Clinical trial results:
An Extension Treatment Protocol for Subjects who have Participated in a Phase 3 Study of Tivozanib vs. Sorafenib in Renal Cell Carcinoma (Protocol AV-951-09-301)

Summary

EudraCT number	2009-015987-32
Trial protocol	FR IT CZ HU PL BG GB
Global end of trial date	04 July 2014

Results information

Result version number	v1 (current)
This version publication date	25 August 2021
First version publication date	25 August 2021

Trial information

Trial identification

Sponsor protocol code	AV-951-09-902

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01076010
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AVEO Pharmaceuticals, Inc.
Sponsor organisation address	30 Winter Street, Boston, MA , United States, 02108
Public contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., 857 400-0101, clinical@aveooncology.com
Scientific contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., 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	03 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2014
Global end of trial reached?	Yes
Global end of trial date	04 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To allow access to tivozanib for subjects who participated in Protocol AV-951-09-301 and AV-951-09-902 and failed sorafenib treatment on either protocol.
•To allow long-term access to tivozanib for subjects who participated in Protocol AV-951-09-301 and demonstrated clinical benefit and acceptable tolerability to tivozanib
•To allow long-term access to sorafenib for subjects who participated in Protocol AV-951-09-301 and demonstrated clinical benefit and acceptable tolerability to sorafenib
•To assess long-term safety in subjects who continued treatment with tivozanib

Protection of trial subjects:

The protocol and amendments, informed consent forms, and any other appropriate study-related information were reviewed and approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC). The study was conducted in accordance with the protocol (and subsequent amendments), the United States (US) Code of Federal Regulations, Title 21 CFR Part 56, principles of Good Clinical Practice (GCP), the International Conference on Harmonization (ICH) Guideline for GCP [E6 (R1)] (reference number CPMP/ICH/135/95), the national laws and regulations of the country in which the research was conducted, and the principles of the Declaration of Helsinki (54th World Medical Association General Assembly, Washington, USA, 2002). Prior to any study-related procedures, the Investigator explained to each subject the aims, methods, anticipated benefits and potential hazards, which were relevant to the subject's decision to participate. An informed consent document approved by the IRB/EC was signed by the subject and the Investigator before any study-related procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Hungary: 6

Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Ukraine: 51
Country: Number of subjects enrolled	Russian Federation: 103
Country: Number of subjects enrolled	Serbia: 15
Worldwide total number of subjects	277
EEA total number of subjects	86

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)	195
From 65 to 84 years	80
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 55 sites (4 sites in Bulgaria, 1 site in Canada, 2 sites in Chile, 1 site in Czech Republic, 2 sites in Hungary, 4 sites in India, 2 sites in Italy, 6 sites in Poland, 4 sites in Romania, 17 sites in Russia, 4 sites in Serbia, 6 sites in Ukraine, 1 site in the United Kingdom, and 1 site in the United States).

Pre-assignment

Screening details:

All subjects underwent inclusion and exclusion criteria assessment and all eligible subjects signed the informed consent before undergoing any study related procedures. All the study assessments were performed as per the schedule of assessment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib Crossover to Tivozanib

Arm description:

The subjects who failed sorafenib (had Response Evaluation Criteria in Solid Tumors [RECIST]-defined progressive disease) on the parent Protocol AV- 951-09-301 were offered tivozanib hydrochloride on Protocol AV- 951-09-902.

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

Dosage and administration details:

Tivozanib was administered at a dose of 1.5 mg orally once daily (QD), at least 1 hour before or 2 hours after ingesting any food or other medication, for as long as the subject tolerated treatment in the absence of disease progression or unacceptable toxicity. Grapefruit juice could not have been ingested during the study. All subjects receiving tivozanib followed the dosing schedule of 3 weeks on treatment (beginning on Day 1) followed by 1 week off treatment. One cycle was defined as 4 weeks of treatment.

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 orally, at a dose of 400 mg (2 x 200 mg tablets) twice daily, beginning on Day 1 of Cycle 1. Subjects received sorafenib continuously (1 cycle = 4 weeks). Sorafenib was to be taken at least 1 hour before or 2 hours after ingesting any food or other medications.

Arm title	First Line Tivozanib

Arm description:

The subjects who were randomized to tivozanib (continued from the parent Protocol AV-951-09-301), and demonstrated clinical benefit and acceptable tolerability in Protocol AV-951-09-301.

Arm type	Experimental

Investigational medicinal product name	Tivozanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tivozanib was administered at a dose of 1.5 mg orally once daily (QD), at least 1 hour before or 2 hours after ingesting any food or other medication, for as long as the subject tolerated treatment in the absence of disease progression or unacceptable toxicity. Grapefruit juice could not have been ingested during the study. All subjects receiving tivozanib followed the dosing schedule of 3 weeks on treatment (beginning on Day 1) followed by 1 week off treatment. One cycle was defined as 4 weeks of treatment.

Arm title	First Line Sorafenib

Arm description:

The subjects who were randomized to sorafenib (continued from the parent Protocol AV-951-09-301) and demonstrated clinical benefit and acceptable tolerability were offered long term access to sorafenib.

Arm type	Experimental
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 orally, at a dose of 400 mg (2 x 200 mg tablets) twice daily, beginning on Day 1 of Cycle 1. Subjects received sorafenib continuously (1 cycle = 4 weeks). Sorafenib was to be taken at least 1 hour before or 2 hours after ingesting any food or other medications.

Number of subjects in period 1	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib
Started	161	88	28
Completed	36	49	26
Not completed	125	39	2
Treatment Interruption for > 2 Weeks	-	1	-
Requirement for a Significant Surgical Procedure	-	1	-
Consent withdrawn by subject	3	-	1
Death	15	1	-
Other	5	2	-
Significant Protocol Deviation	-	1	-
Adverse event	7	2	-
Progressive disease	90	30	1
Lack of efficacy	4	-	-
Noncompliance	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib Crossover to Tivozanib
Reporting group description:	
The subjects who failed sorafenib (had Response Evaluation Criteria in Solid Tumors [RECIST]-defined progressive disease) on the parent Protocol AV- 951-09-301 were offered tivozanib hydrochloride on Protocol AV- 951-09-902.	
Reporting group title	First Line Tivozanib
Reporting group description:	
The subjects who were randomized to tivozanib (continued from the parent Protocol AV-951-09-301), and demonstrated clinical benefit and acceptable tolerability in Protocol AV-951-09-301.	
Reporting group title	First Line Sorafenib
Reporting group description:	
The subjects who were randomized to sorafenib (continued from the parent Protocol AV-951-09-301) and demonstrated clinical benefit and acceptable tolerability were offered long term access to sorafenib.	

Reporting group values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib
Number of subjects	161	88	28
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)	120	58	17
From 65-84 years	40	29	11
85 years and over	1	1	0
Age continuous Units: years			
arithmetic mean	58.6	61.6	61.5
standard deviation	± 9.98	± 9.31	± 8.75
Gender categorical Units: Subjects			
Female	46	33	9
Male	115	55	19

Reporting group values	Total		
Number of subjects	277		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	195		
From 65-84 years	80		
85 years and over	2		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	88		
Male	189		

End points

End points reporting groups

Reporting group title	Sorafenib Crossover to Tivozanib

Reporting group description:

The subjects who failed sorafenib (had Response Evaluation Criteria in Solid Tumors [RECIST]-defined progressive disease) on the parent Protocol AV- 951-09-301 were offered tivozanib hydrochloride on Protocol AV- 951-09-902.

Reporting group title	First Line Tivozanib

Reporting group description:

The subjects who were randomized to tivozanib (continued from the parent Protocol AV-951-09-301), and demonstrated clinical benefit and acceptable tolerability in Protocol AV-951-09-301.

Reporting group title	First Line Sorafenib

Reporting group description:

The subjects who were randomized to sorafenib (continued from the parent Protocol AV-951-09-301) and demonstrated clinical benefit and acceptable tolerability were offered long term access to sorafenib.

Primary: Number of Days Subjects Received Treatment in Each Treatment Arm

End point title	Number of Days Subjects Received Treatment in Each Treatment Arm[1]

End point description:

Number of days subjects received treatment who were from Protocol AV-951-09-301 who either continued on tivozanib (subjects with first-line experience on tivozanib treatment), who crossed over from sorafenib to tivozanib (crossover subjects), and who continued on sorafenib (subjects with first-line experience on sorafenib treatment) in this trial. Subjects could be discontinued due to unacceptable toxicities or clinical or documented PD.

End point type	Primary

End point timeframe:

From enrollment to until all subjects discontinued (due to documented progressive disease [PD] or unacceptable toxicities) or until 3 years after the first subject was enrolled in Protocol AV-951-09-902.

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: No statistical analysis is available for this endpoint.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	88	28	
Units: Days				
arithmetic mean (standard deviation)				
Duration of treatment	290.0 (± 234.37)	325.3 (± 137.79)	369.4 (± 107.60)	
Total days receiving drug	222.36 (± 181.722)	241.00 (± 105.928)	368.14 (± 107.946)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Cycles Subjects Received Treatment in Each Treatment Arm

End point title	Number of Cycles Subjects Received Treatment in Each Treatment Arm[2]

End point description:

Number of cycles subjects received treatment who were from Protocol AV-951-09-301 who either continued on tivozanib (subjects with first-line experience on tivozanib treatment), who crossed over from sorafenib to tivozanib (crossover subjects), and who continued on sorafenib (subjects with first-line experience on sorafenib treatment) in this trial. Subjects could be discontinued due to unacceptable toxicities or clinical or documented PD.

End point type	Primary

End point timeframe:

From enrollment to until all subjects discontinued (due to documented PD or unacceptable toxicities) or until 3 years after the first subject was enrolled in Protocol AV-951-09-902.

Notes:

[2] - 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: No statistical analysis is available for this endpoint.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	88	28	
Units: Number of cycles started				
arithmetic mean (standard deviation)	10.6 (± 8.36)	11.8 (± 4.85)	13.2 (± 3.83)	

Statistical analyses

No statistical analyses for this end point

Primary: Total Dose Administered to Subjects in Each Treatment Arm (mg)

End point title	Total Dose Administered to Subjects in Each Treatment Arm (mg)[3]

End point description:

The total dose administered to subjects who were from Protocol AV-951-09-301 who either continued on tivozanib (subjects with first-line experience on tivozanib treatment), who crossed over from sorafenib to tivozanib (crossover subjects), and who continued on sorafenib (subjects with first-line experience on sorafenib treatment) in this trial. Subjects could be discontinued due to unacceptable toxicities or clinical or documented PD.

End point type	Primary

End point timeframe:

From enrollment to until all subjects discontinued (due to documented PD or unacceptable toxicities) or until 3 years after the first subject was enrolled in Protocol AV-951-09-902.

Notes:

[3] - 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: No statistical analysis is available for this endpoint.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	88	28	
Units: mg				
arithmetic mean (standard deviation)				
Total dose administered	318.84 (± 256.241)	344.58 (± 152.131)	244014.29 (± 116816.715)	

Statistical analyses

No statistical analyses for this end point

Primary: Relative Dose Intensity (RDI) of Treatment Administered to Subjects in Each Treatment Arm

End point title	Relative Dose Intensity (RDI) of Treatment Administered to Subjects in Each Treatment Arm[4]

End point description:

Relative Dose Intensity was defined as 100% times the actual dose intensity divided by the intended dose intensity. The RDI of subjects from Protocol AV-951-09-301 who either continued on tivozanib (subjects with first-line experience on tivozanib treatment), who crossed over from sorafenib to tivozanib (crossover subjects), and who continued on sorafenib (subjects with first-line experience on sorafenib treatment) in this trial. Subjects could be discontinued due to unacceptable toxicities or clinical or documented PD.

End point type	Primary

End point timeframe:

From enrollment to until all subjects discontinued (due to documented PD or unacceptable toxicities) or until 3 years after the first subject was enrolled in Protocol AV-951-09-902.

Notes:

[4] - 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: No statistical analysis is available for this endpoint.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	88	28	
Units: Percentage of Dose				
arithmetic mean (standard deviation)	95.21 (± 9.393)	91.12 (± 14.762)	80.60 (± 28.603)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events[5]

End point description:

Number of subjects with treatment-emergent adverse events (AEs) as assessed by Common Terminology Criteria for Adverse Events v3.0.

End point type	Primary

End point timeframe:

From enrollment assessed up to 3 years of treatment or until follow-up (up to 30 days end-of-trial visit after treatment discontinuation), whichever occured earlier.

Notes:

[5] - 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: No statistical analysis is available for this endpoint.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	88	28	
Units: Subjects				
number (not applicable)				
Any Adverse Event (AE)	124	85	28	
Any AE of Grade 3 or Higher	77	55	19	
Any Treatment-Related AE	86	76	27	
Any Treatment-Related AE of Grade 3 or Higher	39	35	15	
Any AE With Outcome of Death	21	3	0	
Any Treatment-Related AE With Outcome of Death	1	1	0	
Any Serious Adverse Event (SAE)	49	17	4	
Any Treatment-Related SAE	7	7	2	
AE Leading to Study Drug Discontinuation (AEDC)	19	4	0	
Any Treatment-Related AEDC	3	0	0	
Any AE Leading to Study Drug Interruption	27	26	12	
Treatment-Related AE-Study Drug Interruption	13	17	10	
Any AE Leading to Study Drug Dose Reduction	11	11	10	
Treatment-Related AE- Study Drug Dose Reduction	9	11	10	

Statistical analyses

No statistical analyses for this end point

Primary: Average Daily Dose Administered to Subjects in Each Treatment Arm

End point title	Average Daily Dose Administered to Subjects in Each Treatment Arm[6]

End point description:

The average daily dose administered to subjects who were from Protocol AV-951-09-301 who either continued on tivozanib (subjects with first-line experience on tivozanib treatment), who crossed over from sorafenib to tivozanib (crossover subjects), and who continued on sorafenib (subjects with first-line experience on sorafenib treatment) in this trial. Subjects could be discontinued due to unacceptable toxicities or clinical or documented PD.

End point type	Primary

End point timeframe:

From enrollment to until all subjects discontinued (due to documented PD or unacceptable toxicities) or until 3 years after the first subject was enrolled in Protocol AV-951-09-902.

Notes:

[6] - 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: No statistical analysis is available for this endpoint.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	88	28	
Units: mg/day				
arithmetic mean (standard deviation)	1.46 (± 0.121)	1.40 (± 0.196)	651.47 (± 225.410)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Objective Response Rate (ORR) Who Continued Treatment With Tivozanib or Sorafenib and Who Received Tivozanib After Failure of Sorafenib

End point title	Number of Subjects with Objective Response Rate (ORR) Who Continued Treatment With Tivozanib or Sorafenib and Who Received Tivozanib After Failure of Sorafenib

End point description:

ORR is defined as the proportion of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST (Version 1.0), relative to the total population of dosed subjects. CR is disappearance of all target and non-target lesions and normalization of tumor marker levels. At least a 30% decrease in the sum of the loading dose (LD) of target lesions, taking as reference the baseline sum LD.
To allow long-term access to sorafenib for subjects who participated in Protocol AV-951-09-301 (NCT01030783), and demonstrated clinical benefit and acceptable tolerability to sorafenib. Objective did not allow for a measured outcome.

End point type	Secondary

End point timeframe:

From Day 1 to the end of treatment (EOT) Visit, approximately every 8 weeks.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	88	28	
Units: Subjects				
number (not applicable)				
Overall Confirmed ORR	29	49	16	
Overall Unconfirmed ORR	43	55	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

Duration of Response was defined as the time from the first documentation of objective tumor response (confirmed CR or confirmed PR) according to RECIST (Version 1.0) to the first documentation of objective tumor progression or to death due to any reason. DR was calculated for the subgroup of subjects with a confirmed objective tumor response (PR or CR). CR is disappearance of all target and non-target lesions and normalization of tumor marker levels. PR is at least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
99.9999 = Not Available; DR was only summarized for subjects who had an objective tumor response.

End point type	Secondary

End point timeframe:

From the first documentation of objective tumor response to the first documentation of objective tumor progression, assessed up to treatment discontinuation or to death due to any reason or maximum up to 3 years, whichever occurred earlier.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	49	16	
Units: Months				
number (confidence interval 95%)				
25% Quartile	8.0 (4.4 to 12.9)	12.9 (5.6 to 99.9999)	99.9999 (99.9999 to 99.9999)	
50% Quartile	15.2 (11.1 to 99.9999)	99.9999 (99.9999 to 99.9999)	99.9999 (99.9999 to 99.9999)	
75% Quartile	99.9999 (12.9 to 99.9999)	99.9999 (99.9999 to 99.9999)	99.9999 (99.9999 to 99.9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the date of first dose of study drug to the first documentation of objective tumor progression or death due to any reason, whichever occurred first. For the crossover subjects and subjects with first-line experience on tivozanib treatment, the timeframe for PFS assessment started from the date of first dose of tivozanib in the AV-951-09-902 study. For subjects with first-line experience on sorafenib treatment, the timeframe for PFS assessment started from the date of first dose of sorafenib in the AV-951-09-902.
99.9999 = Not available, For the crossover and first line tivozanib subjects the PFS time was calculated from the first dose date of tivozanib in the AV-951-09-902 study. For the first line sorafenib subjects the first dose date of sorafenib in the AV-951-09-902 was used in the PFS calculation.

End point type	Secondary

End point timeframe:

From the date of first dose of study drug (tivozanib or sorafenib) in the AV-951-09-902 study to the first documentation of objective tumor progression or death due to any reason or maximum up to 3 years, whichever occurred first.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	88	28	
Units: Months				
number (confidence interval 95%)				
25% Quartile	3.6 (1.9 to 5.2)	7.2 (3.5 to 9.2)	99.9999 (99.9999 to 99.9999)	
50% Quartile	11.0 (7.3 to 12.7)	99.9999 (10.9 to 99.9999)	99.9999 (99.9999 to 99.9999)	
75% Quartile	20.9 (16.5 to 99.9999)	99.9999 (99.9999 to 99.9999)	99.9999 (99.9999 to 99.9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the first dose of study drug (tivozanib or sorafenib) date on this study to date of death due to any cause.
99.9999 = Not Available, For the crossover and first line tivozanib subjects the overall survival time was calculated from the first dose date of tivozanib in the AV-951-09-902 study. For the first line sorafenib subjects the first dose date of sorafenib in the AV-951-09-902 was used in the overall survival time calculation.

End point type	Secondary

End point timeframe:

From the date of first dose of study drug (tivozanib or sorafenib) in the AV-951-09-902 study to death due to any reason or maximum up to 3 years, whichever occurred first.

End point values	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	88	28	
Units: Months				
number (confidence interval 95%)				
25% Quartile	8.2 (6.0 to 12.1)	99.9999 (99.9999 to 99.9999)	99.9999 (99.9999 to 99.9999)	
50% Quartile	21.6 (17.0 to 27.6)	99.9999 (99.9999 to 99.9999)	99.9999 (99.9999 to 99.9999)	
75% Quartile	30.7 (28.8 to 99.9999)	99.9999 (99.9999 to 99.9999)	99.9999 (99.9999 to 99.9999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment assessed up to 3 years of treatment or until follow-up (up to 30 days end-of-trial visit after treatment discontinuation), whichever occured earlier

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Sorafenib Crossover to Tivozanib

Reporting group description:

The subjects who failed sorafenib (had Response Evaluation Criteria in Solid Tumors [RECIST]-defined progressive disease) on the parent Protocol AV- 951-09-301 were offered tivozanib hydrochloride on Protocol AV- 951-09-902.

Reporting group title	First Line Tivozanib

Reporting group description:

The subjects who were randomized to tivozanib (continued from the parent Protocol AV-951-09-301), and demonstrated clinical benefit and acceptable tolerability in Protocol AV-951-09-301.

Reporting group title	First Line Sorafenib

Reporting group description:

The subjects who were randomized to sorafenib (continued from the parent Protocol AV-951-09-301) and demonstrated clinical benefit and acceptable tolerability were to be offered long term access to sorafenib.

Serious adverse events	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 161 (30.43%)	17 / 88 (19.32%)	4 / 28 (14.29%)
number of deaths (all causes)	21	3	0
number of deaths resulting from adverse events	21	3	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to pleura			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Metastases to soft tissue			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Metastases to the mediastinum			

subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Neoplasm progression			
subjects affected / exposed	4 / 161 (2.48%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	3 / 161 (1.86%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Hypertension			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (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
Hypertensive crisis			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (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
Pelvic venous thrombosis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			

subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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			
Asthenia			
subjects affected / exposed	2 / 161 (1.24%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 161 (1.24%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	1 / 1	0 / 0
Fatigue			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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 physical health deterioration			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	2 / 161 (1.24%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic fluid collection			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 161 (1.24%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Pulmonary embolism			
subjects affected / exposed	1 / 161 (0.62%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 161 (1.24%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Psychiatric disorders			
Delusional disorder, somatic type			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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

Investigations			
Body temperature increased			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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			
Acute myocardial infarction			
subjects affected / exposed	2 / 161 (1.24%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 161 (0.62%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 161 (1.24%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiopulmonary failure			

subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 161 (1.24%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (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
Ischaemic stroke			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Loss of consciousness			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 161 (0.62%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Salivary gland mass			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Cholangitis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Cholecystitis acute			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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

Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (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
Myxoedema			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Pathological fracture			
subjects affected / exposed	1 / 161 (0.62%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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
Device related infection			

subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (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
Pneumonia viral			
subjects affected / exposed	0 / 161 (0.00%)	1 / 88 (1.14%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 88 (0.00%)	0 / 28 (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

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

Non-serious adverse events	Sorafenib Crossover to Tivozanib	First Line Tivozanib	First Line Sorafenib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 161 (54.04%)	82 / 88 (93.18%)	28 / 28 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	41 / 161 (25.47%)	44 / 88 (50.00%)	16 / 28 (57.14%)
occurrences (all)	47	85	21
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	20 / 161 (12.42%)	20 / 88 (22.73%)	3 / 28 (10.71%)
occurrences (all)	26	35	3
Fatigue			
subjects affected / exposed	21 / 161 (13.04%)	20 / 88 (22.73%)	3 / 28 (10.71%)
occurrences (all)	34	39	3
Oedema peripheral			
subjects affected / exposed	0 / 161 (0.00%)	5 / 88 (5.68%)	0 / 28 (0.00%)
occurrences (all)	0	9	0
Pyrexia			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 161 (5.59%)	13 / 88 (14.77%)	2 / 28 (7.14%)
occurrences (all)	10	19	2
Dysphonia			
subjects affected / exposed	9 / 161 (5.59%)	16 / 88 (18.18%)	0 / 28 (0.00%)
occurrences (all)	29	27	0
Dyspnoea			
subjects affected / exposed	9 / 161 (5.59%)	10 / 88 (11.36%)	3 / 28 (10.71%)
occurrences (all)	11	16	3
Oropharyngeal pain			
subjects affected / exposed	0 / 161 (0.00%)	6 / 88 (6.82%)	0 / 28 (0.00%)
occurrences (all)	0	9	0

Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 161 (0.00%)	5 / 88 (5.68%)	0 / 28 (0.00%)
occurrences (all)	0	6	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	3 / 28 (10.71%)
occurrences (all)	0	0	7
Amylase increased			
subjects affected / exposed	0 / 161 (0.00%)	6 / 88 (6.82%)	0 / 28 (0.00%)
occurrences (all)	0	9	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	3 / 28 (10.71%)
occurrences (all)	0	0	4
Blood creatinine increased			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	6
Blood phosphorus decreased			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	5 / 28 (17.86%)
occurrences (all)	0	0	23
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 161 (0.00%)	8 / 88 (9.09%)	0 / 28 (0.00%)
occurrences (all)	0	13	0
Lipase increased			
subjects affected / exposed	0 / 161 (0.00%)	6 / 88 (6.82%)	2 / 28 (7.14%)
occurrences (all)	0	21	4
Weight decreased			
subjects affected / exposed	0 / 161 (0.00%)	21 / 88 (23.86%)	9 / 28 (32.14%)
occurrences (all)	0	43	18
Weight increased			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Neutrophil count decreased			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 161 (0.00%)	14 / 88 (15.91%)	2 / 28 (7.14%)
occurrences (all)	0	16	4
Somnolence			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 161 (0.00%)	5 / 88 (5.68%)	0 / 28 (0.00%)
occurrences (all)	0	6	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 161 (0.00%)	9 / 88 (10.23%)	3 / 28 (10.71%)
occurrences (all)	0	10	7
Abdominal pain upper			
subjects affected / exposed	0 / 161 (0.00%)	10 / 88 (11.36%)	0 / 28 (0.00%)
occurrences (all)	0	15	0
Constipation			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	22 / 161 (13.66%)	35 / 88 (39.77%)	12 / 28 (42.86%)
occurrences (all)	66	155	22
Dyspepsia			
subjects affected / exposed	0 / 161 (0.00%)	7 / 88 (7.95%)	0 / 28 (0.00%)
occurrences (all)	0	8	0
Gastritis			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	5
Nausea			
subjects affected / exposed	0 / 161 (0.00%)	21 / 88 (23.86%)	0 / 28 (0.00%)
occurrences (all)	0	40	0
Stomatitis			
subjects affected / exposed	0 / 161 (0.00%)	11 / 88 (12.50%)	0 / 28 (0.00%)
occurrences (all)	0	40	0
Vomiting			

subjects affected / exposed	0 / 161 (0.00%)	9 / 88 (10.23%)	0 / 28 (0.00%)
occurrences (all)	0	13	0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Generalised erythema			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	4 / 28 (14.29%)
occurrences (all)	0	0	6
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	16 / 161 (9.94%)	21 / 88 (23.86%)	16 / 28 (57.14%)
occurrences (all)	32	68	38
Pruritus			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	5
Rash erythematous			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	3 / 28 (10.71%)
occurrences (all)	0	0	7
Skin exfoliation			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	6 / 28 (21.43%)
occurrences (all)	0	0	7
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 161 (0.00%)	10 / 88 (11.36%)	3 / 28 (10.71%)
occurrences (all)	0	60	12
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 161 (0.00%)	9 / 88 (10.23%)	0 / 28 (0.00%)
occurrences (all)	0	10	0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 161 (0.00%)	11 / 88 (12.50%)	0 / 28 (0.00%)
occurrences (all)	0	12	0
Back pain			
subjects affected / exposed	0 / 161 (0.00%)	10 / 88 (11.36%)	4 / 28 (14.29%)
occurrences (all)	0	11	4
Myalgia			
subjects affected / exposed	0 / 161 (0.00%)	6 / 88 (6.82%)	0 / 28 (0.00%)
occurrences (all)	0	10	0
Pain in extremity			
subjects affected / exposed	0 / 161 (0.00%)	9 / 88 (10.23%)	0 / 28 (0.00%)
occurrences (all)	0	12	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Rash pustular			
subjects affected / exposed	0 / 161 (0.00%)	0 / 88 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 161 (5.59%)	11 / 88 (12.50%)	2 / 28 (7.14%)
occurrences (all)	23	23	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2010	• Added further language regarding long-term survival follow-up. • Updated subject enrollment window to occur within the specified timeframe outlined in the eligibility criteria. • Revised Exclusion Criterion #1, added Exclusion Criteria #2 and #3, and renumbered criteria due to addition of new criteria. • Modified visit windows. • Modified window for clinic visits to occur. • Clarified use of end of treatment (EOT) Visit data for subjects initiating tivozanib and those continuing sorafenib or tivozanib from Protocol AV-951-09-301. • Modified language referring to frequency of labs in the Schedule of Activities. • Clarified that further imaging was required for subjects who had progressive disease (PD) and crossed over to tivozanib after sorafenib failure on this study. • Removed substrates from the cytochrome P450 enzyme 3A4 (CYP3A4) inhibitors and inducers table. • Removed criteria that tumor evaluation would be repeated 4 weeks to allow for confirmation of tumor status for patients with SD. • Modified that follow-up measurements had to have met stable disease (SD) criteria at least once after study entry, at a minimum interval of 4 weeks.
10 November 2010	• Updated pharmacovigilance contact name. • Revised Inclusion Criterion #1 for clarity. • Revised language regarding contact for OS. • Clarified in Table 1: "Schedule of Study Events for Subjects Continuing Tivozanib or Sorafenib Therapy from AV-951-09-301" that the ± 2 day window applied to all visit procedures except study drug administration. • Reformatted Table 2: "Schedule of Study Events for Subjects Initiating Tivozanib After Sorafenib Failure on AV-951-09-301" and combined Cycles 1 and 2 to allow the addition of Cycle 4 (and all even numbered cycles) column. • Clarified the following in Table 2: "Schedule of Study Events for Subjects Initiating Tivozanib After Sorafenib Failure on AV-951-09-301": ± 2 day window applied to all visit procedures except study drug administration, coagulation parameters and thyroid function tests were collected on Day 1 of Cycle 1 only, and disease assessment (CT scan) was performed at end of Cycle 2 only. • Repositioned the "x" under Cycle 3 (and all odd numbered cycles) to show tivozanib administration. • Added a Cycle 4 (and all even numbered cycles) column and the timing of procedures and evaluations required at those time points. • Added contact information for reporting deaths, SAEs, and unexpected AEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported