



Clinical trial results:

A Randomized, Double-Blind Study of Ruxolitinib or Placebo in Combination With Regorafenib in Subjects With Relapsed or Refractory Metastatic Colorectal Cancer

Summary

EudraCT number	2013-004714-18
Trial protocol	IT GB AT ES
Global end of trial date	18 November 2016

Results information

Result version number	v1 (current)
This version publication date	08 December 2017
First version publication date	08 December 2017

Trial information

Trial identification

Sponsor protocol code	INCB 18424-267
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02119676
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cut-Off, Wilmington, DE, United States, 19803
Public contact	Incyte Corporation Call Centre, Incyte Corporation, +44 (0)330 100 3677, globalmedinfo@incyte.com
Scientific contact	Incyte Corporation Call Centre, Incyte Corporation, +44 (0)330 100 3677, globalmedinfo@incyte.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	29 March 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine if ruxolitinib, in combination with regorafenib, is safe and effective in the treatment of metastatic colorectal cancer.

The study consisted of an open-label, Part 1 safety run-in (consisting of 1 to 3 cohorts of 9 subjects each), to confirm the safety of the regorafenib/ruxolitinib combination in subjects with relapsed or refractory metastatic colorectal cancer (CRC). If determined to be tolerable, Part 2 was to proceed as a randomized, double-blind study evaluating ruxolitinib or placebo in combination with regorafenib in subjects with relapsed or refractory metastatic CRC previously treated with fluoropyrimidine, oxaliplatin, and/or irinotecan based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy and if Kirsten rat sarcoma (KRAS) wild type an anti-epidermal growth factor receptor (EGFR) therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2014
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	United States: 302
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	396
EEA total number of subjects	54

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)	261
From 65 to 84 years	135
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In Substudy 1, the first subject was enrolled on 29 OCT 2014, and the last subject was enrolled on 23 JUL 2015. In Substudy 2, the first subject was enrolled on 05 NOV 2014, and the last subject was enrolled on 02 OCT 2015.

Pre-assignment

Screening details:

Substudy 1; 4 participants were assigned a randomization number but were not given study drug because of clinical deterioration or withdrawal of consent. Substudy 2; 9 participants were assigned a randomization number, but weren't given study drug due to clinical deterioration, withdrawal of consent or not meeting all of the eligibility criteria.

Period 1

Period 1 title	Overall Period (overall period)
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	Substudy 1: Ruxolitinib + Regorafenib

Arm description:

Subjects with modified Glasgow Prognostic Score (mGPS) of 1 or 2 who were randomly assigned to receive ruxolitinib 15 mg twice daily (BID) continuous with regorafenib 160 mg once daily (QD) for the first 21 days of each 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	Jakafi ®, Jakavi ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ruxolitinib 15 mg (5 mg tablets) twice daily (BID).

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	Stivarga ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Regorafenib 160mg (40 mg tablets) once daily for the first 21 days of each 28-day cycle. (NOTE: Dose interruptions and modifications for regorafenib are expected when toxicities occur in which dose interruptions or modifications are appropriate.)

Arm title	Substudy 1: Placebo + Regorafenib
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Arm description:

Subjects with modified Glasgow Prognostic Score (mGPS) of 1 or 2 who were randomly assigned to receive Placebo twice daily (BID) continuous with regorafenib 160 mg once daily (QD) for the first 21 days of each 28-day cycle.

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

Dosage and administration details:

Regorafenib 160mg once daily for the first 21 days of each 28-day cycle. (NOTE: Dose interruptions and modifications for regorafenib are expected when toxicities occur in which dose interruptions or modifications are appropriate.)

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

Dosage and administration details:

5 mg matching placebo tablets to be administered by mouth

Arm title	Substudy 2: Ruxolitinib + Regorafenib
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Arm description:

Ruxolitinib 15 mg BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	Jakafi ®, Jakavi ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ruxolitinib 20 mg twice a day (BID) (Part 1) (NOTE: The starting dose for the randomized portion of study (Part 2) was 15 mg BID based on results from Part 1.)

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	Stivarga ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Regorafenib 160mg once daily for the first 21 days of each 28-day cycle. (NOTE: Dose interruptions and modifications for regorafenib are expected when toxicities occur in which dose interruptions or modifications are appropriate.)

Arm title	Substudy 2: Placebo + Regorafenib
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Arm description:

Placebo BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

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

Dosage and administration details:

5 mg matching placebo tablets to be administered by mouth

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	Stivarga ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Regorafenib 160mg once daily for the first 21 days of each 28-day cycle. (NOTE: Dose interruptions and modifications for regorafenib are expected when toxicities occur in which dose interruptions or modifications are appropriate.)

Number of subjects in period 1	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib
Started	87	88	110
Treated Patients	85	86	106
Completed	4	2	13
Not completed	83	86	97
Physician decision	4	2	3
Disease progression	53	55	68
Adverse event, non-fatal	9	17	10
Patient decision, inc. consent withdrawn	4	5	5
Death	9	3	2
Other, unspecified	2	1	3
Did not receive study med	2	2	4
Lost to follow-up	-	-	1
Noncompliance	-	1	-
Protocol deviation	-	-	1

Number of subjects in period 1	Substudy 2: Placebo + Regorafenib
Started	111
Treated Patients	106
Completed	10
Not completed	101
Physician decision	2
Disease progression	73
Adverse event, non-fatal	10
Patient decision, inc. consent withdrawn	6
Death	1
Other, unspecified	4

Did not receive study med	5
Lost to follow-up	-
Noncompliance	-
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Period
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Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	396	396	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	261	261	
From 65-84 years	135	135	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	59.6		
full range (min-max)	19 to 84	-	
Gender categorical			
Units: Subjects			
Female	168	168	
Male	228	228	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	21	21	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	27	27	
White	304	304	
Other	35	35	
Missing	8	8	

End points

End points reporting groups

Reporting group title	Substudy 1: Ruxolitinib + Regorafenib
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Reporting group description:

Subjects with modified Glasgow Prognostic Score (mGPS) of 1 or 2 who were randomly assigned to receive ruxolitinib 15 mg twice daily (BID) continuous with regorafenib 160 mg once daily (QD) for the first 21 days of each 28-day cycle.

Reporting group title	Substudy 1: Placebo + Regorafenib
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Reporting group description:

Subjects with modified Glasgow Prognostic Score (mGPS) of 1 or 2 who were randomly assigned to receive Placebo twice daily (BID) continuous with regorafenib 160 mg once daily (QD) for the first 21 days of each 28-day cycle.

Reporting group title	Substudy 2: Ruxolitinib + Regorafenib
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Reporting group description:

Ruxolitinib 15 mg BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

Reporting group title	Substudy 2: Placebo + Regorafenib
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Reporting group description:

Placebo BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival is defined as the time from randomization to death due to any cause. Participants without death observed at the time of the analysis will be censored at last date known to be alive. The median overall survival time was estimated using the Kaplan-Meier method. Overall survival was compared between treatment groups using log-rank test.

End point type	Primary
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End point timeframe:

Baseline until death due to any cause; data cut-off 27 Jan 2016 for Substudy 1 and 11 Feb 2016 for Substudy 2.

End point values	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib	Substudy 2: Placebo + Regorafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[1]	88 ^[2]	110 ^[3]	111 ^[4]
Units: months				
median (confidence interval 95%)	4.6 (3.5 to 5.4)	5.3 (4.3 to 6.0)	11.4 (9.0 to 13.2)	10.9 (7.2 to 999.99)

Notes:

[1] - Intent-to-treat (ITT) population-all subjects randomized in Substudy 1 & Substudy 2 of the study.

[2] - ITT population-all subjects randomized in Substudy 1 & Substudy 2 of the study.

[3] - ITT population-all subjects randomized in Substudy 1 & Substudy 2 of the study.

[4] - ITT population

999.99= Not estimable due to insufficient number of participants with events.

Statistical analyses

Statistical analysis title	Overall Survival Substudy 1:
Comparison groups	Substudy 1: Ruxolitinib + Regorafenib v Substudy 1: Placebo + Regorafenib
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.588 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.49

Notes:

[5] - Log-rank test stratified by modified Glasgow Prognostic Score (mGPS) and geographical region.

Statistical analysis title	Overall Survival Substudy 2
Comparison groups	Substudy 2: Ruxolitinib + Regorafenib v Substudy 2: Placebo + Regorafenib
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.136 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.23

Notes:

[6] - Log rank test stratified by geographical region.

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
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End point description:

PFS is defined as the number of days from randomization until the earliest date of disease progression determined by investigator assessment of objective radiographic disease assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause if sooner.

Progressive Disease (PD) is defined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as at least a 20% increase in the sum of the Longest Diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started, unequivocal progression of non-target lesions, or the appearance of new lesions.

End point type	Secondary
End point timeframe:	
Baseline through disease progression, data cut-off 27 Jan 2016 for Substudy 1 and 11 Feb 2016 for Substudy 2.	

End point values	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib	Substudy 2: Placebo + Regorafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[7]	88 ^[8]	110 ^[9]	111 ^[10]
Units: months				
median (confidence interval 95%)	2.2 (1.9 to 3.0)	2.1 (1.8 to 2.7)	3.5 (3.0 to 3.8)	2.0 (1.9 to 3.1)

Notes:

[7] - ITT population-all subjects randomized in Substudy 1 & Substudy 2 of the study.

[8] - ITT population-all subjects randomized in Substudy 1 & Substudy 2 of the study.

[9] - ITT population-all subjects randomized in Substudy 1 & Substudy 2 of the study.

[10] - ITT population-all subjects randomized in Substudy 1 & Substudy 2 of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
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End point description:

Response defined per Response Evaluation Criteria In Solid Tumors (RECIST) criteria: Complete Response (CR)=disappearance of all target and non-target lesions without new lesion; Partial Response (PR)=30% decrease in sum of longest diameter of target lesions, non-target lesion not progressed, and no new lesion; Progressive Disease=20% increase in sum of longest diameter of target lesions, or non-target lesion progression, or identification of new lesion; Stable Disease=small changes that do not meet above criteria. ORR was defined as the proportion of participants who achieved a best response of either CR or PR. ORR=number of participants with CR or PR/number of participants randomized.

End point type	Secondary
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End point timeframe:

Baseline through end of study; data cut-off 27 Jan 2016 for Substudy 1 and 11 Feb 2016 for Substudy 2.

End point values	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib	Substudy 2: Placebo + Regorafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[11]	88 ^[12]	110 ^[13]	111 ^[14]
Units: percentage of responders				
number (confidence interval 95%)	0.0 (0.0 to 4.2)	0.0 (0.0 to 4.1)	2.7 (0.6 to 7.8)	4.5 (1.5 to 10.2)

Notes:

- [11] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.
[12] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.
[13] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.
[14] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
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End point description:

Duration of response is defined as the time from response (CR/PR) until the earliest date of disease progression determined by investigator assessment of objective radiographic disease assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause.

No data displayed because outcome measure has not been analyzed. Duration of response analyses was not done since there were no responders in Substudy 1 and very few responders in Substudy 2 at data cutoff (27JAN2016 for Substudy 1 and 11Feb2016 for Substudy 2). Duration of response analysis was not done in both substudies.

End point type	Secondary
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End point timeframe:

Baseline through end of study; data cut-off 27 Jan 2016 for Substudy 1 and 11 Feb 2016 for Substudy 2.

End point values	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib	Substudy 2: Placebo + Regorafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[15]	0 ^[16]	0 ^[17]	0 ^[18]
Units: months				
number (not applicable)				

Notes:

- [15] - No data displayed because outcome measure has not been analyzed.
[16] - No data displayed because outcome measure has not been analyzed.
[17] - No data displayed because outcome measure has not been analyzed.
[18] - No data displayed because outcome measure has not been analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Disease Control

End point title	Percentage of Participants Achieving Disease Control
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End point description:

Disease control as measured by the percentage of participants whose best response was complete response (CR), partial response (PR), or stable disease (SD) per RECIST v.1.1.

End point type	Secondary
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End point timeframe:

Baseline through end of study; data cut-off 27 Jan 2016 for Substudy 1 and 11 Feb 2016 for Substudy 2.

End point values	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib	Substudy 2: Placebo + Regorafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87 ^[19]	88 ^[20]	110 ^[21]	111 ^[22]
Units: Percentage of participants				
number (confidence interval 95%)	40.2 (29.9 to 51.3)	34.1 (24.3 to 45.0)	61.8 (52.1 to 70.9)	36.9 (28.0 to 46.6)

Notes:

[19] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.

[20] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.

[21] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.

[22] - ITT population included all subjects randomized in Substudy 1 and Substudy 2 of the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication up to 16 months or data cut-off 29MAR2016.

Adverse event reporting additional description:

The safety evaluable population consisted of all participants exposed to at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Substudy 1: Ruxolitinib + Regorafenib
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Reporting group description:

Ruxolitinib 15 mg BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

Reporting group title	Substudy 1: Placebo + Regorafenib
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Reporting group description:

Placebo BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

Reporting group title	Substudy 2: Ruxolitinib + Regorafenib
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Reporting group description:

Ruxolitinib 15 mg BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

Reporting group title	Substudy 2: Placebo + Regorafenib
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Reporting group description:

Placebo BID continuous with regorafenib 160 mg QD for the first 21 days of each 28-day cycle.

Serious adverse events	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 85 (58.82%)	43 / 86 (50.00%)	40 / 106 (37.74%)
number of deaths (all causes)	12	6	4
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Neoplasm progression			

subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 85 (0.00%)	2 / 86 (2.33%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	0 / 106 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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 / 85 (2.35%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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

Disease progression			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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	4 / 85 (4.71%)	3 / 86 (3.49%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Multi-organ failure			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Obstruction			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Oedema			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcer haemorrhage			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia obstructive			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Pain			
subjects affected / exposed	0 / 85 (0.00%)	3 / 86 (3.49%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 85 (4.71%)	2 / 86 (2.33%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 85 (1.18%)	2 / 86 (2.33%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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

Dyspnoea			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	4 / 106 (3.77%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Hypoxia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	3 / 106 (2.83%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	0 / 106 (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
Pneumonitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Blood bilirubin increased			
subjects affected / exposed	5 / 85 (5.88%)	1 / 86 (1.16%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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

Lipase increased			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Liver function test abnormal			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Platelet count decreased			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	0 / 106 (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
Femur fracture			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia, obstructive			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Supraventricular tachycardia subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders Cerebrospinal fistula subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Cerebrovascular accident subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Encephalopathy			

subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	0 / 106 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Headache			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Hepatic encephalopathy			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Lacunar infarction			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Syncope			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Grand mal convulsion			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Anaemia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	4 / 106 (3.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	9 / 85 (10.59%)	7 / 86 (8.14%)	4 / 106 (3.77%)
occurrences causally related to treatment / all	0 / 9	0 / 7	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	0 / 106 (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
Ascites			
subjects affected / exposed	3 / 85 (3.53%)	0 / 86 (0.00%)	0 / 106 (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
Bloody peritoneal effluent			

subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Anal haemorrhage			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dieulafoy's vascular malformation			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Enteritis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 85 (2.35%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Haematemesis			

subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Intestinal obstruction			
subjects affected / exposed	1 / 85 (1.18%)	3 / 86 (3.49%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	2 / 85 (2.35%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Nausea			
subjects affected / exposed	4 / 85 (4.71%)	2 / 86 (2.33%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal food impaction			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	3 / 85 (3.53%)	1 / 86 (1.16%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Subileus			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Vomiting			
subjects affected / exposed	2 / 85 (2.35%)	4 / 86 (4.65%)	3 / 106 (2.83%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Cholelithiasis			

subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	2 / 85 (2.35%)	0 / 86 (0.00%)	0 / 106 (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
Hepatorenal syndrome			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Hyperbilirubinaemia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Jaundice cholestatic			
subjects affected / exposed	2 / 85 (2.35%)	1 / 86 (1.16%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Hydronephrosis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	3 / 85 (3.53%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vesical fistula			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Renal vein thrombosis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	3 / 85 (3.53%)	1 / 86 (1.16%)	3 / 106 (2.83%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Pathological fracture			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Atypical pneumonia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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

Biliary sepsis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Gastroenteritis viral			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Hepatic infection bacterial			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Infection			
subjects affected / exposed	2 / 85 (2.35%)	1 / 86 (1.16%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Perirectal abscess			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Peritonitis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Peritonitis bacterial			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	5 / 85 (5.88%)	2 / 86 (2.33%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 5	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	6 / 85 (7.06%)	1 / 86 (1.16%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 6	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 85 (2.35%)	1 / 86 (1.16%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	0 / 106 (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
Biliary tract infection			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
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 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Hypocalcaemia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Malnutrition			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	0 / 106 (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
Hypokalaemia			

subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Substudy 2: Placebo + Regorafenib		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 106 (36.79%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm progression			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			

subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulcer haemorrhage				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hernia obstructive				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				

subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pleural effusion			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract inflammation			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incisional hernia, obstructive			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seroma			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial tachycardia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrospinal fistula			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lacunar infarction			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bloody peritoneal effluent			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dieulafoy's vascular malformation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal inflammation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			

subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	3 / 106 (2.83%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Oesophageal food impaction				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	5 / 106 (4.72%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis acute			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatorenal syndrome			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			

subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal failure acute			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vesical fistula			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal vein thrombosis			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteric obstruction			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal pain			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Systemic lupus erythematosus			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary sepsis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic infection bacterial			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver abscess			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Perirectal abscess			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	2 / 106 (1.89%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Substudy 1: Ruxolitinib + Regorafenib	Substudy 1: Placebo + Regorafenib	Substudy 2: Ruxolitinib + Regorafenib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 85 (95.29%)	83 / 86 (96.51%)	106 / 106 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 85 (21.18%)	21 / 86 (24.42%)	43 / 106 (40.57%)
occurrences (all)	22	23	64
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	20 / 85 (23.53%)	21 / 86 (24.42%)	19 / 106 (17.92%)
occurrences (all)	25	25	29
Chills			
subjects affected / exposed	2 / 85 (2.35%)	5 / 86 (5.81%)	5 / 106 (4.72%)
occurrences (all)	2	5	5
Fatigue			
subjects affected / exposed	29 / 85 (34.12%)	31 / 86 (36.05%)	43 / 106 (40.57%)
occurrences (all)	30	35	47
Chest pain			
subjects affected / exposed	3 / 85 (3.53%)	3 / 86 (3.49%)	7 / 106 (6.60%)
occurrences (all)	3	3	7
Oedema peripheral			
subjects affected / exposed	8 / 85 (9.41%)	8 / 86 (9.30%)	2 / 106 (1.89%)
occurrences (all)	8	8	3
Pain			
subjects affected / exposed	5 / 85 (5.88%)	1 / 86 (1.16%)	2 / 106 (1.89%)
occurrences (all)	7	1	2
Pyrexia			
subjects affected / exposed	14 / 85 (16.47%)	13 / 86 (15.12%)	19 / 106 (17.92%)
occurrences (all)	19	18	22
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 85 (10.59%)	8 / 86 (9.30%)	10 / 106 (9.43%)
occurrences (all)	13	8	10
Dysphonia			

subjects affected / exposed	11 / 85 (12.94%)	14 / 86 (16.28%)	22 / 106 (20.75%)
occurrences (all)	12	16	25
Dyspnoea			
subjects affected / exposed	10 / 85 (11.76%)	13 / 86 (15.12%)	12 / 106 (11.32%)
occurrences (all)	11	17	13
Epistaxis			
subjects affected / exposed	6 / 85 (7.06%)	4 / 86 (4.65%)	4 / 106 (3.77%)
occurrences (all)	7	4	5
Oropharyngeal pain			
subjects affected / exposed	5 / 85 (5.88%)	5 / 86 (5.81%)	7 / 106 (6.60%)
occurrences (all)	7	5	8
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	0 / 106 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	7 / 85 (8.24%)	5 / 86 (5.81%)	11 / 106 (10.38%)
occurrences (all)	7	5	11
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 85 (5.88%)	8 / 86 (9.30%)	8 / 106 (7.55%)
occurrences (all)	5	8	8
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 85 (8.24%)	14 / 86 (16.28%)	12 / 106 (11.32%)
occurrences (all)	7	18	13
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 85 (3.53%)	6 / 86 (6.98%)	4 / 106 (3.77%)
occurrences (all)	3	8	5
Blood bilirubin increased			
subjects affected / exposed	8 / 85 (9.41%)	11 / 86 (12.79%)	7 / 106 (6.60%)
occurrences (all)	8	13	11
Lipase increased			
subjects affected / exposed	0 / 85 (0.00%)	5 / 86 (5.81%)	5 / 106 (4.72%)
occurrences (all)	0	5	6
Weight decreased			

subjects affected / exposed occurrences (all)	13 / 85 (15.29%) 14	15 / 86 (17.44%) 15	13 / 106 (12.26%) 13
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 85 (4.71%)	5 / 86 (5.81%)	11 / 106 (10.38%)
occurrences (all)	4	6	13
Dysgeusia			
subjects affected / exposed	6 / 85 (7.06%)	6 / 86 (6.98%)	6 / 106 (5.66%)
occurrences (all)	6	9	7
Headache			
subjects affected / exposed	13 / 85 (15.29%)	16 / 86 (18.60%)	21 / 106 (19.81%)
occurrences (all)	14	18	24
Paraesthesia			
subjects affected / exposed	0 / 85 (0.00%)	4 / 86 (4.65%)	5 / 106 (4.72%)
occurrences (all)	0	4	5
Neuropathy peripheral			
subjects affected / exposed	2 / 85 (2.35%)	2 / 86 (2.33%)	9 / 106 (8.49%)
occurrences (all)	2	2	9
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 85 (11.76%)	12 / 86 (13.95%)	24 / 106 (22.64%)
occurrences (all)	14	16	34
Thrombocytopenia			
subjects affected / exposed	3 / 85 (3.53%)	1 / 86 (1.16%)	4 / 106 (3.77%)
occurrences (all)	3	1	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	21 / 85 (24.71%)	26 / 86 (30.23%)	25 / 106 (23.58%)
occurrences (all)	22	29	27
Abdominal pain upper			
subjects affected / exposed	4 / 85 (4.71%)	6 / 86 (6.98%)	6 / 106 (5.66%)
occurrences (all)	4	6	8
Abdominal distension			
subjects affected / exposed	2 / 85 (2.35%)	4 / 86 (4.65%)	1 / 106 (0.94%)
occurrences (all)	2	6	1
Ascites			

subjects affected / exposed	4 / 85 (4.71%)	2 / 86 (2.33%)	2 / 106 (1.89%)
occurrences (all)	4	2	4
Constipation			
subjects affected / exposed	27 / 85 (31.76%)	20 / 86 (23.26%)	23 / 106 (21.70%)
occurrences (all)	31	25	25
Diarrhoea			
subjects affected / exposed	32 / 85 (37.65%)	27 / 86 (31.40%)	40 / 106 (37.74%)
occurrences (all)	48	35	77
Dry mouth			
subjects affected / exposed	3 / 85 (3.53%)	6 / 86 (6.98%)	4 / 106 (3.77%)
occurrences (all)	4	6	4
Flatulence			
subjects affected / exposed	5 / 85 (5.88%)	6 / 86 (6.98%)	5 / 106 (4.72%)
occurrences (all)	5	8	5
Nausea			
subjects affected / exposed	19 / 85 (22.35%)	20 / 86 (23.26%)	30 / 106 (28.30%)
occurrences (all)	24	26	40
Stomatitis			
subjects affected / exposed	20 / 85 (23.53%)	18 / 86 (20.93%)	19 / 106 (17.92%)
occurrences (all)	22	19	26
Vomiting			
subjects affected / exposed	16 / 85 (18.82%)	18 / 86 (20.93%)	23 / 106 (21.70%)
occurrences (all)	18	23	29
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 85 (1.18%)	6 / 86 (6.98%)	3 / 106 (2.83%)
occurrences (all)	1	6	3
Dry skin			
subjects affected / exposed	6 / 85 (7.06%)	6 / 86 (6.98%)	8 / 106 (7.55%)
occurrences (all)	7	6	8
Palmar-plantar erythrodysaesthesia			
subjects affected / exposed	36 / 85 (42.35%)	38 / 86 (44.19%)	60 / 106 (56.60%)
occurrences (all)	46	51	86
Pruritus			
subjects affected / exposed	5 / 85 (5.88%)	3 / 86 (3.49%)	3 / 106 (2.83%)
occurrences (all)	6	3	4

Rash			
subjects affected / exposed	8 / 85 (9.41%)	12 / 86 (13.95%)	15 / 106 (14.15%)
occurrences (all)	9	13	16
Rash maculo-papular			
subjects affected / exposed	1 / 85 (1.18%)	5 / 86 (5.81%)	2 / 106 (1.89%)
occurrences (all)	1	5	2
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	6 / 85 (7.06%)	1 / 86 (1.16%)	2 / 106 (1.89%)
occurrences (all)	7	2	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 85 (4.71%)	6 / 86 (6.98%)	4 / 106 (3.77%)
occurrences (all)	4	6	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 85 (8.24%)	4 / 86 (4.65%)	7 / 106 (6.60%)
occurrences (all)	7	4	7
Back pain			
subjects affected / exposed	14 / 85 (16.47%)	10 / 86 (11.63%)	12 / 106 (11.32%)
occurrences (all)	15	10	15
Muscle spasms			
subjects affected / exposed	7 / 85 (8.24%)	2 / 86 (2.33%)	9 / 106 (8.49%)
occurrences (all)	9	2	12
Muscular weakness			
subjects affected / exposed	5 / 85 (5.88%)	0 / 86 (0.00%)	3 / 106 (2.83%)
occurrences (all)	5	0	3
Myalgia			
subjects affected / exposed	6 / 85 (7.06%)	5 / 86 (5.81%)	7 / 106 (6.60%)
occurrences (all)	7	5	8
Musculoskeletal pain			
subjects affected / exposed	3 / 85 (3.53%)	3 / 86 (3.49%)	6 / 106 (5.66%)
occurrences (all)	3	3	6
Pain in extremity			
subjects affected / exposed	5 / 85 (5.88%)	2 / 86 (2.33%)	10 / 106 (9.43%)
occurrences (all)	6	3	10

Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	9 / 85 (10.59%) 11	6 / 86 (6.98%) 7	8 / 106 (7.55%) 9
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	31 / 85 (36.47%) 38	31 / 86 (36.05%) 37	29 / 106 (27.36%) 35
Dehydration subjects affected / exposed occurrences (all)	10 / 85 (11.76%) 11	7 / 86 (8.14%) 7	7 / 106 (6.60%) 9
Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 85 (3.53%) 3	6 / 86 (6.98%) 6	0 / 106 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	8 / 85 (9.41%) 8	6 / 86 (6.98%) 9	5 / 106 (4.72%) 5
Hypophosphataemia subjects affected / exposed occurrences (all)	11 / 85 (12.94%) 12	5 / 86 (5.81%) 5	8 / 106 (7.55%) 10

Non-serious adverse events	Substudy 2: Placebo + Regorafenib		
Total subjects affected by non-serious adverse events subjects affected / exposed	104 / 106 (98.11%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	42 / 106 (39.62%) 53		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	23 / 106 (21.70%) 26		
Chills subjects affected / exposed occurrences (all)	4 / 106 (3.77%) 5		
Fatigue			

subjects affected / exposed	47 / 106 (44.34%)		
occurrences (all)	56		
Chest pain			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	8 / 106 (7.55%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	13 / 106 (12.26%)		
occurrences (all)	17		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 106 (6.60%)		
occurrences (all)	7		
Dysphonia			
subjects affected / exposed	27 / 106 (25.47%)		
occurrences (all)	29		
Dyspnoea			
subjects affected / exposed	17 / 106 (16.04%)		
occurrences (all)	17		
Epistaxis			
subjects affected / exposed	10 / 106 (9.43%)		
occurrences (all)	10		
Oropharyngeal pain			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	5		
Insomnia			

subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 106 (10.38%)		
occurrences (all)	11		
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 106 (12.26%)		
occurrences (all)	14		
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	5		
Blood bilirubin increased			
subjects affected / exposed	14 / 106 (13.21%)		
occurrences (all)	18		
Lipase increased			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	16 / 106 (15.09%)		
occurrences (all)	16		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	26 / 106 (24.53%)		
occurrences (all)	34		
Paraesthesia			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
Neuropathy peripheral			

subjects affected / exposed	6 / 106 (5.66%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 106 (11.32%)		
occurrences (all)	13		
Thrombocytopenia			
subjects affected / exposed	6 / 106 (5.66%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 106 (25.47%)		
occurrences (all)	31		
Abdominal pain upper			
subjects affected / exposed	11 / 106 (10.38%)		
occurrences (all)	12		
Abdominal distension			
subjects affected / exposed	7 / 106 (6.60%)		
occurrences (all)	7		
Ascites			
subjects affected / exposed	7 / 106 (6.60%)		
occurrences (all)	12		
Constipation			
subjects affected / exposed	22 / 106 (20.75%)		
occurrences (all)	26		
Diarrhoea			
subjects affected / exposed	30 / 106 (28.30%)		
occurrences (all)	42		
Dry mouth			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Flatulence			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	6		
Nausea			

subjects affected / exposed	19 / 106 (17.92%)		
occurrences (all)	23		
Stomatitis			
subjects affected / exposed	21 / 106 (19.81%)		
occurrences (all)	23		
Vomiting			
subjects affected / exposed	13 / 106 (12.26%)		
occurrences (all)	15		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	10 / 106 (9.43%)		
occurrences (all)	13		
Palmar-plantar erythrodysesthesia			
subjects affected / exposed	50 / 106 (47.17%)		
occurrences (all)	61		
Pruritus			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	11 / 106 (10.38%)		
occurrences (all)	12		
Rash maculo-papular			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	5		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	8 / 106 (7.55%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	11 / 106 (10.38%)		
occurrences (all)	12		
Muscle spasms			
subjects affected / exposed	11 / 106 (10.38%)		
occurrences (all)	12		
Muscular weakness			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	13 / 106 (12.26%)		
occurrences (all)	16		
Musculoskeletal pain			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	10 / 106 (9.43%)		
occurrences (all)	14		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 106 (7.55%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	34 / 106 (32.08%)		
occurrences (all)	36		
Dehydration			
subjects affected / exposed	10 / 106 (9.43%)		
occurrences (all)	11		
Hypoalbuminaemia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Hypokalaemia			

subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	5		
Hypophosphataemia			
subjects affected / exposed	13 / 106 (12.26%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2014	The primary purpose of the amendment was to be able to test alternate decreased dosing of the reference therapy regorafenib in the event that the labeled dose of 160 mg QD was not tolerated. • Revision of inclusion Criterion 4 to specify that subjects who had previous anti-VEGF therapy or anti-EGFR therapy had to have no contraindication; subjects had to have progressed after the last administration of approved therapy; and subjects who discontinued previous treatment due to unacceptable toxicity were also allowed in the study. • The number of subjects in the safety run-in was increased from 27 to 81 due to the number of cohorts increasing. • Subjects were allowed to take the reference therapy regorafenib in the evening with a low-fat meal with approval, except on days of PK sampling. • Platelet requirement for continuing treatment was revised from $> 50 \times 10^9/L$ to $> 75 \times 10^9/L$. • Modified dose reduction allowance to describe dose modifications when starting doses are lower than 160 mg QD. • An optional dose escalation section for regorafenib to allow the option to increase the dose for subjects who can tolerate an increase. • Text was added that males and females must continue to use contraception for 2 months after stopping regorafenib.
17 September 2014	The primary purpose of the amendment was to simplify and reduce the planned cohorts within the study. • Testing of the regorafenib 80 mg QD dosing cohort was removed from Part 1, the safety run-in. The description of dosing cohort sequences was shortened, including removing the reduction of the regorafenib in the statement that defines the MTD with hematologic toxicities. • The number of subjects tested in Part 1 safety run-in was changed from 81 to 54. • Study completion was defined as when the prespecified number of deaths required for analysis of the primary endpoint had occurred in both substudies and no subjects were on study treatment. – SS1 was considered completed when 121 deaths had been observed and no subjects were on study treatment. – SS2 was considered completed when 125 deaths had been observed and no subjects were on study treatment. • Laboratory sampling for TSH, lipase, and amylase was added to be aligned with the regorafenib Summary of Product Characteristics.
09 October 2014	The primary purpose of the amendment was to address the FDA's 01 OCT 2014 advice/information request. • Neutropenic fever definition was amended to match CTCAE v4.03 guidelines • To match the prescribing information for regorafenib and to provide clarity, regorafenib dose modification tables were revised and text was revised to: – Temporarily or permanently withhold regorafenib for severe or uncontrolled hypertension. – State there would be no permitted dose escalations for regorafenib. • Clarification of DLT criteria, measured as ≥ 3 of the first 9 evaluable subjects in a given cohort with a DLT in the first cycle. • Optional tumor tissue biopsy sample was added. Exploratory objective and endpoint was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 January 2016	Termination of Substudy 1 occurred on 27 January 2016 followed by the termination of Substudy 2 on 11 February 2016.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Substudy 1 was terminated for futility at interim analysis and Substudy 2 was terminated per sponsor decision.
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Notes: