



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 |
|-----------------------|----------------|

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 |
|------------------|-----------------------------------|

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 |
|------------------|---------------------------------------|

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 |
|------------------|-----------------------------------|

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 |
|-----------------------|----------------|

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 |
|-----------------------|---------------------------------------|

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 |
|-----------------------|-----------------------------------|

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 |
|-----------------------|---------------------------------------|

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 |
|-----------------------|-----------------------------------|

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) |
|-----------------|-----------------------|

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 |
|----------------|---------|

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) |
|-----------------|---------------------------------|

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) |
|-----------------|-----------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|----------------------|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Substudy 1: Ruxolitinib + Regorafenib |
|-----------------------|---------------------------------------|

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 |
|-----------------------|-----------------------------------|

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 |
|-----------------------|---------------------------------------|

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 |
|-----------------------|-----------------------------------|

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 | <p>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.</p> <ul style="list-style-type: none">• 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 | <p>The primary purpose of the amendment was to simplify and reduce the planned cohorts within the study.</p> <ul style="list-style-type: none">• 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.<ul style="list-style-type: none">– 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 | <p>The primary purpose of the amendment was to address the FDA's 01 OCT 2014 advice/information request.</p> <ul style="list-style-type: none">• 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:<ul style="list-style-type: none">– 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. |
|--|

Notes: