

**Clinical trial results:****A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy****Summary**

EudraCT number	2013-001010-14
Trial protocol	HU AT SE BE CZ PT IE IT NL SK GB ES DE DK FR FI PL
Global end of trial date	19 August 2020

Results information

Result version number	v1 (current)
This version publication date	25 April 2022
First version publication date	25 April 2022

Trial information**Trial identification**

Sponsor protocol code	XL184-308
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01865747
WHO universal trial number (UTN)	U1111-1144-7394

Notes:

Sponsors

Sponsor organisation name	Exelixis, Inc.
Sponsor organisation address	1851 Harbor Bay Parkway, Alameda, United States, 94502
Public contact	Exelixis Medical Affairs, Exelixis, Inc., +1 8883935494, druginfo@exelixis.com
Scientific contact	Exelixis Medical Affairs, Exelixis, Inc., +1 8883935494, druginfo@exelixis.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	22 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 May 2015
Global end of trial reached?	Yes
Global end of trial date	19 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the effect of cabozantinib compared with everolimus on progression-free survival (PFS) and overall survival (OS) in subjects with advanced renal cell cancer that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.

Protection of trial subjects:

Study protocol, informed consent form, and other study documents reviewed and approved by ethics committees and regulatory agencies, as required. All subjects signing informed consent prior to study related procedures (including screening assessments), and throughout the study as new information became available. An IDMC was established to review safety data on an ongoing basis and make recommendations to the Sponsor if deemed warranted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2013
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	Poland: 17
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 57
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	United States: 200

Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Chile: 12
Worldwide total number of subjects	658
EEA total number of subjects	275

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)	394
From 65 to 84 years	263
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening evaluations were completed within 28 days prior to randomization to determine eligibility of subjects.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	Cabozantinib
------------------	--------------

Arm description: -

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

Dosage and administration details:

Cabozantinib administered once daily

Arm title	Everolimus
------------------	------------

Arm description: -

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

Dosage and administration details:

Everolimus administered orally once daily

Number of subjects in period 1	Cabozantinib	Everolimus
Started	330	328
Completed	330	328

Baseline characteristics

Reporting groups

Reporting group title	Cabozantinib
Reporting group description: -	
Reporting group title	Everolimus
Reporting group description: -	

Reporting group values	Cabozantinib	Everolimus	Total
Number of subjects	330	328	658
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)	196	198	394
From 65-84 years	133	130	263
85 years and over	1	0	1
Age continuous Units: years			
median	62.5	62.0	
full range (min-max)	32 to 86	31 to 84	-
Gender categorical Units: Subjects			
Female	77	86	163
Male	253	241	494
Missing (not recorded)	0	1	1

End points

End points reporting groups

Reporting group title	Cabozantinib
Reporting group description: -	
Reporting group title	Everolimus
Reporting group description: -	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe:	
assessed until 247 PFS events were observed in the first 375 randomized subjects	

End point values	Cabozantinib	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	188		
Units: months				
median (confidence interval 95%)	7.4 (3.7 to 13.5)	3.8 (3.7 to 5.4)		

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	Cabozantinib v Everolimus
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.76

Secondary: Overall Survival

End point title	Overall Survival
-----------------	------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

assessed at a pre-specified secondary interim analysis (320 deaths observed)

End point values	Cabozantinib	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	328		
Units: months				
median (confidence interval 95%)	21.4 (18.7 to 21.4)	16.5 (7.5 to 16.5)		

Statistical analyses

Statistical analysis title	OS analysis
----------------------------	-------------

Comparison groups	Cabozantinib v Everolimus
-------------------	---------------------------

Number of subjects included in analysis	658
---	-----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	superiority
---------------	-------------

P-value	= 0.0003
---------	----------

Method	Logrank
--------	---------

Parameter estimate	Hazard ratio (HR)
--------------------	-------------------

Point estimate	0.66
----------------	------

Confidence interval

level	95 %
-------	------

sides	2-sided
-------	---------

lower limit	0.53
-------------	------

upper limit	0.83
-------------	------

Secondary: Objective Response Rate

End point title	Objective Response Rate
-----------------	-------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Analyzed at the time of the PFS analysis, in all subjects

End point values	Cabozantinib	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	328		
Units: percentage of patients	17	3		

Statistical analyses

Statistical analysis title	ORR Analysis
Comparison groups	Cabozantinib v Everolimus
Number of subjects included in analysis	658
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:
reported through the primary PFS analysis

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

Reporting groups

Reporting group title	Cabozantinib
-----------------------	--------------

Reporting group description: -

Reporting group title	Everolimus
-----------------------	------------

Reporting group description: -

Serious adverse events	Cabozantinib	Everolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	131 / 331 (39.58%)	139 / 322 (43.17%)	
number of deaths (all causes)	15	23	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	2 / 331 (0.60%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 331 (0.30%)	5 / 322 (1.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	2 / 331 (0.60%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	4 / 331 (1.21%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 331 (1.21%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 331 (0.60%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	6 / 331 (1.81%)	5 / 322 (1.55%)	
occurrences causally related to treatment / all	4 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 331 (1.21%)	6 / 322 (1.86%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	1 / 1	1 / 1	
Generalised oedema			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
local swelling			

subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 331 (0.00%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
multi-organ failure			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	5 / 331 (1.51%)	4 / 322 (1.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			

subjects affected / exposed	3 / 331 (0.91%)	4 / 322 (1.24%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 331 (1.81%)	13 / 322 (4.04%)	
occurrences causally related to treatment / all	0 / 6	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 331 (0.00%)	3 / 322 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	10 / 331 (3.02%)	6 / 322 (1.86%)	
occurrences causally related to treatment / all	1 / 10	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 331 (0.00%)	3 / 322 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonitis			
subjects affected / exposed	0 / 331 (0.00%)	8 / 322 (2.48%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	4 / 331 (1.21%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 331 (1.81%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	5 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 331 (0.60%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Decreased appetite			
subjects affected / exposed	2 / 331 (0.60%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 331 (0.91%)	7 / 322 (2.17%)	
occurrences causally related to treatment / all	3 / 3	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypercalcaemia			
subjects affected / exposed	4 / 331 (1.21%)	4 / 322 (1.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 331 (0.60%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 331 (0.60%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	4 / 331 (1.21%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 331 (1.21%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 331 (0.30%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 331 (0.60%)	3 / 322 (0.93%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conduction disorder			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
convulsion			

subjects affected / exposed	2 / 331 (0.60%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 331 (0.60%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 331 (0.30%)	4 / 322 (1.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	6 / 331 (1.81%)	12 / 322 (3.73%)	
occurrences causally related to treatment / all	2 / 6	7 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhagic anaemia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 331 (3.02%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	3 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 331 (2.11%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	6 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	7 / 331 (2.11%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	2 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 331 (0.60%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestine obstruction			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestine perforation			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen tongue			

subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 331 (1.81%)	4 / 322 (1.24%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
bile duct obstruction			
subjects affected / exposed	2 / 331 (0.60%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 331 (0.30%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure acute			
subjects affected / exposed	0 / 331 (0.00%)	5 / 322 (1.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 331 (0.30%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 331 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 331 (1.81%)	4 / 322 (1.24%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 331 (0.30%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			

subjects affected / exposed	2 / 331 (0.60%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
subjects affected / exposed	1 / 331 (0.30%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 331 (0.30%)	3 / 322 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infection			
subjects affected / exposed	2 / 331 (0.60%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 331 (1.81%)	13 / 322 (4.04%)	
occurrences causally related to treatment / all	0 / 6	2 / 13	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory tract infection			
subjects affected / exposed	0 / 331 (0.00%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 331 (0.30%)	3 / 322 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 331 (0.60%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fall			

subjects affected / exposed	3 / 331 (0.91%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 331 (0.00%)	2 / 322 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	2 / 331 (0.60%)	0 / 322 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 331 (0.30%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cabozantinib	Everolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	328 / 331 (99.09%)	270 / 322 (83.85%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	53 / 331 (16.01%)	19 / 322 (5.90%)	
occurrences (all)	53	19	
Aspartate aminotransferase increased			
subjects affected / exposed	58 / 331 (17.52%)	18 / 322 (5.59%)	
occurrences (all)	58	18	
Blood thyroid stimulating hormone increased			

subjects affected / exposed occurrences (all)	23 / 331 (6.95%) 23	3 / 322 (0.93%) 3	
Weight decreased subjects affected / exposed occurrences (all)	104 / 331 (31.42%) 104	39 / 322 (12.11%) 39	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	122 / 331 (36.86%) 122	23 / 322 (7.14%) 23	
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	78 / 331 (23.56%) 78	30 / 322 (9.32%) 30	
General disorders and administration site conditions fatigue subjects affected / exposed occurrences (all)	185 / 331 (55.89%) 185	149 / 322 (46.27%) 149	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	50 / 331 (15.11%) 50	30 / 322 (9.32%) 30	
Abdominal pain upper subjects affected / exposed occurrences (all)	26 / 331 (7.85%) 26	7 / 322 (2.17%) 7	
Constipation subjects affected / exposed occurrences (all)	83 / 331 (25.08%) 83	61 / 322 (18.94%) 61	
Diarrhoea subjects affected / exposed occurrences (all)	245 / 331 (74.02%) 245	88 / 322 (27.33%) 88	
Dyspepsia subjects affected / exposed occurrences (all)	40 / 331 (12.08%) 40	15 / 322 (4.66%) 15	
Flatulence subjects affected / exposed occurrences (all)	32 / 331 (9.67%) 32	6 / 322 (1.86%) 6	

Nausea subjects affected / exposed occurrences (all)	164 / 331 (49.55%) 164	89 / 322 (27.64%) 89	
Vomiting subjects affected / exposed occurrences (all)	105 / 331 (31.72%) 105	44 / 322 (13.66%) 44	
Respiratory, thoracic and mediastinal disorders Dysphonia subjects affected / exposed occurrences (all)	66 / 331 (19.94%) 66	12 / 322 (3.73%) 12	
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	139 / 331 (41.99%) 139	19 / 322 (5.90%) 19	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	68 / 331 (20.54%) 68	2 / 322 (0.62%) 2	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	42 / 331 (12.69%) 42 46 / 331 (13.90%) 46	16 / 322 (4.97%) 16 25 / 322 (7.76%) 25	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	152 / 331 (45.92%) 152 50 / 331 (15.11%) 50	108 / 322 (33.54%) 108 5 / 322 (1.55%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2014	The amendment added details around study assessments and procedures after the study objectives were completed. Additional clarifications were added.

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.

Presentation of SAEs limited to those observed >2 subjects across arms. Efficacy results: based on initial statistical analyses that may differ from product labeling. Upper limits of confidence intervals not reached shown as median values.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26406150>

<http://www.ncbi.nlm.nih.gov/pubmed/27279544>