



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 occurred 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 (\pm 0.121) | 1.40 (\pm 0.196) | 651.47 (\pm 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 occurred 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 occurrences (all) | 0 / 161 (0.00%) 0 | 9 / 88 (10.23%) 13 | 0 / 28 (0.00%) 0 |
| Hepatobiliary disorders Cholecystitis acute subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 0 / 88 (0.00%) 0 | 2 / 28 (7.14%) 2 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 0 / 88 (0.00%) 0 | 2 / 28 (7.14%) 3 |
| Generalised erythema subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 0 / 88 (0.00%) 0 | 4 / 28 (14.29%) 6 |
| Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 16 / 161 (9.94%) 32 | 21 / 88 (23.86%) 68 | 16 / 28 (57.14%) 38 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 0 / 88 (0.00%) 0 | 2 / 28 (7.14%) 5 |
| Rash erythematous subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 0 / 88 (0.00%) 0 | 3 / 28 (10.71%) 7 |
| Skin exfoliation subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 0 / 88 (0.00%) 0 | 2 / 28 (7.14%) 2 |
| Alopecia subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 0 / 88 (0.00%) 0 | 6 / 28 (21.43%) 7 |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 10 / 88 (11.36%) 60 | 3 / 28 (10.71%) 12 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 161 (0.00%) 0 | 9 / 88 (10.23%) 10 | 0 / 28 (0.00%) 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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