Clinical trial results:
A Prospective, Randomized, Double-Blinded, Placebo-Controlled, Multinational, Multicenter, Parallel-group, Phase III Study to Evaluate the Efficacy and Safety of Apatinib Plus Best Supportive Care (BSC) Compared to Placebo Plus BSC in Patients With Advanced or Metastatic Gastric Cancer

Summary

EudraCT number	2016-003984-20
Trial protocol	GB DE PL FR IT RO
Global end of trial date	23 September 2020

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	LSK-AM301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03042611
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Elevar Therapeutics, Inc
Sponsor organisation address	2755 E Cottonwood Pkwy #540, Salt Lake City, United States, 84121
Public contact	Elevar Clinical Trials, Elevar Therapeutics, Inc, 1 801 3037440, info-clinicalstudy@elevartherapeutics.com
Scientific contact	Elevar Clinical Trials, Elevar Therapeutics, Inc, 1 801 3037440, info-clinicalstudy@elevartherapeutics.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	23 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of rivoceranib plus best supportive care (BSC) compared to placebo plus BSC in participants with advanced or metastatic gastric cancer (GC).

Protection of trial subjects:

The study was conducted in accordance with the Good Clinical Practice (GCP) guideline developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The clinical trial was also conducted in compliance with Declaration of Helsinki, protocol, Standard specified in the Section 3 in the Article 14 and the Section 2 in the Article 80 in Pharmaceutical Law, Notification 28 from MHLW dated March 27th, 1997 "Ordinance on the criteria for the implementation of clinical trials of the drug (GCP)".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	Korea, Republic of: 214
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Ukraine: 27
Worldwide total number of subjects	460
EEA total number of subjects	78

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)	292
From 65 to 84 years	167
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized to receive either rivoceranib +best supportive care (BSC) or placebo +BSC for approximately 24 months. Participants who benefited from rivoceranib were permitted to continue rivoceranib during an extension period of the study, up to approximately 36 months.

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivoceranib Plus Best Supportive Care (BSC)

Arm description:

Participants received rivoceranib 700 milligrams (mg) orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

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

Dosage and administration details:

Participants received rivoceranib 700 milligrams (mg) orally once per day during each cycle plus BSC. BSC is
defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

Arm title	Placebo Plus BSC

Arm description:

Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

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

Dosage and administration details:

Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC. BSC is
defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

Number of subjects in period 1	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC
Started	308	152
Received at Least 1 Dose of Study Drug	307	151
Completed	52	28
Not completed	256	124
Consent withdrawn by subject	13	4
Physician decision	7	2
Death	232	110
Study Closed	-	1
Lost to follow-up	4	7

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Extension Phase: Rivoceranib Plus BSC

Arm description:

Participants received rivoceranib 700 mg orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

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

Dosage and administration details:

Participants received rivoceranib 700 mg orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

Arm title	Extension Phase: Placebo Plus BSC

Arm description:

Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

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

Dosage and administration details:

Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC.

BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

Number of subjects in period 2	Extension Phase: Rivoceranib Plus BSC	Extension Phase: Placebo Plus BSC
Started	52	28
Completed	0	0
Not completed	52	28
Death	34	16
Study Closed	17	11
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Rivoceranib Plus Best Supportive Care (BSC)
Reporting group description:	
Participants received rivoceranib 700 milligrams (mg) orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.	
Reporting group title	Placebo Plus BSC
Reporting group description:	
Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.	

Reporting group values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC	Total
Number of subjects	308	152	460
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)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: years			
arithmetic mean	60.03	59.96	
standard deviation	± 11.11	± 10.63	-
Sex: Female, Male Units: participants			
Female	67	40	107
Male	241	112	353
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	0	5
Not Hispanic or Latino	303	152	455
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	207	105	312
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	100	46	146
More than one race	0	0	0

Unknown or Not Reported	1	1	2

End points

End points reporting groups

Reporting group title	Rivoceranib Plus Best Supportive Care (BSC)
Reporting group description:	
Participants received rivoceranib 700 milligrams (mg) orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.	
Reporting group title	Placebo Plus BSC
Reporting group description:	
Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.	
Reporting group title	Extension Phase: Rivoceranib Plus BSC
Reporting group description:	
Participants received rivoceranib 700 mg orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.	
Reporting group title	Extension Phase: Placebo Plus BSC
Reporting group description:	
Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]
End point description:	
OS was defined as the time from randomization to death. Participants alive or lost to follow-up at the end of study (EOS) were censored. The Intent-to-treat (ITT) set for the OS final analysis consisted of data from all participants who were randomized, including participants who were still in OS follow-up at the time of primary analysis. In the ITT set, participants were included in the group to which they were randomized.	
End point type	Primary
End point timeframe:	
Day 1 (randomization) up to approximately 36 months	
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: Summary statistics only	

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	152		
Units: Months				
median (confidence interval 95%)	5.82 (5.26 to 6.47)	5.13 (4.47 to 6.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Progression-free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

PFS was defined as the time from randomization to either documented radiological progression or death from any cause. Participants alive and free of progression at the EOS were censored.

The ITT set consisted of data from all participants who were randomized. In the ITT set, participants were included in the group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 24 months

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	152		
Units: Months				
median (confidence interval 95%)	2.83 (2.07 to 3.52)	1.77 (1.71 to 1.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) Per RECIST 1.1

End point title	Objective Response Rate (ORR) Per RECIST 1.1

End point description:

ORR was defined as the percentage of participants in the analysis population with the best overall response of Complete Response (CR: disappearance of all target lesions and reduction in short axis of any nodal target lesions to <10 millimeter [mm]) or a Partial Response (PR: ≥30% decrease in the sum of the longest diameters of the target lesions, taking as a reference the baseline sum diameters) per RECIST 1.1.

The ITT set consisted of data from all participants who were randomized. In the ITT set, participants were included in the group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 24 months

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	152		
Units: Percentage of Participants				
number (confidence interval 95%)	6.5 (3.74 to 9.25)	1.3 (0.16 to 4.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DCR was defined as the proportion of participants with a Best Overall Response of CR, PR, or stable disease (SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameter while on study) per RECIST 1.1.

The ITT set consisted of data from all participants who were randomized. In the ITT set, participants were included in the group to which they were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 24 months

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	152		
Units: Percentage of Participants				
number (confidence interval 95%)	40.3 (34.78 to 45.74)	13.2 (7.78 to 18.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Global Health Status/Quality of Life (QoL) Measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

End point title	Change From Baseline in Global Health Status/Quality of Life (QoL) Measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30 is a cancer specific Questionnaire with 30 questions for assessing the health-related QOL of cancer participants. The questionnaire incorporates 5 functional scales, 4 symptom scales, a global QOL scale, and single items for the assessment of additional systems commonly reported by cancer participants. All items are scored on 4-point Likert scales, ranging from 1 ('not at all') to 4 ('very much'), with the exception of 2 items in the global QOL scale which use modified 7-point linear analog scales. All scores and single-items were transformed to a scale of 0 to 100. For the functioning scales, a higher score indicated greater functioning and for the symptom scales, a higher score indicated a greater symptom burden.

The ITT set consisted of data from all participants who were randomized. In the ITT set, participants were included in the group to which they were randomized. Overall number of participants indicates total number of participants.

End point type	Secondary

End point timeframe:

Baseline, End of Treatment (EOT) (Up to 24 months)

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	99		
Units: units on a scale				
arithmetic mean (standard deviation)	-17.51 (± 22.72)	-18.01 (± 26.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Stomach Cancer Specific (EORTC QLQ-STO22) Score

End point title	Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Stomach Cancer Specific (EORTC QLQ-STO22) Score

End point description:

EORTC QLQ-STO22 is a 22-item gastric cancer-specific questionnaire-integrating system for assessing the health-related QOL of gastric cancer participants. Most questions use 4-point scale (1 'Not at all' to 4 'Very much'; 1 question was a yes or no answer). A linear transformation was used to standardize all scores and single-items to a scale of 0 to 100. For the functioning scales, a higher score indicates greater functioning and for the symptom scales, a higher score indicates a greater symptom burden.

The ITT set consisted of data from all participants who were randomized. In the ITT set, participants were included in the group to which they were randomized. Overall number of participants indicates total at baseline, number of participants analyzed indicates number of participants with evaluable data.

End point type	Secondary

End point timeframe:

Baseline, EOT (Up to 24 months)

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	99		
Units: units on a scale				
arithmetic mean (standard deviation)				
Body Image	11.71 (± 29.95)	9.43 (± 35.01)		
Dyspnea	16.64 (± 26.34)	16.50 (± 24.91)		
Pain	12.72 (± 23.96)	13.75 (± 21.91)		
Reflux Symptoms	11.46 (± 24.80)	8.31 (± 21.73)		
Eating Restrictions	18.12 (± 26.45)	17.76 (± 22.89)		
Anxiety	13.69 (± 23.64)	10.55 (± 26.91)		
Dry Mouth	20.77 (± 33.22)	11.56 (± 29.15)		
Taste	15.30 (± 32.46)	14.48 (± 30.18)		
Hair Loss	-15.37 (± 33.71)	-18.69 (± 30.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol 5-Dimension 5-Level Visual Analogue Scale (EQ-5D-5L VAS) Score

End point title	Change From Baseline in EuroQol 5-Dimension 5-Level Visual Analogue Scale (EQ-5D-5L VAS) Score

End point description:

EQ-5D-5L Questionnaire consists of EQ-5D-5L descriptive system and the visual analogue scale (VAS). The descriptive system comprises the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension has 5 levels. The VAS is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state.

The ITT set consisted of data from all participants who were randomized. In the ITT set, participants were included in the group to which they were randomized. Overall number of participants indicates total number of participants with evaluable data.

End point type	Secondary

End point timeframe:

Baseline, EOT (Up to 24 months)

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	98		
Units: units on a scale				
arithmetic mean (standard deviation)	-18.48 (± 19.11)	-15.36 (± 21.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants per QOL Dimension Response as Measured by the EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

End point title	Number of Participants per QOL Dimension Response as Measured by the EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

End point description:

EQ-5D-5L Questionnaire comprises the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension has 5 levels of response.

The ITT set consisted of data from all participants who were randomized. In the ITT set, participants were included in the group to which they were randomized. Overall number of participants indicates total at baseline.

End point type	Secondary

End point timeframe:

EOT (Month 24)

End point values	Rivoceranib Plus Best Supportive Care (BSC)	Placebo Plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	152		
Units: Number				
Mobility: No problems	46	27		
Mobility: Slight problems	60	27		
Mobility: Moderate problems	51	23		
Mobility: Severe problems	43	17		
Mobility: Unable	8	6		
Mobility: Missing	100	52		
Self Care: No problems	100	54		
Self Care: Slight problems	47	22		
Self Care: Moderate problems	40	10		
Self Care: Severe problems	14	7		
Self Care: Unable	7	7		
Self Care: Missing	100	52		
Usual Activities: No problems	36	24		
Usual Activities: Slight problems	61	36		

Usual Activities: Moderate problems	56	18		
Usual Activities: Severe problems	43	13		
Usual Activities: Unable	12	9		
Usual Activities: Missing	100	52		
Pain/Discomfort: No pain or discomfort	25	13		
Pain/Discomfort: Slight pain or discomfort	61	36		
Pain/Discomfort: Moderate pain or discomfort	67	26		
Pain/Discomfort: Severe pain or discomfort	47	19		
Pain/Discomfort: Extreme pain or discomfort	8	6		
Pain/Discomfort: Missing	100	52		
Anxiety/Depression: Not anxious or depressed	49	26		
Anxiety/Depression: Slightly anxious or depressed	60	36		
Anxiety/Depression: Moderately anxious/depressed	62	25		
Anxiety/Depression: Severely anxious or depressed	29	8		
Anxiety/Depression: Extremely anxious or depressed	8	5		
Anxiety/Depression: Missing	100	52		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 36 months

Adverse event reporting additional description:

The Safety set consisted of data from all participants in the ITT set who received at least 1 dose of rivoceranib or placebo. In the Safety set, participants were included in the group based on the treatment that was received. Safety data was analyzed by the Safety set which includes participants who were alive and on treatment or in OS follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo Plus BSC

Reporting group description:

Participants received matching placebo to rivoceranib orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

Reporting group title	Rivoceranib Plus Best Supportive Care (BSC)

Reporting group description:

Participants received rivoceranib 700 mg orally once per day during each cycle plus BSC. BSC is defined as palliative, non-cancer therapy. Each cycle duration was 28 days.

Serious adverse events	Placebo Plus BSC	Rivoceranib Plus Best Supportive Care (BSC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 151 (43.71%)	149 / 307 (48.53%)	
number of deaths (all causes)	134	283	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	3 / 151 (1.99%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 2	
Cancer pain			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastric cancer			

subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 151 (5.30%)	8 / 307 (2.61%)	
occurrences causally related to treatment / all	0 / 18	2 / 16	
deaths causally related to treatment / all	0 / 9	0 / 9	
Pyrexia			
subjects affected / exposed	1 / 151 (0.66%)	6 / 307 (1.95%)	
occurrences causally related to treatment / all	0 / 2	2 / 12	
deaths causally related to treatment / all	0 / 1	0 / 7	
Pain			
subjects affected / exposed	2 / 151 (1.32%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 1	
General physical health deterioration			
subjects affected / exposed	2 / 151 (1.32%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 3	
Disease progression			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	

Death			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Localised oedema			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 151 (1.32%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 5	
Dyspnoea			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cough			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pneumonia aspiration			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Delusion			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood bilirubin increased			

subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 4	
Lipase increased			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Amylase increased			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood creatinine increased			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Subdural haemorrhage			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Radiation mucositis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal anastomosis complication			

subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal compression fracture			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			

subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
Spinal cord compression			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epilepsy			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			

subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 151 (1.32%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 6	1 / 5	
deaths causally related to treatment / all	0 / 3	0 / 3	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 151 (1.99%)	15 / 307 (4.89%)	
occurrences causally related to treatment / all	0 / 6	1 / 31	
deaths causally related to treatment / all	0 / 3	0 / 16	
Ileus			
subjects affected / exposed	4 / 151 (2.65%)	5 / 307 (1.63%)	
occurrences causally related to treatment / all	0 / 16	0 / 12	
deaths causally related to treatment / all	0 / 8	0 / 6	
Vomiting			
subjects affected / exposed	2 / 151 (1.32%)	5 / 307 (1.63%)	
occurrences causally related to treatment / all	0 / 4	1 / 13	
deaths causally related to treatment / all	0 / 2	0 / 7	
Gastric haemorrhage			
subjects affected / exposed	2 / 151 (1.32%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 6	4 / 6	
deaths causally related to treatment / all	0 / 3	0 / 5	
Dysphagia			
subjects affected / exposed	3 / 151 (1.99%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 3	0 / 4	

Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 151 (1.32%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	1 / 3	3 / 7	
deaths causally related to treatment / all	0 / 2	0 / 5	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 151 (0.00%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 5	
Obstruction gastric			
subjects affected / exposed	2 / 151 (1.32%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Small intestinal obstruction			
subjects affected / exposed	2 / 151 (1.32%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Ascites			
subjects affected / exposed	1 / 151 (0.66%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 3	
Diarrhoea			
subjects affected / exposed	0 / 151 (0.00%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 0	3 / 13	
deaths causally related to treatment / all	0 / 0	0 / 8	
Pancreatitis			
subjects affected / exposed	0 / 151 (0.00%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Abdominal pain upper			
subjects affected / exposed	1 / 151 (0.66%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Subileus			

subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Gastric perforation			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastric stenosis			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haematochezia			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Mechanical ileus			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Large intestine perforation			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Stomatitis			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Intestinal infarction			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute abdomen			

subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
Abdominal distension			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestinal obstruction			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant dysphagia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			

subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal pain			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal stenosis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis acute			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Volvulus			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	4 / 151 (2.65%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 14	0 / 4	
deaths causally related to treatment / all	0 / 7	0 / 2	
Bile duct obstruction			
subjects affected / exposed	0 / 151 (0.00%)	5 / 307 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 5	
Hepatic failure			

subjects affected / exposed	0 / 151 (0.00%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 5	
Jaundice cholestatic			
subjects affected / exposed	1 / 151 (0.66%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 151 (0.66%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Biliary dilatation			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
Hepatic function abnormal			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cholecystitis			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hepatitis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Jaundice			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bile duct stenosis			

subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholangitis acute			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver disorder			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 151 (0.66%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 2	2 / 6	
deaths causally related to treatment / all	0 / 1	0 / 4	
Renal impairment			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nephropathy toxic			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal pain			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 151 (0.00%)	8 / 307 (2.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 20	
deaths causally related to treatment / all	0 / 0	0 / 11	
Peritonitis			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	

Septic shock			
subjects affected / exposed	1 / 151 (0.66%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Biliary sepsis			
subjects affected / exposed	0 / 151 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Biliary tract infection			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Escherichia sepsis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal candidiasis			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urethritis			
subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	4 / 151 (2.65%)	8 / 307 (2.61%)	
occurrences causally related to treatment / all	0 / 12	5 / 17	
deaths causally related to treatment / all	0 / 6	0 / 11	
Hyponatraemia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Hypernatraemia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cachexia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dehydration			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperuricaemia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemia			
subjects affected / exposed	0 / 151 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypophagia			

subjects affected / exposed	1 / 151 (0.66%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Placebo Plus BSC	Rivoceranib Plus Best Supportive Care (BSC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 151 (92.72%)	299 / 307 (97.39%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 151 (7.28%)	71 / 307 (23.13%)	
occurrences (all)	30	274	
Weight decreased			
subjects affected / exposed	12 / 151 (7.95%)	69 / 307 (22.48%)	
occurrences (all)	30	201	
Alanine aminotransferase increased			
subjects affected / exposed	9 / 151 (5.96%)	64 / 307 (20.85%)	
occurrences (all)	23	190	
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 151 (8.61%)	43 / 307 (14.01%)	
occurrences (all)	33	149	
Platelet count decreased			
subjects affected / exposed	6 / 151 (3.97%)	46 / 307 (14.98%)	
occurrences (all)	29	127	
Blood bilirubin increased			
subjects affected / exposed	8 / 151 (5.30%)	37 / 307 (12.05%)	
occurrences (all)	17	142	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 151 (3.31%)	106 / 307 (34.53%)	
occurrences (all)	6	303	
Nervous system disorders			
Headache			

subjects affected / exposed	5 / 151 (3.31%)	41 / 307 (13.36%)	
occurrences (all)	8	62	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 151 (19.87%)	83 / 307 (27.04%)	
occurrences (all)	71	190	
Fatigue			
subjects affected / exposed	16 / 151 (10.60%)	77 / 307 (25.08%)	
occurrences (all)	26	145	
Pyrexia			
subjects affected / exposed	17 / 151 (11.26%)	36 / 307 (11.73%)	
occurrences (all)	44	89	
Oedema peripheral			
subjects affected / exposed	5 / 151 (3.31%)	18 / 307 (5.86%)	
occurrences (all)	9	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	41 / 151 (27.15%)	64 / 307 (20.85%)	
occurrences (all)	141	333	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	30 / 151 (19.87%)	78 / 307 (25.41%)	
occurrences (all)	65	199	
Diarrhoea			
subjects affected / exposed	22 / 151 (14.57%)	92 / 307 (29.97%)	
occurrences (all)	36	207	
Nausea			
subjects affected / exposed	34 / 151 (22.52%)	72 / 307 (23.45%)	
occurrences (all)	69	147	
Stomatitis			
subjects affected / exposed	5 / 151 (3.31%)	69 / 307 (22.48%)	
occurrences (all)	7	148	
Vomiting			
subjects affected / exposed	21 / 151 (13.91%)	53 / 307 (17.26%)	
occurrences (all)	46	110	
Constipation			

subjects affected / exposed	23 / 151 (15.23%)	51 / 307 (16.61%)	
occurrences (all)	47	123	
Abdominal pain upper			
subjects affected / exposed	8 / 151 (5.30%)	29 / 307 (9.45%)	
occurrences (all)	14	61	
Dyspepsia			
subjects affected / exposed	10 / 151 (6.62%)	24 / 307 (7.82%)	
occurrences (all)	18	51	
Ascites			
subjects affected / exposed	13 / 151 (8.61%)	15 / 307 (4.89%)	
occurrences (all)	31	74	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	2 / 151 (1.32%)	44 / 307 (14.33%)	
occurrences (all)	2	59	
Dyspnoea			
subjects affected / exposed	12 / 151 (7.95%)	16 / 307 (5.21%)	
occurrences (all)	25	31	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 151 (3.97%)	81 / 307 (26.38%)	
occurrences (all)	6	170	
Rash			
subjects affected / exposed	4 / 151 (2.65%)	19 / 307 (6.19%)	
occurrences (all)	6	27	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 151 (6.62%)	18 / 307 (5.86%)	
occurrences (all)	20	38	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	11 / 151 (7.28%)	90 / 307 (29.32%)	
occurrences (all)	20	308	
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	8 / 151 (5.30%) 22	17 / 307 (5.54%) 32	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	45 / 151 (29.80%) 82	132 / 307 (43.00%) 287	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	16 / 151 (10.60%) 55	34 / 307 (11.07%) 156	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2016	Protocol version under which patient enrollment to begin. Updated based on FDA, CHMP/EMA and PMDA comments and advice to adjust inclusion/exclusion and study evaluations and to clarify and require study activity that address these comments.
03 February 2017	Protocol version to clarify and make slight modifications to inclusion/exclusion criteria. Updated to include Japan specific PMDA requirements to global protocol version and to add more clear parameters for patients to qualify and consent to continued study treatment after disease progression.
07 February 2018	Change of inclusion criteria to allow for later line study treatment in some study regions where recent approval of therapy or standardization of therapy in later line has occurred. This is to maintain the target study population to be subjects who failed approved standard therapies.
16 November 2018	Created open-label extension period for patients taking apatinib after unblinding study results during final analysis. Extended trial period estimation. Clarified ECG data collection. Integrated previous country specific protocol versions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported