Clinical trial results:
Phase I Trial of CEDIRANIB (AZD2171), an Orally Bioavailable Antiangiogenic Agent, in Children and Adolescents With Refractory or Recurrent Solid Tumors

Summary

EudraCT number	2012-001155-39
Trial protocol	Outside EU/EEA
Global end of trial date	01 October 2011

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	060152, 06-C-0152, D8480C00016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00321581
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	NA, Sodertalje, Sweden, S-151-85
Public contact	Information Centre, AstraZeneca, Information.centre@astrazeneca.com
Scientific contact	Information Centre, AstraZeneca, Information.centre@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 August 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• Determine the maximum tolerated dose (MTD) and dose-limiting toxicities of orally administered cediranib on a daily dose for 28 consecutive days schedule in children and adolescents with refractory childhood solid tumors.
• Define the toxicity spectrum of oral cediranib in children and adolescents.
• Assess the pharmacokinetics of oral cediranib in the pediatric population.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice (GCP).

Patients who were 18 years of age were offered the opportunity to assign a Durable Power of Attorney (DPA) so that another person could make decisions about their medical care if they became incapacitated or cognitively impaired. Adults (18 years and over) who were cognitively impaired prior to study entry and who have not previously assigned DPA to a family member or friend were not eligible for the study, because they could not give informed consent.

All patients or their legal guardians (if the patients were <18 years old) signed an informed consent form prior to the determination of patient eligibility. After confirmation of patient eligibility all patients or their legal guardians voluntarily signed the IRB approved informed consent form to document their understanding of the investigational nature and the risks of the study before any protocol related procedures were performed.

The parent who signed the consent for a minor was a legally recognized parent or guardian. Where deemed appropriate by the clinician and the child's parents or guardian, the child was also included in all discussions about the study and verbal assent obtained. Investigators from the Pharmacology & Experimental Therapeutics Section of the Paediatric Oncology Branch, or investigators from participating institutions, led these discussions.

The study was conducted by paediatric oncologists who have extensive experience in performing investigational drug studies in children

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	01 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	18
EEA total number of subjects	0

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)	4
Adolescents (12-17 years)	12
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose level 8 mg/m2/d

Arm description: -

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

Dosage and administration details:
8 mg/m2/d

Arm title	Dose level 12 mg/m2/d

Arm description: -

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

Dosage and administration details:
12 mg/m2/d

Arm title	Dose level 17 mg/m2/d

Arm description: -

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

Dosage and administration details:
17 mg/m2/d

Number of subjects in period 1	Dose level 8 mg/m2/d	Dose level 12 mg/m2/d	Dose level 17 mg/m2/d
Started	3	10	5
Completed	3	10	5

Period 2	
Period 2 title	Dose escalation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Cohort 1 - Dose level 12 mg/m2/d
Arm description: Dose level 12 mg/m2/d	
Arm type	Experimental
Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 12 mg/m2/d	
Arm title	Cohort 2 - Dose level 8 mg/m2/d
Arm description: Dose level 8 mg/m2/d	
Arm type	Experimental
Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 8 mg/m2/d	
Arm title	Cohort 3 - Dose level 12 mg/m2/d
Arm description: Dose level 12 mg/m2/d	
Arm type	Experimental

Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
12 mg/m2/d

Arm title	Cohort 4 - Dose level 17 mg/m2/d

Arm description:
Dose level 17 mg/m2/d

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

Dosage and administration details:
17 mg/m2/d

Number of subjects in period 2	Cohort 1 - Dose level 12 mg/m2/d	Cohort 2 - Dose level 8 mg/m2/d	Cohort 3 - Dose level 12 mg/m2/d
Started	2	3	8
Completed	2	3	8

Number of subjects in period 2	Cohort 4 - Dose level 17 mg/m2/d
Started	5
Completed	5

Period 3

Period 3 title	Overall Study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose level 8 mg/m2/d

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
8 mg/m2/d

Arm title	Dose level 12 mg/m2/d

Arm description: -

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

Dosage and administration details:
12 mg/m2/d

Arm title	Dose level 17 mg/m2/d

Arm description: -

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

Dosage and administration details:
17 mg/m2/d

Number of subjects in period 3	Dose level 8 mg/m2/d	Dose level 12 mg/m2/d	Dose level 17 mg/m2/d
Started	3	10	5
Completed	0	0	0
Not completed	3	10	5
30 days after last dose	-	1	1
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	-	3	1
Disease progression	3	1	-
Redused treatment	-	1	1
Lost to follow-up	-	1	2
30 days off therapy	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	18	18	
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)	4	4	
Adolescents (12-17 years)	12	12	
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	15		
full range (min-max)	8 to 18	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	10	10	
Diagnosis Units: Subjects			
Ewing sarcoma	4	4	
Osteosarcoma	4	4	
Synovial sarcoma recurrent	2	2	
Alveolar soft part sarcoma recurrent	2	2	
Other	6	6	

End points

End points reporting groups

Reporting group title	Dose level 8 mg/m2/d
Reporting group description: -	
Reporting group title	Dose level 12 mg/m2/d
Reporting group description: -	
Reporting group title	Dose level 17 mg/m2/d
Reporting group description: -	
Reporting group title	Cohort 1 - Dose level 12 mg/m2/d
Reporting group description: Dose level 12 mg/m2/d	
Reporting group title	Cohort 2 - Dose level 8 mg/m2/d
Reporting group description: Dose level 8 mg/m2/d	
Reporting group title	Cohort 3 - Dose level 12 mg/m2/d
Reporting group description: Dose level 12 mg/m2/d	
Reporting group title	Cohort 4 - Dose level 17 mg/m2/d
Reporting group description: Dose level 17 mg/m2/d	
Reporting group title	Dose level 8 mg/m2/d
Reporting group description: -	
Reporting group title	Dose level 12 mg/m2/d
Reporting group description: -	
Reporting group title	Dose level 17 mg/m2/d
Reporting group description: -	

Primary: Toxicity

End point title	Toxicity[1]
End point description: First cycle of treatment	
End point type	Primary
End point timeframe: Cycle 1	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a dose escalation study, there is no formal statistical analysis. A count of toxicities associated with each dose level is presented

End point values	Cohort 1 - Dose level 12 mg/m2/d	Cohort 2 - Dose level 8 mg/m2/d	Cohort 3 - Dose level 12 mg/m2/d	Cohort 4 - Dose level 17 mg/m2/d
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[2]	3	7	4
Units: Subject				
Leukopenia	0	0	2	0
Neutropenia	0	0	1	0
Abdominal pain	0	1	3	4

Anorexia	0	2	1	3
Constipation	0	0	1	2
Diarrhea	1	1	2	4
Stomatitis	0	0	0	1
Nausea	1	1	4	4
Vomiting	1	0	1	2
Fatigue	0	1	4	1
lethargy	1	0	0	0
Weight loss	0	1	2	2
Prolonger QTc	1	0	0	0
Premature ventricular complexes	1	0	0	0
Decreased left ventricular function	1	2	1	1
Hypertension	1	0	0	1
Infection, Grade 1 or 2 ANC	0	0	2	0
Increased AST	1	0	0	1
Increased ALT	1	0	0	1
Hypoalbuminemia	0	0	2	0
Hypoglycemia	0	1	0	0
Proteinuria	0	1	0	0
Chest pain	0	0	0	2
Headache	0	0	2	2
Cystitis	0	1	0	0

Notes:

[2] - Both patients had DLT.Dose de-escalated to 8 mg/m2/d,re-escalated to12mg/m2/d,then 17mg/m2/d

Statistical analyses

No statistical analyses for this end point

Secondary: AUC

End point title	AUC

End point description:

End point type	Secondary

End point timeframe:

48 hours

End point values	Dose level 8 mg/m2/d	Dose level 12 mg/m2/d	Dose level 17 mg/m2/d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	2	
Units: ngxh/mL				
arithmetic mean (geometric coefficient of variation)				
0-24hrs	440 (± 36)	800 (± 45)	1140 (± 96)	
0-48hrs	530 (± 37)	1000 (± 44)	1570 (± 95)	
0-inf	540 (± 39)	1070 (± 43)	1870 (± 95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax

End point title	Cmax

End point description:

End point type	Secondary

End point timeframe:

48 hours

End point values	Dose level 8 mg/m2/d	Dose level 12 mg/m2/d	Dose level 17 mg/m2/d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	2	
Units: ng/mL				
arithmetic mean (geometric coefficient of variation)	52 (± 46)	70 (± 35)	106 (± 105)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax

End point title	Tmax

End point description:

Tmax

End point type	Secondary

End point timeframe:

48 hours

End point values	Dose level 8 mg/m2/d	Dose level 12 mg/m2/d	Dose level 17 mg/m2/d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	2	
Units: hours				
median (full range (min-max))	3 (2.1 to 4)	4 (2.2 to 8.2)	4.5 (3 to 6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose to end of study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0
Reporting groups	
Reporting group title	12 mg/m2
Reporting group description: Dose level 12 mg/m2	
Reporting group title	8 mg/m2
Reporting group description: Dose level 8mg/m2	
Reporting group title	17 mg/m2
Reporting group description: Dose level 17mg/m2	

Serious adverse events	12 mg/m2	8 mg/m2	17 mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	1 / 3 (33.33%)	2 / 5 (40.00%)
number of deaths (all causes)	7	0	2
number of deaths resulting from adverse events	2	0	0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Cardiac disorders			
Left ventricular failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Ventricular extrasystoles			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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 disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory tract haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 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	12 mg/m2	8 mg/m2	17 mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	3 / 3 (100.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	2 / 5 (40.00%)
occurrences (all)	6	1	4
Hypotension			

subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	3 / 5 (60.00%)
occurrences (all)	3	0	6
Chills			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	7 / 10 (70.00%)	2 / 3 (66.67%)	3 / 5 (60.00%)
occurrences (all)	10	7	10
Ill-defined disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	4 / 10 (40.00%)	1 / 3 (33.33%)	3 / 5 (60.00%)
occurrences (all)	16	2	5
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	2 / 5 (40.00%)
occurrences (all)	3	3	11
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Bronchospasm			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Cough			
subjects affected / exposed	3 / 10 (30.00%)	2 / 3 (66.67%)	2 / 5 (40.00%)
occurrences (all)	3	4	2
Dysphonia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	2 / 3 (66.67%)	1 / 5 (20.00%)
occurrences (all)	1	2	2
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pneumothorax			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	2 / 5 (40.00%)
occurrences (all)	7	0	3
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Anxiety			

subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	1	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	9
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	2	1	11
Blood albumin decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	2	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	5
Blood bicarbonate decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	2	2
Blood calcium decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood calcium increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood glucose decreased			

subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	1	2	1
Blood phosphorus decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood sodium decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Ear, nose and throat examination abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	4	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haemoglobin urine present			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	4	4	0
Neutrophil count decreased			

subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Protein urine present			
subjects affected / exposed	0 / 10 (0.00%)	2 / 3 (66.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	4 / 10 (40.00%)	2 / 3 (66.67%)	4 / 5 (80.00%)
occurrences (all)	8	2	7
Weight increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	5	0	1
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Cardiac disorder			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Left ventricular failure			
subjects affected / exposed	2 / 10 (20.00%)	3 / 3 (100.00%)	1 / 5 (20.00%)
occurrences (all)	2	3	1
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pericarditis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	3	3	0

Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	4 / 10 (40.00%)	1 / 3 (33.33%)	3 / 5 (60.00%)
occurrences (all)	14	1	27
Blood and lymphatic system disorders			
Lymphatic disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Eye disorders			
Eyelid function disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 10 (50.00%)	1 / 3 (33.33%)	4 / 5 (80.00%)
occurrences (all)	10	3	13
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	3 / 5 (60.00%)
occurrences (all)	5	1	4
Diarrhoea			
subjects affected / exposed	7 / 10 (70.00%)	2 / 3 (66.67%)	5 / 5 (100.00%)
occurrences (all)	57	5	21
Gastrointestinal disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	8 / 10 (80.00%)	1 / 3 (33.33%)	4 / 5 (80.00%)
occurrences (all)	10	8	21

Stomatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Tooth disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	5 / 10 (50.00%)	1 / 3 (33.33%)	3 / 5 (60.00%)
occurrences (all)	7	1	8
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Exfoliative rash			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	3	0	2
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Pruritus			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	5	2	0
Skin disorder			
subjects affected / exposed	1 / 10 (10.00%)	2 / 3 (66.67%)	0 / 5 (0.00%)
occurrences (all)	1	5	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Urogenital disorder			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	2 / 5 (40.00%)
occurrences (all)	1	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	2 / 5 (40.00%)
occurrences (all)	2	1	3
Bone pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	3 / 5 (60.00%)
occurrences (all)	1	0	5
Musculoskeletal disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	1 / 5 (20.00%)
occurrences (all)	1	6	4
Neck pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Infection			
subjects affected / exposed	3 / 10 (30.00%)	2 / 3 (66.67%)	0 / 5 (0.00%)
occurrences (all)	5	5	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 6	2 / 3 (66.67%) 3	4 / 5 (80.00%) 7
Dehydration subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 13	0 / 3 (0.00%) 0	2 / 5 (40.00%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2007	The first protocol amendment (CSP Version 01 Aug 07) was initiated to update hypertension management guidelines, clarify the dose limiting hypertension and proteinuria and add DCEMRI instructions to the protocol along with other administrative changes.
28 January 2008	The second protocol amendment (CSP Version 29 Jan 08) was initiated to incorporate an additional dose level (Dose level -1 (8 mg/m2)) and to increase the study accrual to n=40. EKG and electrocardiogram safety monitoring assessments were incorporated along with update thyroid dysfunction management guidelines. Eligibility criteria were updated to incorporate to add cardiac dysfunction and the safety measures for the assessment of prolonged QTc. Updated information on dose limiting toxicities was added to the protocol along with other administrative changes.
11 February 2009	The third protocol amendment (CSP Version 11 Feb 09) was initiated to incorporate non-contrast MRI measures to assess distal femoral growth plate in patients. Information on how to disperse cediranib tablets for oral dosing was added to the protocol along with updated safety data from the data from Investigator Brochure. Consent form revisions were also made along with other administrative changes.
09 March 2009	The fourth protocol amendment (CSP Version 03 Mar 09) was initiated to remove the exclusion of patients with brain metastases. Updates data on the activity of cediranib in alveolar soft part sarcoma was added to the protocol along with other administrative changes.
01 October 2009	The fifth protocol Amendment (CSP Version 01 Oct 09) was initiated to clarify inconsistencies in the protocol regarding criteria for dose escalation and dose interruptions. The number of children <12 to be treated at the MTD was increased from 3 to 6, therefore increasing the accrual ceiling from 33 to 36. The risk of pneumothorax was added to the protocol and consent form along with other administrative changes.
30 November 2009	The sixth protocol amendment (CSP Version 30 Nov 09) was initiated to record a change in Principle Investigator. The amendment also covered the removal of AML cohort at the request of the sponsor and clarification of timing of grow plate analysis (Scanograms and MRI). The interval between tumor restaging evaluations after cycle 8 was increased from every 2 months to every 4 months along with other administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study sponsored by AZ, conducted by NCI; analysis and reporting was performed exclusively by NCI group [see link]. To provide as complete a report online as possible, summaries for demo, AE were generated by AZ for all 18 patients who received drug.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21060028