary therapy/primary stage IVb			
Minimisation factor: Disease-free survival after primary therapy/primary stage IVb			
Units: Subjects			
<=12 months	16	14	30
>12 months	16	17	33
Treatment naive stage IVb	3	3	6

Subject analysis sets

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomised	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised patients who received at least 1 dose of study medication	

Reporting group values	Intention-to-treat	Safety	
Number of subjects	69	67	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	65	63	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous			
Units: years			
median	44	44	
inter-quartile range (Q1-Q3)	35 to 57	35 to 57	
Gender categorical			
Units: Subjects			
Female	69	67	
Male	0	0	
ECOG Performance Status at Randomisation			
Minimisation factor: ECOG Performance Status at Randomisation			
Units: Subjects			
ECOG 0	31		
ECOG 1	38		
Number of lines of previous treatment			
Minimisation factor: Number of lines of previous treatment			
Units: Subjects			

0 lines	12		
1 line	57		
Disease site			
Minimisation factor: Disease site			
Units: Subjects			
Local relapse only	9		
Extra pelvic metastases only	21		
Local relapse and extra pelvic metastases	39		
Disease-free survival after primary therapy/primary stage IVb			
Minimisation factor: Disease-free survival after primary therapy/primary stage IVb			
Units: Subjects			
<=12 months	30		
>12 months	33		
Treatment naive stage IVb	6		

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Placebo	
Reporting group title	Experimental
Reporting group description:	
Cediranib	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomised	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised patients who received at least 1 dose of study medication	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe:	
Patients were assessed after chemotherapy cycles 2, 4 and 6 and then every 2 months during follow-up	

End point values	Control	Experimental	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	35	34	69	
Units: months				
median (confidence interval 80%)	6.7 (6.2 to 7.2)	8.1 (7.4 to 8.8)	7.2 (6.7 to 7.7)	

Statistical analyses

Statistical analysis title	Cox
Statistical analysis description:	
Cox proportional hazards model incorporating study stratification factors	
Comparison groups	Experimental v Control

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.032 ^[2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.4
upper limit	0.85

Notes:

[1] - Cox

[2] - 1-sided, 20% significance level

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were followed until resolution or for at least 30 days after discontinuation of study medication, whichever came first, or until toxicity was resolved to baseline or < Grade 1, or until the toxicity was considered to be irreversible

Adverse event reporting additional description:

Adverse events were reported following every cycle of chemotherapy and every 2 months during follow-up

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	4.0
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Reporting groups

Reporting group title	Control
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Reporting group description:

Placebo

Reporting group title	Experimental
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Reporting group description:

Cediranib

Serious adverse events	Control	Experimental	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 35 (51.43%)	19 / 32 (59.38%)	
number of deaths (all causes)	27	25	
number of deaths resulting from adverse events	0	1	
Investigations			
Creatinine increased			
subjects affected / exposed	4 / 35 (11.43%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 35 (0.00%)	4 / 32 (12.50%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 35 (0.00%)	3 / 32 (9.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 35 (17.14%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	4 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 35 (0.00%)	5 / 32 (15.63%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	4 / 35 (11.43%)	6 / 32 (18.75%)	
occurrences causally related to treatment / all	1 / 4	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 35 (5.71%)	3 / 32 (9.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 35 (5.71%)	4 / 32 (12.50%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 35 (0.00%)	4 / 32 (12.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 35 (5.71%)	6 / 32 (18.75%)	
occurrences causally related to treatment / all	1 / 3	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 35 (8.57%)	3 / 32 (9.38%)	
occurrences causally related to treatment / all	3 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 35 (0.00%)	4 / 32 (12.50%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic perforation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)	4 / 32 (12.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleuritic pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	2 / 35 (5.71%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations - Other			
subjects affected / exposed	0 / 35 (0.00%)	4 / 32 (12.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 35 (5.71%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 35 (0.00%)	3 / 32 (9.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control	Experimental	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)	32 / 32 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 35 (5.71%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	9 / 35 (25.71%)	18 / 32 (56.25%)	
occurrences (all)	13	40	
Lymphoedema			
subjects affected / exposed	4 / 35 (11.43%)	0 / 32 (0.00%)	
occurrences (all)	9	0	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	6 / 35 (17.14%)	5 / 32 (15.63%)	
occurrences (all)	11	7	
Fatigue			
subjects affected / exposed	30 / 35 (85.71%)	31 / 32 (96.88%)	
occurrences (all)	119	146	
Flu like symptoms			
subjects affected / exposed	2 / 35 (5.71%)	2 / 32 (6.25%)	
occurrences (all)	2	5	
Injection site reaction			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	6	
Pain			
subjects affected / exposed	20 / 35 (57.14%)	19 / 32 (59.38%)	
occurrences (all)	35	39	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	3 / 35 (8.57%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Vaginal discharge			
subjects affected / exposed	6 / 35 (17.14%)	0 / 32 (0.00%)	
occurrences (all)	15	0	

Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	3 / 32 (9.38%) 3	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 9	5 / 32 (15.63%) 7	
Dyspnoea subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 11	9 / 32 (28.13%) 16	
Epistaxis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 32 (6.25%) 2	
Hoarseness subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 32 (6.25%) 3	
Sore throat subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	0 / 32 (0.00%) 0	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	0 / 32 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	4 / 32 (12.50%) 4	
Investigations			
Creatinine increased subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 32 (0.00%) 0	
Neutrophil count decreased subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	4 / 32 (12.50%) 4	
Weight loss subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 32 (6.25%) 3	

White blood cell decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	3 / 32 (9.38%) 5	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	0 / 32 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 32 (6.25%) 7	
Dysgeusia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	3 / 32 (9.38%) 9	
Headache subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	6 / 32 (18.75%) 9	
Paresthesia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	0 / 32 (0.00%) 0	
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5	7 / 32 (21.88%) 12	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	16 / 35 (45.71%) 56	18 / 32 (56.25%) 70	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	8 / 35 (22.86%) 17	4 / 32 (12.50%) 8	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 9	6 / 32 (18.75%) 8	
Constipation subjects affected / exposed occurrences (all)	23 / 35 (65.71%) 40	20 / 32 (62.50%) 38	

Diarrhoea			
subjects affected / exposed	18 / 35 (51.43%)	29 / 32 (90.63%)	
occurrences (all)	29	130	
Dry mouth			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	5	
Dyspepsia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Mucositis oral			
subjects affected / exposed	11 / 35 (31.43%)	12 / 32 (37.50%)	
occurrences (all)	14	19	
Nausea			
subjects affected / exposed	23 / 35 (65.71%)	23 / 32 (71.88%)	
occurrences (all)	59	63	
Vomiting			
subjects affected / exposed	15 / 35 (42.86%)	15 / 32 (46.88%)	
occurrences (all)	24	27	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 35 (60.00%)	17 / 32 (53.13%)	
occurrences (all)	84	62	
Pain of skin			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Rash acneiform			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Rash maculo-papular			

subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 7	2 / 32 (6.25%) 2	
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 35 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	3 / 35 (8.57%)	3 / 32 (9.38%)	
occurrences (all)	7	6	
Proteinuria			
subjects affected / exposed	10 / 35 (28.57%)	11 / 32 (34.38%)	
occurrences (all)	22	27	
Urinary tract obstruction			
subjects affected / exposed	2 / 35 (5.71%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 35 (14.29%)	5 / 32 (15.63%)	
occurrences (all)	15	7	
Back pain			
subjects affected / exposed	12 / 35 (34.29%)	6 / 32 (18.75%)	
occurrences (all)	27	17	
Myalgia			
subjects affected / exposed	8 / 35 (22.86%)	7 / 32 (21.88%)	
occurrences (all)	22	7	
Pain in extremity			
subjects affected / exposed	2 / 35 (5.71%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Infections and infestations			
Infections and infestation - Other			
subjects affected / exposed	3 / 35 (8.57%)	0 / 32 (0.00%)	
occurrences (all)	6	0	
Skin infection			
subjects affected / exposed	2 / 35 (5.71%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Tooth infection			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 32 (6.25%) 2	
Upper respiratory infection subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	3 / 32 (9.38%) 3	
Urinary tract infection subjects affected / exposed occurrences (all)	8 / 35 (22.86%) 9	6 / 32 (18.75%) 10	
Vaginal infection subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 32 (6.25%) 2	
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 10	9 / 32 (28.13%) 27	
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	3 / 32 (9.38%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2012	<p>The protocol for the study was amended to reduce the sample size of the study from 130 patients to 80 patients. This amendment was made as result of AstraZeneca manufacturers of cediranib informing following negative results in other studies using Cediranib they had no plans to further develop the drug or manufacture further supplies of the drug. Due to this AZ informed they would require the majority of patients on CIRCCa to have completed study treatment by end of December 2012, they had confirmed they would commit to supply cediranib to patients for at least a further 6 months after this and any patients who are clearly continuing to benefit beyond that point.</p> <p>Based on this information the implications of this in relation to CIRCCa were discussed with the Independent Data Monitoring Committee (DMC) and Trial Steering Committee (TSC). The DMC and TSC carefully reviewed the CIRCCa documentation (Protocol and Patient Information Sheet/Consent Form) in relation to the information received from AZ, taking into account the associated translational aspects of CIRCCa .After carefully considering and taking into account all the information, the DMC and TSC endorsed the scientific importance of the study and felt that it should continue. They gave the following recommendations:</p> <p>If feasible should consider reducing the sample size for the study to ensure completion of the study by December 2012. The statistics for the study were reviewed, for the study to deliver a study with 80% power, 20% 1-sided level of statistical significance, the study will require at least 80 patients. Protocol was amended accordingly to reduce the sample size.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported