Clinical trial results:
A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib Hydrochloride to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma

Summary

EudraCT number	2015-003607-30
Trial protocol	DE GB BE CZ DK ES HU FR PL IT
Global end of trial date	21 June 2021

Results information

Result version number	v1 (current)
This version publication date	10 February 2023
First version publication date	10 February 2023

Trial information

Trial identification

Sponsor protocol code	AV-951-15-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02627963
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AVEO Pharmaceuticals, Inc.
Sponsor organisation address	30 Winter Street, Boston, United States, MA 02108
Public contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., +1 857 400-0101, clinical@aveooncology.com
Scientific contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., +1 857 400-0101, clinical@aveooncology.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	21 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2018
Global end of trial reached?	Yes
Global end of trial date	21 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the progression-free survival (PFS) of participants with refractory advanced renal cell carcinoma (RCC) randomised to treatment with tivozanib or sorafenib as assessed by blinded independent radiological review (IRR) of computerized tomography (CT) or magnetic resonance imaging (MRI).

Protection of trial subjects:

The study was conducted in compliance with International Council for Harmonisation (ICH) E6 current Good Clinical Practice (cGCP) and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2016
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	Canada: 12
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czechia: 30
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Italy: 62
Worldwide total number of subjects	350
EEA total number of subjects	263

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)	193
From 65 to 84 years	154
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 350 participants were randomised and 343 were treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tivozanib Hydrochloride

Arm description:

Participants randomised to this arm received the study drug, tivozanib hydrochloride.

Arm type	Experimental
Investigational medicinal product name	Tivozanib hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tivozanib hydrochloride was administered on a 3 weeks on/1 week off schedule in 4-week cycles.

Arm title	Sorafenib

Arm description:

Participants randomised to this arm received the comparator drug, sorafenib.

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

Dosage and administration details:

Sorafenib was administered continuously in 4-week cycles.

Number of subjects in period 1	Tivozanib Hydrochloride	Sorafenib
Started	175	175
Completed	173	169
Not completed	2	6
Randomized but not treated	2	6

Baseline characteristics

Reporting groups	
Reporting group title	Tivozanib Hydrochloride
Reporting group description:	
Participants randomised to this arm received the study drug, tivozanib hydrochloride.	
Reporting group title	Sorafenib
Reporting group description:	
Participants randomised to this arm received the comparator drug, sorafenib.	

Reporting group values	Tivozanib Hydrochloride	Sorafenib	Total
Number of subjects	175	175	350
Age categorical Units: Subjects			
Age continuous Units: years			
median	62	63	
full range (min-max)	34 to 88	30 to 90	-
Gender categorical Units: Subjects			
Female	49	47	96
Male	126	128	254
Race/Ethnicity Units: Subjects			
White	165	167	332
Non-white	10	8	18
Previous therapies Units: Subjects			
Two VEGFR TKIs	79	80	159
Checkpoint inhibitor plus VEGFR TKI	47	44	91
VEGFR TKI plus other systemic agent	49	51	100
IMDC risk category Units: Subjects			
Favourable	34	36	70
Intermediate	109	105	214
Poor	32	34	66

End points

End points reporting groups

Reporting group title	Tivozanib Hydrochloride
Reporting group description:	
Participants randomised to this arm received the study drug, tivozanib hydrochloride.	
Reporting group title	Sorafenib
Reporting group description:	
Participants randomised to this arm received the comparator drug, sorafenib.	

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
End point description:	
The PFS, as assessed by a blinded IRR, is defined as the time from randomisation to first documentation of objective tumor progression (progressive disease) or death due to any reasons whichever comes first. Disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria is defined as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. Intent-to-treat (ITT) population.	
End point type	Primary
End point timeframe:	
From date of randomisation until the date of first documented progression or date of death from any cause, whichever came first. Disease progression was assessed every 8 weeks	

End point values	Tivozanib Hydrochloride	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	175		
Units: Months				
median (confidence interval 95%)	5.59 (5.29 to 7.33)	3.88 (3.71 to 5.55)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib v Tivozanib Hydrochloride
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0165 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.94

Notes:

[1] - A one-sided, log-rank test stratified for IMDC risk category and prior therapy (two VEGFR TKIs vs. a checkpoint inhibitor plus a VEGFR TKI vs. a VEGFR TKI plus any other systemic agent) at a significance level of α = 0.025 will be used.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The OS is defined as the time from the date of randomisation to date of death due to any cause. ITT Population.

End point type	Secondary

End point timeframe:

Date of randomisation to date of death

End point values	Tivozanib Hydrochloride	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	175		
Units: Months				
median (confidence interval 95%)	16.39 (13.44 to 22.21)	19.15 (14.95 to 24.21)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tivozanib Hydrochloride v Sorafenib
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8174
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.25

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR is defined as the percentage of participants who have at least a 30% reduction in the sum of diameters per RECIST 1.1. ITT Population.

End point type	Secondary

End point timeframe:

Every 8 weeks from date of randomisation until disease progression

End point values	Tivozanib Hydrochloride	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	175		
Units: Participants	31	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

The DOR is defined as the time from the first documentation of objective tumor response to the first documentation of tumor progression per RECIST 1.1 or to death due to any cause. ITT Population. '99999' signifies data not calculable because an insufficient number of participants reached the event.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks from date of randomisation until date of progression

End point values	Tivozanib Hydrochloride	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	175		
Units: Months				
median (confidence interval 95%)	99999 (12.91 to 99999)	5.65 (5.55 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose to last dose plus 30 days	
Adverse event reporting additional description:	
Serious Treatment-Emergent Adverse Events and Treatment-Emergent Adverse Events in SAF Population Reported	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Tivozanib Hydrochloride
Reporting group description:	
Participants randomised to this arm received the study drug, tivozanib hydrochloride.	
Reporting group title	Sorafenib
Reporting group description:	
Participants randomised to this arm received the comparator drug, sorafenib.	

Serious adverse events	Tivozanib Hydrochloride	Sorafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 173 (46.82%)	67 / 170 (39.41%)	
number of deaths (all causes)	19	14	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spinal cord			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			
subjects affected / exposed	4 / 173 (2.31%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 4	
Prostate cancer			

subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Rehabilitation therapy			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 173 (1.73%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	2 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 173 (0.58%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 3	

Fatigue			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 173 (1.16%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchial ulceration			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 173 (1.73%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 173 (1.73%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 173 (3.47%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory arrest			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 173 (1.16%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 173 (1.73%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Head injury			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 173 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 173 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
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	1 / 173 (0.58%)	5 / 170 (2.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain compression			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	4 / 173 (2.31%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coma			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			

subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frontal lobe epilepsy			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 173 (0.58%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (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 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 173 (0.58%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disease			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Diabetic foot			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 173 (0.00%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 173 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash morbilliform			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 173 (1.73%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Proteinuria			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 173 (0.58%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 173 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			

subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 173 (3.47%)	6 / 170 (3.53%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 3	0 / 2	
Post procedural infection			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 173 (1.73%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased appetite			
subjects affected / exposed	3 / 173 (1.73%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	1 / 173 (0.58%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tivozanib Hydrochloride	Sorafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	171 / 173 (98.84%)	170 / 170 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	73 / 173 (42.20%)	51 / 170 (30.00%)	
occurrences (all)	153	67	
Hypotension			
subjects affected / exposed	9 / 173 (5.20%)	2 / 170 (1.18%)	
occurrences (all)	11	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	64 / 173 (36.99%)	41 / 170 (24.12%)	
occurrences (all)	110	77	
Asthenia			
subjects affected / exposed	56 / 173 (32.37%)	40 / 170 (23.53%)	
occurrences (all)	132	66	
Oedema peripheral			
subjects affected / exposed	16 / 173 (9.25%)	12 / 170 (7.06%)	
occurrences (all)	21	17	

Pyrexia			
subjects affected / exposed	13 / 173 (7.51%)	18 / 170 (10.59%)	
occurrences (all)	16	19	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	47 / 173 (27.17%)	16 / 170 (9.41%)	
occurrences (all)	55	18	
Dyspnoea			
subjects affected / exposed	25 / 173 (14.45%)	17 / 170 (10.00%)	
occurrences (all)	42	20	
Cough			
subjects affected / exposed	38 / 173 (21.97%)	26 / 170 (15.29%)	
occurrences (all)	47	32	
Investigations			
Weight decreased			
subjects affected / exposed	30 / 173 (17.34%)	37 / 170 (21.76%)	
occurrences (all)	55	60	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	12 / 173 (6.94%)	2 / 170 (1.18%)	
occurrences (all)	13	2	
Blood creatinine increased			
subjects affected / exposed	13 / 173 (7.51%)	2 / 170 (1.18%)	
occurrences (all)	19	2	
Lipase increased			
subjects affected / exposed	9 / 173 (5.20%)	4 / 170 (2.35%)	
occurrences (all)	19	5	
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 173 (5.20%)	3 / 170 (1.76%)	
occurrences (all)	13	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	17 / 173 (9.83%)	8 / 170 (4.71%)	
occurrences (all)	28	12	
Headache			

subjects affected / exposed	20 / 173 (11.56%)	16 / 170 (9.41%)	
occurrences (all)	34	16	
Dysgeusia			
subjects affected / exposed	10 / 173 (5.78%)	8 / 170 (4.71%)	
occurrences (all)	10	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 173 (9.83%)	23 / 170 (13.53%)	
occurrences (all)	22	38	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	74 / 173 (42.77%)	91 / 170 (53.53%)	
occurrences (all)	260	230	
Stomatitis			
subjects affected / exposed	36 / 173 (20.81%)	38 / 170 (22.35%)	
occurrences (all)	55	53	
Nausea			
subjects affected / exposed	51 / 173 (29.48%)	31 / 170 (18.24%)	
occurrences (all)	117	49	
Vomiting			
subjects affected / exposed	31 / 173 (17.92%)	25 / 170 (14.71%)	
occurrences (all)	74	47	
Abdominal pain			
subjects affected / exposed	21 / 173 (12.14%)	16 / 170 (9.41%)	
occurrences (all)	27	23	
Abdominal pain upper			
subjects affected / exposed	18 / 173 (10.40%)	12 / 170 (7.06%)	
occurrences (all)	29	14	
Constipation			
subjects affected / exposed	19 / 173 (10.98%)	31 / 170 (18.24%)	
occurrences (all)	24	37	
Dyspepsia			
subjects affected / exposed	16 / 173 (9.25%)	3 / 170 (1.76%)	
occurrences (all)	35	3	
Gastrooesophageal reflux disease			

subjects affected / exposed	9 / 173 (5.20%)	1 / 170 (0.59%)	
occurrences (all)	10	1	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	28 / 173 (16.18%)	69 / 170 (40.59%)	
occurrences (all)	52	147	
Rash			
subjects affected / exposed	17 / 173 (9.83%)	42 / 170 (24.71%)	
occurrences (all)	19	57	
Dry skin			
subjects affected / exposed	11 / 173 (6.36%)	9 / 170 (5.29%)	
occurrences (all)	12	9	
Alopecia			
subjects affected / exposed	6 / 173 (3.47%)	37 / 170 (21.76%)	
occurrences (all)	6	38	
Erythema			
subjects affected / exposed	3 / 173 (1.73%)	12 / 170 (7.06%)	
occurrences (all)	5	12	
Pruritus			
subjects affected / exposed	4 / 173 (2.31%)	20 / 170 (11.76%)	
occurrences (all)	4	21	
Rash maculo-papular			
subjects affected / exposed	1 / 173 (0.58%)	11 / 170 (6.47%)	
occurrences (all)	1	22	
Hyperkeratosis			
subjects affected / exposed	1 / 173 (0.58%)	9 / 170 (5.29%)	
occurrences (all)	1	9	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	17 / 173 (9.83%)	6 / 170 (3.53%)	
occurrences (all)	40	9	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	31 / 173 (17.92%)	13 / 170 (7.65%)	
occurrences (all)	37	15	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	32 / 173 (18.50%)	26 / 170 (15.29%)	
occurrences (all)	47	37	
Arthralgia			
subjects affected / exposed	18 / 173 (10.40%)	15 / 170 (8.82%)	
occurrences (all)	23	20	
Pain in extremity			
subjects affected / exposed	18 / 173 (10.40%)	11 / 170 (6.47%)	
occurrences (all)	28	19	
Muscle spasms			
subjects affected / exposed	12 / 173 (6.94%)	7 / 170 (4.12%)	
occurrences (all)	37	11	
Musculoskeletal pain			
subjects affected / exposed	9 / 173 (5.20%)	4 / 170 (2.35%)	
occurrences (all)	9	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 173 (6.94%)	1 / 170 (0.59%)	
occurrences (all)	14	1	
Urinary tract infection			
subjects affected / exposed	7 / 173 (4.05%)	11 / 170 (6.47%)	
occurrences (all)	8	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	68 / 173 (39.31%)	51 / 170 (30.00%)	
occurrences (all)	110	73	
Hyperkalaemia			
subjects affected / exposed	12 / 173 (6.94%)	6 / 170 (3.53%)	
occurrences (all)	40	9	
Hypocalcaemia			
subjects affected / exposed	4 / 173 (2.31%)	10 / 170 (5.88%)	
occurrences (all)	6	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2016	The following changes were made: • Revised dates for first and last participant enrolled • Removed the requirement for neuropilin-1 (NRP-1) sampling • The relationship between tivozanib and sorafenib drug levels and activity and tivozanib and sorafenib drug levels and adverse events (AEs) were added as tertiary objectives • Revised start of treatment from within 10 days to within 14 days after randomisation • Clarified classification of prior treatment for the purpose of stratification: "In the event a participant had both 2 TKIs and a checkpoint inhibitor, the participant will be stratified according to the most recent line of therapy." • Revised inclusion criteria (IC) and exclusion criteria (EC): o IC - removed "mixed tumor containing predominantly sarcomatoid cells" o EC – clarified eligibility of patients with CNS metastasis; removed "Participants are not considered to have a currently active malignancy if they have completed anti-cancer therapy and have been disease free for >2 years". o EC – allowed for creatinine clearance to be calculated or measured o EC – clarified uncontrolled hypertension, removed "documented on 2 consecutive measurements taken at least 24 hours apart." • Increased the duration of contraceptive use after the last dose of study drug for females • Tests for bicarbonate and total triiodothyronine (T3) are optional • Clarified timing of study drug shipment to the site • Clarified determination of PFS using RECIST 1.1 • Clarified dose modification for drug-related AEs • Provided further detail on the safety monitoring committee (SMC) • Updated Appendix (RECIST 1.1) to require brain scans at screening • Updated Appendix (Cytochrome P450 [CYP3A4] Inhibitors and Inducers) to include only strong inducers or inhibitors of CYP3A4 • Updated Appendix (Sorafenib Prescribing Information) • Interactive voice response system was deleted • Clarified treatment stratification
01 October 2018	The primary data analysis was based on a data cut-off on 04 Oct 2018 with a targeted number of 242 PFS events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported