



Clinical trial results:

A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2009-017957-37 |
| Trial protocol | BE FI NL DE GB AT FR ES IT |
| Global end of trial date | 26 April 2019 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 23 April 2020 |
| First version publication date | 23 April 2020 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | 14874 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01271712 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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 | 09 May 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 April 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary: To compare the treatment groups in terms of Progression-Free Survival (PFS), per blinded central radiology review, according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).

Secondary: To compare the regorafenib and placebo treatment groups in terms of overall survival (OS), time to progression (TTP), disease control rate (DCR), tumor response rate (RR), duration of response (DOR), and safety of regorafenib.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Best supportive care (BSC)

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 04 January 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 8 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | China: 11 |
| Country: Number of subjects enrolled | Japan: 17 |
| Country: Number of subjects enrolled | Singapore: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 16 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Belgium: 6 |
| Country: Number of subjects enrolled | Canada: 10 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Germany: 32 |
| Country: Number of subjects enrolled | Israel: 1 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Italy: 20 |
| Country: Number of subjects enrolled | Netherlands: 10 |
| Country: Number of subjects enrolled | Poland: 10 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | United States: 26 |
| Worldwide total number of subjects | 199 |
| EEA total number of subjects | 115 |

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) | 136 |
| From 65 to 84 years | 62 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

A total of 240 participants with metastatic and/or unresectable GIST whose disease had progressed despite prior treatments with at least imatinib and sunitinib were screened; 199 were randomized. Patients must have shown objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib treatment.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to receive either regorafenib (133 patients) or placebo (66 patients). Randomization was stratified according 3rd vs. 4th line of therapy (at least 50% of patients were to be 3rd line), and geographical region (Asia vs.rest of world).

Period 1

| | |
|------------------------------|---|
| Period 1 title | Double blind treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Assessor |

Arms

| | |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Regorafenib (Stivarga, BAY73-4506) |

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Regorafenib |
| Investigational medicinal product code | BAY73-4506 |
| Other name | Stivarga |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Double blind phase: Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

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

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| Number of subjects in period 1 | Regorafenib (Stivarga, BAY73-4506) | Placebo |
|---------------------------------|---------------------------------------|---------|
| Started | 133 | 66 |
| Participants Received Treatment | 132 | 66 |
| Completed | 91 | 58 |
| Not completed | 42 | 8 |
| Adverse event, serious fatal | 2 | - |
| Consent withdrawn by subject | 4 | 1 |
| Adverse event, non-fatal | 9 | 4 |
| receive no study drug | 1 | - |
| Progressive disease | 23 | 3 |
| Non compliance with study drug | 2 | - |
| Lack of efficacy | 1 | - |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Open label treatment |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Regorafenib (Stivarga, BAY73-4506) |

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Regorafenib |
| Investigational medicinal product code | BAY73-4506 |
| Other name | Stivarga |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| | |
|------------------|--|
| Arm title | Placebo first, then Option of Open Label Regorafenib Treatment |
|------------------|--|

Arm description:

Open Label phase: Participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| Number of subjects in period 2 | Regorafenib (Stivarga, BAY73-4506) | Placebo first, then Option of Open Label Regorafenib Treatment |
|--------------------------------|---------------------------------------|---|
| | | |
| Started | 91 | 58 |
| Completed | 0 | 0 |
| Not completed | 91 | 58 |
| Adverse event, serious fatal | 6 | 5 |
| Consent withdrawn by subject | 6 | 11 |
| Physician decision | 2 | - |
| Adverse event, non-fatal | 14 | 8 |
| transferred to rollover study | 1 | - |
| Non-compliance with study drug | 1 | - |
| Switching to other therapy | 2 | 1 |
| Progressive disease | 59 | 32 |
| Protocol deviation | - | 1 |

Period 3

| | |
|------------------------------|-------------------------|
| Period 3 title | Safety follow-up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Regorafenib (Stivarga, BAY73-4506) |

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-------------|
| Investigational medicinal product name | Regorafenib |
| Investigational medicinal product code | BAY73-4506 |
| Other name | Stivarga |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| | |
|------------------|--|
| Arm title | Placebo first, then Option of Open Label Regorafenib Treatment |
|------------------|--|

Arm description:

Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

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

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| Number of subjects in period 3 | Regorafenib (Stivarga, BAY73-4506) | Placebo first, then Option of Open Label Regorafenib Treatment |
|---------------------------------------|---------------------------------------|---|
| Started | 118 | 52 |
| Completed | 97 | 37 |
| Not completed | 21 | 15 |
| Adverse event, serious fatal | 11 | 7 |
| Consent withdrawn by subject | 4 | 2 |
| Not analyzed after cutoff 08Jun2015 | 3 | 4 |
| No follow-up | 1 | 1 |
| Progressive disease | 1 | - |
| Protocol deviation | 1 | 1 |

Period 4

| | |
|------------------------------|-----------------------------|
| Period 4 title | Survival Follow-up |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|------------------------------------|
| Arm title | Regorafenib (Stivarga, BAY73-4506) |
|------------------|------------------------------------|

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Regorafenib |
| Investigational medicinal product code | BAY73-4506 |
| Other name | Stivarga |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| | |
|------------------|--|
| Arm title | Placebo first, then Option of Open Label Regorafenib Treatment |
|------------------|--|

Arm description:

Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

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

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

| Number of subjects in period 4 | Regorafenib (Stivarga, BAY73-4506) | Placebo first, then Option of Open Label Regorafenib Treatment |
|-------------------------------------|---------------------------------------|---|
| | | |
| Started | 100 | 39 |
| Completed | 85 | 33 |
| Not completed | 15 | 6 |
| Not analyzed after cutoff 08Jun2015 | 15 | 6 |

Baseline characteristics

Reporting groups

| | |
|---|------------------------------------|
| Reporting group title | Regorafenib (Stivarga, BAY73-4506) |
| Reporting group description: | |
| Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Double blind phase: Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks | |

| Reporting group values | Regorafenib (Stivarga, BAY73-4506) | Placebo | Total |
|---|---------------------------------------|---------|-------|
| Number of subjects | 133 | 66 | 199 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 58.2 | 58.1 | - |
| standard deviation | ± 12.5 | ± 13.9 | - |
| Sex: Female, Male Units: | | | |
| Female | 48 | 24 | 72 |
| Male | 85 | 42 | 127 |
| ECOG Performance Status (PS)] | | | |
| ECOG = Eastern cooperative oncology group PS levels are 0 (Fully active, able to carry on all pre-disease performance), 1 (ambulatory and able to carry out work of a light or sedentary), 2 (Ambulatory and capable of all selfcare but unable to carry out any work activities), 3 (Capable of only limited selfcare, confined to bed or chair more than 50% of awake time), 4 (Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair) and 5 (death). | | | |
| Units: Subjects | | | |
| PS 0 | 73 | 37 | 110 |
| PS 1 | 60 | 29 | 89 |
| PS 2 | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 |
| Prior anti-cancer drug group | | | |
| 3rd line: 3rd in sequence of multiple therapies: imatinib (1st); sunitinib (2nd). 4th line and beyond: 4th in sequence of multiple therapies: imatinib (1st); sunitinib (2nd); other (3rd). | | | |
| Units: Subjects | | | |

| | | | |
|---------------------|----|----|-----|
| 3rd line | 74 | 39 | 113 |
| 4th line and beyond | 59 | 27 | 86 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Regorafenib (Stivarga, BAY73-4506) |
| Reporting group description: Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks | |
| Reporting group title | Placebo |
| Reporting group description: Double blind phase: Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks | |
| Reporting group title | Regorafenib (Stivarga, BAY73-4506) |
| Reporting group description: Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks | |
| Reporting group title | Placebo first, then Option of Open Label Regorafenib Treatment |
| Reporting group description: Open Label phase: Participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. | |
| Reporting group title | Regorafenib (Stivarga, BAY73-4506) |
| Reporting group description: Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks | |
| Reporting group title | Placebo first, then Option of Open Label Regorafenib Treatment |
| Reporting group description: Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. | |
| Reporting group title | Regorafenib (Stivarga, BAY73-4506) |
| Reporting group description: Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks | |
| Reporting group title | Placebo first, then Option of Open Label Regorafenib Treatment |
| Reporting group description: Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. | |

Primary: Progression-free Survival

| | |
|---|---------------------------|
| End point title | Progression-free Survival |
| End point description: Progression-free Survival (PFS) was defined as the time from date of randomization to radiological disease progression or death due to any cause, whichever occurs first. PFS was based on central radiological assessment using modified RECIST (Response Evaluation Criteria in Solid Tumors) v.1.1. Progression is defined as at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study; or unequivocal progression of existing non-target lesions; or appearance of new lesions. Subjects without progression or death at the time of analysis were censored at their last date of tumor evaluation. Results are based on central evaluation. | |
| End point type | Primary |
| End point timeframe: From randomization of the first subject until approximately 144 progression-free survival events had | |

| End point values | Regorafenib (Stivarga, BAY73-4506) | Placebo | | |
|----------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 | 66 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 147 (122 to 173) | 28 (28 to 32) | | |

Statistical analyses

| Statistical analysis title | Progression-free Survival analysis |
|----------------------------|------------------------------------|
|----------------------------|------------------------------------|

Statistical analysis description:

The two treatment groups were compared using a stratified log rank test with a one-sided alpha of 0.01 stratified by (3rd vs 4th-line; and geographical region). The null hypothesis that both treatment arms have the same PFS distribution was tested against the alternative hypothesis that the distribution of PFS in the regorafenib arm is different from the control arm according to a proportional hazards relation between the treatment arms.

| | |
|---|--|
| Comparison groups | Regorafenib (Stivarga, BAY73-4506) v Placebo |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.000001 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.268 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.185 |
| upper limit | 0.388 |

Notes:

[1] - Hazard ratio and its 95% CI (Confidence Interval) was based on stratified Cox Regression Model

[2] - stratified logrank

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall Survival (OS) was defined as the time from date of randomization to death due to any cause. Subjects still alive at the time of analysis were censored at their date of last contact. Median OS was not observed at the time of PFS analysis and first analysis of OS, therefore only the proportion of death events was reported in the results posting system. This approach was maintained for the subsequent updates in the results posting system.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization of the first subject until date of database cutoff (08 Jun 2015)

| End point values | Regorafenib (Stivarga, BAY73-4506) | Placebo | | |
|--|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 | 66 | | |
| Units: Percentage of patients with death | | | | |
| number (not applicable) | 82.0 | 80.3 | | |

Statistical analyses

| Statistical analysis title | Overall survival analysis |
|--|--|
| Statistical analysis description: | |
| Hazard ratio and its 95% CI was based on stratified Cox Regression Model | |
| Comparison groups | Regorafenib (Stivarga, BAY73-4506) v Placebo |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.285777 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.909 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.653 |
| upper limit | 1.265 |

Notes:

[3] - Regorafenib over control. 58 (87.9%) patients in placebo group and 91 (68.4%) patients in regorafenib had started open-label treatment with regorafenib before time of final database cutoff 08 Jun 2015.

[4] - stratified Log Rank

Secondary: Time to Progression (TTP)

| End point title | Time to Progression (TTP) |
|--|---------------------------|
| End point description: | |
| Time to progression (TTP) was defined as the time from date of randomization to disease progression (based on central radiological assessment using modified RECIST [Response Evaluation Criteria in Solid Tumors] v.1.1). Progression is defined as at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study; or unequivocal progression of existing non-target lesions; or appearance of new lesions. Subjects without progression at the time of analysis were censored at their last date of tumor evaluation. Results are based on central evaluation. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year | |

| | | | | |
|----------------------------------|--|-----------------|--|--|
| End point values | Regorafenib (Stivarga, BAY73-4506) | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 | 66 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 165 (125 to 174) | 28 (28 to 34) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Time to progression analysis |
| Statistical analysis description: as of the data cutoff date of 26 JAN 2012 | |
| Comparison groups | Regorafenib (Stivarga, BAY73-4506) v Placebo |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | < 0.001 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.248 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.17 |
| upper limit | 0.364 |

Notes:

[5] - Hazard ratio and its 95% CI was based on stratified Cox Regression Model regorafenib over control. 58 (87.9%) patients in placebo group and 91 (68.4%) patients in regorafenib had started open-label treatment with regorafenib before time of final database cutoff 08 Jun 2015.

[6] - Stratified log rank

Secondary: Tumor Response

| | |
|---|----------------|
| End point title | Tumor Response |
| End point description: Tumor Response of a subject was defined as the best tumor response (Complete Response [CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target).], Partial Response [PR: at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.], Stable Disease [SD: steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.], or Progressive Disease [PD: at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study or unequivocal progression of existing non-target lesions, or appearance of new lesions.]) observed during the trial period and assessed according to RECIST v1.1 criteria. Results are based on central evaluation. | |
| End point type | Secondary |
| End point timeframe: From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year | |

| End point values | Regorafenib (Stivarga, BAY73-4506) | Placebo | | |
|-----------------------------------|--|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 | 66 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Complete Response (CR) | 0 (0 to 0) | 0 (0 to 0) | | |
| Partial Response (PR) | 4.5 (1.7 to 9.6) | 1.5 (0 to 8.2) | | |
| Stable Disease (SD) | 71.4 (63.0 to 78.9) | 33.3 (22.2 to 46.0) | | |
| Progressive Disease (PD) | 21.1 (14.5 to 29.0) | 63.6 (50.9 to 75.1) | | |
| Not Assessable | 3.0 (0.8 to 7.5) | 1.5 (0 to 8.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

| | |
|-----------------|-------------------------|
| End point title | Objective response rate |
|-----------------|-------------------------|

End point description:

Objective response rate was defined as the percentage of subjects whose best response was Complete Response (CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target).) or Partial Response (PR: at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Results are based on central evaluation.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year.

| End point values | Regorafenib (Stivarga, BAY73-4506) | Placebo | | |
|-----------------------------------|--|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 | 66 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 4.5 (1.7 to 9.6) | 1.5 (0.0 to 8.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

| | |
|-----------------|----------------------------|
| End point title | Disease Control Rate (DCR) |
|-----------------|----------------------------|

End point description:

Disease Control Rate (DCR) was defined as the percentage of subjects whose best response was Complete Response (CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target).), Partial Response (PR: at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.), or Stable Disease (SD: steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.) according to RECIST v1.1 criteria. SD had to be maintained for at least 12 weeks from the first demonstration of that rating. Results are based on central evaluation.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year

| End point values | Regorafenib (Stivarga, BAY73-4506) | Placebo | | |
|-----------------------------------|--|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 | 66 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 52.6 (43.8 to 61.3) | 9.1 (3.4 to 18.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

| | |
|-----------------|----------------------------|
| End point title | Duration of Response (DOR) |
|-----------------|----------------------------|

End point description:

Duration of Response was defined as the time from date of first response (Complete Response or Partial Response) to the date when Progressive Disease is first documented, or to the date of death, whichever occurs first, according to RECIST v1.1. Subjects still having CR or PR and have not died at the time of analysis were censored at their last date of tumor evaluation. Duration of response defined for responders only, i.e CR or PR. Results are based on central evaluation. "99999" entered in confidence interval (CI) stands for "data cannot be calculated because there were too few patients in the data set." The lower limit of CI in placebo arm (30) was a place-holder, as there was only 1 patient in the data set.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year

| | | | | |
|----------------------------------|--|---------------------|--|--|
| End point values | Regorafenib (Stivarga, BAY73-4506) | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 1 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 99 (42 to 99999) | 30 (30 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization of the first subject until date of database cutoff (15 Apr 2019).

Adverse event reporting additional description:

At cutoff 26JAN2012 blinded patients were reported in "Regorafenib (DoubleBlindOnly)" and "Placebo (DoubleBlindOnly)"; patients after unblinding were reported in "Placebo, OpenLabelOnly(Switch to Regorafenib)". This safety update (cutoff 15APR2019) was reported in "Treated with Regorafenib at any time" and "Treated with Regorafenib for>1 year".

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Regorafenib (Double Blind Only) |
|-----------------------|---------------------------------|

Reporting group description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| | |
|-----------------------|-----------------------------|
| Reporting group title | Placebo (Double Blind Only) |
|-----------------------|-----------------------------|

Reporting group description:

Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| | |
|-----------------------|--|
| Reporting group title | Placebo, Open Label Only (Switch to Regorafenib) |
|-----------------------|--|

Reporting group description:

Participants switched to Open-label Regorafenib treatment from Placebo. Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Treated with Regorafenib at any time |
|-----------------------|--------------------------------------|

Reporting group description:

Treated with Regorafenib at any time: At any time, participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Treated with Regorafenib for > 1 year |
|-----------------------|---------------------------------------|

Reporting group description:

Treated with Regorafenib for > 1 year: For more than a year, participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

| Serious adverse events | Regorafenib (Double Blind Only) | Placebo (Double Blind Only) | Placebo, Open Label Only (Switch to Regorafenib) |
|---|---------------------------------|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 41 (56.10%) | 8 / 8 (100.00%) | 31 / 58 (53.45%) |
| number of deaths (all causes) | 40 | 7 | 47 |
| number of deaths resulting from adverse events | 8 | 3 | 12 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other | | | |

| | | | |
|--|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 3 / 58 (5.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Tumor pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Vascular disorders - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Peripheral ischemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Thromboembolic event | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Surgical and medical procedures | | | |
| Surgical and medical procedures - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death NOS | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 8 (25.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| Edema limbs | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 8 (12.50%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 3 / 4 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Fever | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 0 / 58 (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 |
| General disorders and administration site conditions - Other | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 8 (12.50%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pain | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Adult respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Dyspnea | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mania | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Psychiatric disorders - Other subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Creatinine increased subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| INR increased subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Neutrophil count decreased subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations - Other subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Congenital, familial and genetic disorders - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 fibrillation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| 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 arrest | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Chest pain - cardiac | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Conduction disorder | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Heart failure | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 disorders - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Hypoglossal nerve disorder | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Intracranial hemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Nervous system disorders - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Paresthesia | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Reversible posterior leukoencephalopathy syndrome | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Stroke | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Transient ischemic attacks | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 | | | |
| Anemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Eye disorders | | | |
| Eye disorders - Other | | | |

| | | | |
|---|-----------------|---------------|----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Ascites | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 8 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic fistula | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Colonic obstruction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic perforation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Constipation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhea | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Gastric hemorrhage | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Intra-abdominal hemorrhage | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Ileus | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Gastrointestinal disorders - Other | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Peritoneal necrosis | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Retroperitoneal hemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| Hepatic hemorrhage | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| Renal and urinary disorders - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 colic | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue | | | |

| | | | | |
|--|----------------|---------------|----------------|--|
| disorders | | | | |
| Back pain | | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Generalized muscle weakness | | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 | |
| Musculoskeletal and connective tissue disorder - Other | | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Muscle weakness right-sided | | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 | |
| Infections and infestations | | | | |
| Abdominal infection | | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 | |
| Appendicitis | | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 | |
| Bronchial infection | | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 | |
| Catheter related infection | | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|---------------|----------------|
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations - Other | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 4 / 58 (6.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Upper respiratory infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Anorexia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 0 / 58 (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 |
| Hyperglycemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 0 / 58 (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 |
| Hyperkalemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 0 / 58 (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 |

| Serious adverse events | Treated with Regorafenib at any time | Treated with Regorafenib for > 1 year | |
|---|--------------------------------------|---------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 103 / 190 (54.21%) | 39 / 75 (52.00%) | |
| number of deaths (all causes) | 155 | 48 | |
| number of deaths resulting from adverse events | 33 | 9 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other | | | |
| subjects affected / exposed | 6 / 190 (3.16%) | 3 / 75 (4.00%) | |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Tumor pain | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders - Other | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peripheral ischemia | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thromboembolic event | | | |
| subjects affected / exposed | 4 / 190 (2.11%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Surgical and medical procedures - Other | | | |
| subjects affected / exposed | 4 / 190 (2.11%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death NOS | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Edema limbs | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 190 (2.63%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 5 / 7 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|----------------|--|
| Fever | | | |
| subjects affected / exposed | 5 / 190 (2.63%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions - Other | | | |
| subjects affected / exposed | 5 / 190 (2.63%) | 3 / 75 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Pain | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Adult respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnea | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mania | | | |
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders - Other | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 2 / 6 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Blood bilirubin increased | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Creatinine increased | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INR increased | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations - Other | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 4 / 190 (2.11%) | 3 / 75 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|----------------|--|
| Congenital, familial and genetic disorders | | | |
| Congenital, familial and genetic disorders - Other | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 7 / 190 (3.68%) | 6 / 75 (8.00%) | |
| occurrences causally related to treatment / all | 2 / 7 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Chest pain - cardiac | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Conduction disorder | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heart failure | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac disorders - Other | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglossal nerve disorder | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial hemorrhage | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders - Other | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Paresthesia | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reversible posterior leukoencephalopathy syndrome | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stroke | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 190 (1.05%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Transient ischemic attacks | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eye disorders - Other | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 190 (4.74%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 3 / 190 (1.58%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic fistula | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic obstruction | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic perforation | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhea | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 4 / 4 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric hemorrhage | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intra-abdominal hemorrhage | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lower gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders - Other | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peritoneal necrosis | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Retroperitoneal hemorrhage | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal hemorrhage | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 2 / 75 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Hepatic hemorrhage | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders - Other | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|-----------------------------------|----------------------------------|--|
| Rash maculo-papular subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 190 (0.53%) 1 / 1 0 / 0 | 1 / 75 (1.33%) 1 / 1 0 / 0 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 4 / 190 (2.11%) 2 / 5 1 / 2 | 1 / 75 (1.33%) 0 / 1 0 / 0 | |
| Renal and urinary disorders - Other subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 3 / 190 (1.58%) 1 / 4 0 / 1 | 1 / 75 (1.33%) 0 / 2 0 / 1 | |
| Renal colic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 190 (0.53%) 0 / 1 0 / 0 | 1 / 75 (1.33%) 0 / 1 0 / 0 | |
| Urinary retention subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 190 (1.05%) 0 / 2 0 / 0 | 1 / 75 (1.33%) 0 / 1 0 / 0 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 190 (1.05%) 0 / 2 0 / 0 | 1 / 75 (1.33%) 0 / 1 0 / 0 | |
| Generalized muscle weakness subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 190 (0.53%) 1 / 1 0 / 0 | 1 / 75 (1.33%) 1 / 1 0 / 0 | |
| Musculoskeletal and connective tissue disorder - Other | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle weakness right-sided | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal infection | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial infection | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Catheter related infection | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 190 (1.05%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations - Other | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 8 / 190 (4.21%) | 3 / 75 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 3 / 75 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Anorexia | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 190 (1.58%) | 3 / 75 (4.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycemia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 190 (0.00%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalemia | | | |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Regorafenib (Double Blind Only) | Placebo (Double Blind Only) | Placebo, Open Label Only (Switch to Regorafenib) |
|---|---------------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 41 (97.56%) | 7 / 8 (87.50%) | 58 / 58 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumor pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 8 (12.50%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 1 | 4 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 18 / 41 (43.90%) | 3 / 8 (37.50%) | 37 / 58 (63.79%) |
| occurrences (all) | 32 | 3 | 97 |
| Thromboembolic event | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 8 (25.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 2 | 1 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 1 | 0 | 4 |
| Edema limbs | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 3 / 8 (37.50%) | 11 / 58 (18.97%) |
| occurrences (all) | 4 | 3 | 20 |

| | | | |
|--|------------------|----------------|------------------|
| Fatigue | | | |
| subjects affected / exposed | 18 / 41 (43.90%) | 3 / 8 (37.50%) | 32 / 58 (55.17%) |
| occurrences (all) | 32 | 4 | 83 |
| Fever | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 1 / 8 (12.50%) | 18 / 58 (31.03%) |
| occurrences (all) | 17 | 1 | 24 |
| Flu like symptoms | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 0 | 3 |
| Localized edema | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 8 (12.50%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 1 | 5 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions - Other | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 1 | 0 | 5 |
| Pain | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 1 / 8 (12.50%) | 19 / 58 (32.76%) |
| occurrences (all) | 8 | 1 | 46 |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 8 (12.50%) | 11 / 58 (18.97%) |
| occurrences (all) | 1 | 1 | 18 |
| Dyspnea | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 0 / 8 (0.00%) | 7 / 58 (12.07%) |
| occurrences (all) | 6 | 0 | 9 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 0 | 6 |
| Hiccups | | | |

| | | | |
|--|----------------------|---------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 58 (0.00%) 0 |
| Hoarseness subjects affected / exposed occurrences (all) | 8 / 41 (19.51%) 8 | 0 / 8 (0.00%) 0 | 9 / 58 (15.52%) 11 |
| Pneumonitis subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 3 / 58 (5.17%) 3 |
| Voice alteration subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 1 / 8 (12.50%) 1 | 11 / 58 (18.97%) 12 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | 0 / 8 (0.00%) 0 | 3 / 58 (5.17%) 4 |
| Confusion subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 1 / 8 (12.50%) 1 | 1 / 58 (1.72%) 1 |
| Depression subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 0 / 8 (0.00%) 0 | 2 / 58 (3.45%) 2 |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | 1 / 8 (12.50%) 1 | 3 / 58 (5.17%) 4 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 9 | 1 / 8 (12.50%) 2 | 6 / 58 (10.34%) 15 |
| Alkaline phosphatase increased subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 1 / 8 (12.50%) 1 | 3 / 58 (5.17%) 6 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 9 | 2 / 8 (25.00%) 2 | 8 / 58 (13.79%) 15 |
| Blood bilirubin increased | | | |

| | | | |
|-----------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 4 / 41 (9.76%) | 1 / 8 (12.50%) | 9 / 58 (15.52%) |
| occurrences (all) | 6 | 3 | 15 |
| GGT increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 2 | 2 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 0 | 11 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 0 | 0 | 8 |
| Investigations - Other | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 0 | 14 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 5 | 0 | 25 |
| White blood cell decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 0 | 2 |
| Weight gain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 1 | 3 |
| Weight loss | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 2 / 8 (25.00%) | 11 / 58 (18.97%) |
| occurrences (all) | 5 | 2 | 20 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 1 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 8 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 2 | 0 | 4 |
| Headache | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 0 / 8 (0.00%) | 11 / 58 (18.97%) |
| occurrences (all) | 4 | 0 | 21 |

| | | | |
|---|------------------------|---------------------|------------------------|
| Paresthesia subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 3 / 58 (5.17%) 5 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 5 / 41 (12.20%) 7 | 0 / 8 (0.00%) 0 | 4 / 58 (6.90%) 8 |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 58 (0.00%) 0 |
| Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 7 | 0 / 8 (0.00%) 0 | 11 / 58 (18.97%) 25 |
| Blood and lymphatic system disorders - Other subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 58 (3.45%) 9 |
| Ear and labyrinth disorders Hearing impaired alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 0 / 8 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Ear and labyrinth disorders - Other subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 4 / 58 (6.90%) 4 |
| Eye disorders Blurred vision subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 58 (3.45%) 2 |
| Eye disorders - Other subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 14 / 41 (34.15%) 18 | 0 / 8 (0.00%) 0 | 16 / 58 (27.59%) 23 |
| Ascites | | | |

| | | | |
|--|------------------|----------------|------------------|
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 8 (12.50%) | 2 / 58 (3.45%) |
| occurrences (all) | 2 | 1 | 2 |
| Bloating | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 5 / 8 (62.50%) | 16 / 58 (27.59%) |
| occurrences (all) | 14 | 6 | 30 |
| Diarrhea | | | |
| subjects affected / exposed | 15 / 41 (36.59%) | 1 / 8 (12.50%) | 24 / 58 (41.38%) |
| occurrences (all) | 20 | 1 | 67 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 1 / 8 (12.50%) | 6 / 58 (10.34%) |
| occurrences (all) | 4 | 2 | 9 |
| Dry mouth | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 0 / 8 (0.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 5 | 0 | 6 |
| Flatulence | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 0 / 8 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 4 | 0 | 3 |
| Mucositis oral | | | |
| subjects affected / exposed | 14 / 41 (34.15%) | 2 / 8 (25.00%) | 21 / 58 (36.21%) |
| occurrences (all) | 18 | 3 | 48 |
| Nausea | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 3 / 8 (37.50%) | 18 / 58 (31.03%) |
| occurrences (all) | 12 | 4 | 33 |
| Gastrointestinal disorders - Other | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 0 / 8 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 4 | 0 | 7 |
| Stomach pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 0 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 10 / 41 (24.39%) | 3 / 8 (37.50%) | 12 / 58 (20.69%) |
| occurrences (all) | 11 | 5 | 24 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|------------------|----------------|------------------|
| Alopecia | | | |
| subjects affected / exposed | 7 / 41 (17.07%) | 0 / 8 (0.00%) | 21 / 58 (36.21%) |
| occurrences (all) | 9 | 0 | 26 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 8 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 3 | 0 | 3 |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 1 | 0 | 3 |
| Erythroderma | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 0 | 5 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 2 | 2 |
| Skin and subcutaneous tissue disorders - Other | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 8 (0.00%) | 7 / 58 (12.07%) |
| occurrences (all) | 3 | 0 | 10 |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 17 / 41 (41.46%) | 1 / 8 (12.50%) | 39 / 58 (67.24%) |
| occurrences (all) | 37 | 1 | 151 |
| Pruritus | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 1 / 8 (12.50%) | 7 / 58 (12.07%) |
| occurrences (all) | 4 | 2 | 8 |
| Rash acneiform | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 8 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 0 | 3 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 0 / 8 (0.00%) | 8 / 58 (13.79%) |
| occurrences (all) | 7 | 0 | 10 |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------------|---------------------|------------------------|
| Hematuria subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 0 / 8 (0.00%) 0 | 3 / 58 (5.17%) 3 |
| Renal and urinary disorders - Other subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | 0 / 8 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Proteinuria subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 6 / 58 (10.34%) 11 |
| Urinary frequency subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 2 / 58 (3.45%) 2 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | 0 / 8 (0.00%) 0 | 6 / 58 (10.34%) 6 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 0 / 8 (0.00%) 0 | 4 / 58 (6.90%) 7 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 1 / 8 (12.50%) 1 | 4 / 58 (6.90%) 6 |
| Bone pain subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 58 (1.72%) 3 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Generalized muscle weakness subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 1 / 8 (12.50%) 1 | 4 / 58 (6.90%) 7 |
| Myalgia subjects affected / exposed occurrences (all) | 5 / 41 (12.20%) 5 | 3 / 8 (37.50%) 3 | 10 / 58 (17.24%) 17 |
| Neck pain | | | |

| | | | |
|---|----------------------|---------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 1 / 8 (12.50%) 1 | 0 / 58 (0.00%) 0 |
| Musculoskeletal and connective tissue disorder - Other subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 0 / 8 (0.00%) 0 | 4 / 58 (6.90%) 5 |
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 41 (12.20%) 5 | 1 / 8 (12.50%) 2 | 7 / 58 (12.07%) 15 |
| Infections and infestations | | | |
| Bronchial infection subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 4 / 58 (6.90%) 4 |
| Infections and infestations - Other subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 3 | 0 / 8 (0.00%) 0 | 5 / 58 (8.62%) 7 |
| Rash pustular subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 0 / 8 (0.00%) 0 | 2 / 58 (3.45%) 17 |
| Sinusitis subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 0 / 8 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Skin infection subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 3 / 58 (5.17%) 4 |
| Tooth infection subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Upper respiratory infection subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 0 / 8 (0.00%) 0 | 9 / 58 (15.52%) 12 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 3 | 0 / 8 (0.00%) 0 | 2 / 58 (3.45%) 4 |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|------------------|----------------|------------------|
| Anorexia | | | |
| subjects affected / exposed | 15 / 41 (36.59%) | 3 / 8 (37.50%) | 20 / 58 (34.48%) |
| occurrences (all) | 21 | 5 | 42 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 5 / 58 (8.62%) |
| occurrences (all) | 0 | 1 | 5 |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 8 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 0 | 3 |
| Hypocalcemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 0 | 8 |
| Hypokalemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 8 (0.00%) | 12 / 58 (20.69%) |
| occurrences (all) | 0 | 0 | 18 |
| Hyponatremia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 8 (25.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 2 | 4 |
| Hypophosphatemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypercalcemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 8 (12.50%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 1 | 3 |
| Hyperglycemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 8 (0.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 3 | 0 | 5 |
| Hyperuricemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 8 (12.50%) | 2 / 58 (3.45%) |
| occurrences (all) | 1 | 1 | 2 |

| Non-serious adverse events | Treated with Regorafenib at any time | Treated with Regorafenib for > 1 year | |
|---|--------------------------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 189 / 190 (99.47%) | 75 / 75 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|---------------------------|-------------------------|--|
| Tumor pain subjects affected / exposed occurrences (all) | 7 / 190 (3.68%) 9 | 2 / 75 (2.67%) 2 | |
| Vascular disorders | | | |
| Hypotension subjects affected / exposed occurrences (all) | 7 / 190 (3.68%) 8 | 4 / 75 (5.33%) 5 | |
| Hypertension subjects affected / exposed occurrences (all) | 124 / 190 (65.26%) 697 | 62 / 75 (82.67%) 552 | |
| Thromboembolic event subjects affected / exposed occurrences (all) | 6 / 190 (3.16%) 7 | 5 / 75 (6.67%) 5 | |
| General disorders and administration site conditions | | | |
| Chills subjects affected / exposed occurrences (all) | 11 / 190 (5.79%) 19 | 8 / 75 (10.67%) 16 | |
| Edema limbs subjects affected / exposed occurrences (all) | 33 / 190 (17.37%) 72 | 17 / 75 (22.67%) 53 | |
| Fatigue subjects affected / exposed occurrences (all) | 104 / 190 (54.74%) 251 | 46 / 75 (61.33%) 137 | |
| Fever subjects affected / exposed occurrences (all) | 52 / 190 (27.37%) 83 | 25 / 75 (33.33%) 46 | |
| Flu like symptoms subjects affected / exposed occurrences (all) | 18 / 190 (9.47%) 22 | 14 / 75 (18.67%) 17 | |
| Localized edema subjects affected / exposed occurrences (all) | 8 / 190 (4.21%) 10 | 5 / 75 (6.67%) 7 | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 7 / 190 (3.68%) 8 | 6 / 75 (8.00%) 7 | |
| General disorders and administration site conditions - Other | | | |

| | | | |
|--|--------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 10 / 190 (5.26%) 11 | 5 / 75 (6.67%) 6 | |
| Pain subjects affected / exposed occurrences (all) | 55 / 190 (28.95%) 115 | 29 / 75 (38.67%) 73 | |
| Immune system disorders Allergic reaction subjects affected / exposed occurrences (all) | 4 / 190 (2.11%) 4 | 4 / 75 (5.33%) 4 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 27 / 190 (14.21%) 44 | 15 / 75 (20.00%) 32 | |
| Dyspnea subjects affected / exposed occurrences (all) | 22 / 190 (11.58%) 32 | 11 / 75 (14.67%) 16 | |
| Epistaxis subjects affected / exposed occurrences (all) | 10 / 190 (5.26%) 15 | 7 / 75 (9.33%) 10 | |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 190 (0.00%) 0 | 0 / 75 (0.00%) 0 | |
| Hoarseness subjects affected / exposed occurrences (all) | 42 / 190 (22.11%) 71 | 17 / 75 (22.67%) 36 | |
| Pneumonitis subjects affected / exposed occurrences (all) | 5 / 190 (2.63%) 5 | 4 / 75 (5.33%) 4 | |
| Voice alteration subjects affected / exposed occurrences (all) | 28 / 190 (14.74%) 32 | 14 / 75 (18.67%) 17 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 9 / 190 (4.74%) 10 | 4 / 75 (5.33%) 5 | |
| Confusion | | | |

| | | | |
|--------------------------------------|-------------------|------------------|--|
| subjects affected / exposed | 2 / 190 (1.05%) | 0 / 75 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Depression | | | |
| subjects affected / exposed | 10 / 190 (5.26%) | 4 / 75 (5.33%) | |
| occurrences (all) | 11 | 5 | |
| Insomnia | | | |
| subjects affected / exposed | 21 / 190 (11.05%) | 14 / 75 (18.67%) | |
| occurrences (all) | 22 | 15 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 20 / 190 (10.53%) | 4 / 75 (5.33%) | |
| occurrences (all) | 41 | 10 | |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 11 / 190 (5.79%) | 3 / 75 (4.00%) | |
| occurrences (all) | 21 | 4 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 23 / 190 (12.11%) | 6 / 75 (8.00%) | |
| occurrences (all) | 58 | 24 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 22 / 190 (11.58%) | 7 / 75 (9.33%) | |
| occurrences (all) | 52 | 27 | |
| GGT increased | | | |
| subjects affected / exposed | 4 / 190 (2.11%) | 1 / 75 (1.33%) | |
| occurrences (all) | 4 | 1 | |
| Lipase increased | | | |
| subjects affected / exposed | 6 / 190 (3.16%) | 3 / 75 (4.00%) | |
| occurrences (all) | 19 | 14 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 13 / 190 (6.84%) | 6 / 75 (8.00%) | |
| occurrences (all) | 25 | 12 | |
| Investigations - Other | | | |
| subjects affected / exposed | 14 / 190 (7.37%) | 10 / 75 (13.33%) | |
| occurrences (all) | 49 | 28 | |
| Platelet count decreased | | | |

| | | | |
|---|-------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 15 / 190 (7.89%) 46 | 10 / 75 (13.33%) 34 | |
| White blood cell decreased subjects affected / exposed occurrences (all) | 6 / 190 (3.16%) 17 | 4 / 75 (5.33%) 15 | |
| Weight gain subjects affected / exposed occurrences (all) | 3 / 190 (1.58%) 4 | 2 / 75 (2.67%) 3 | |
| Weight loss subjects affected / exposed occurrences (all) | 40 / 190 (21.05%) 72 | 22 / 75 (29.33%) 44 | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 6 / 190 (3.16%) 16 | 6 / 75 (8.00%) 16 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 17 / 190 (8.95%) 19 | 9 / 75 (12.00%) 11 | |
| Headache subjects affected / exposed occurrences (all) | 37 / 190 (19.47%) 72 | 23 / 75 (30.67%) 55 | |
| Paresthesia subjects affected / exposed occurrences (all) | 11 / 190 (5.79%) 19 | 9 / 75 (12.00%) 13 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 16 / 190 (8.42%) 22 | 6 / 75 (8.00%) 7 | |
| Somnolence subjects affected / exposed occurrences (all) | 0 / 190 (0.00%) 0 | 0 / 75 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Anemia subjects affected / exposed occurrences (all) | 35 / 190 (18.42%) 77 | 17 / 75 (22.67%) 35 | |
| Blood and lymphatic system disorders - Other | | | |

| | | | |
|---|--------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 6 / 190 (3.16%) 17 | 4 / 75 (5.33%) 9 | |
| Ear and labyrinth disorders Hearing impaired alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 7 / 190 (3.68%) 7 | 5 / 75 (6.67%) 5 | |
| Ear and labyrinth disorders - Other subjects affected / exposed occurrences (all) | 7 / 190 (3.68%) 7 | 4 / 75 (5.33%) 4 | |
| Eye disorders Blurred vision subjects affected / exposed occurrences (all) | 7 / 190 (3.68%) 7 | 7 / 75 (9.33%) 7 | |
| Eye disorders - Other subjects affected / exposed occurrences (all) | 6 / 190 (3.16%) 6 | 4 / 75 (5.33%) 4 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 62 / 190 (32.63%) 122 | 26 / 75 (34.67%) 60 | |
| Ascites subjects affected / exposed occurrences (all) | 6 / 190 (3.16%) 8 | 1 / 75 (1.33%) 3 | |
| Bloating subjects affected / exposed occurrences (all) | 7 / 190 (3.68%) 10 | 6 / 75 (8.00%) 9 | |
| Constipation subjects affected / exposed occurrences (all) | 63 / 190 (33.16%) 101 | 28 / 75 (37.33%) 52 | |
| Diarrhea subjects affected / exposed occurrences (all) | 96 / 190 (50.53%) 353 | 53 / 75 (70.67%) 281 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 19 / 190 (10.00%) 39 | 11 / 75 (14.67%) 30 | |

| | | | |
|--|-------------------|------------------|--|
| Dry mouth | | | |
| subjects affected / exposed | 15 / 190 (7.89%) | 5 / 75 (6.67%) | |
| occurrences (all) | 16 | 6 | |
| Flatulence | | | |
| subjects affected / exposed | 10 / 190 (5.26%) | 5 / 75 (6.67%) | |
| occurrences (all) | 11 | 6 | |
| Mucositis oral | | | |
| subjects affected / exposed | 81 / 190 (42.63%) | 38 / 75 (50.67%) | |
| occurrences (all) | 174 | 111 | |
| Nausea | | | |
| subjects affected / exposed | 61 / 190 (32.11%) | 32 / 75 (42.67%) | |
| occurrences (all) | 110 | 66 | |
| Gastrointestinal disorders - Other | | | |
| subjects affected / exposed | 17 / 190 (8.95%) | 11 / 75 (14.67%) | |
| occurrences (all) | 21 | 15 | |
| Stomach pain | | | |
| subjects affected / exposed | 7 / 190 (3.68%) | 5 / 75 (6.67%) | |
| occurrences (all) | 7 | 5 | |
| Vomiting | | | |
| subjects affected / exposed | 48 / 190 (25.26%) | 21 / 75 (28.00%) | |
| occurrences (all) | 85 | 54 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 62 / 190 (32.63%) | 33 / 75 (44.00%) | |
| occurrences (all) | 84 | 49 | |
| Dry skin | | | |
| subjects affected / exposed | 13 / 190 (6.84%) | 7 / 75 (9.33%) | |
| occurrences (all) | 15 | 8 | |
| Erythema multiforme | | | |
| subjects affected / exposed | 10 / 190 (5.26%) | 7 / 75 (9.33%) | |
| occurrences (all) | 17 | 12 | |
| Erythroderma | | | |
| subjects affected / exposed | 9 / 190 (4.74%) | 6 / 75 (8.00%) | |
| occurrences (all) | 11 | 6 | |
| Hyperhidrosis | | | |

| | | | |
|--|--------------------|------------------|--|
| subjects affected / exposed | 6 / 190 (3.16%) | 4 / 75 (5.33%) | |
| occurrences (all) | 11 | 9 | |
| Skin and subcutaneous tissue disorders - Other | | | |
| subjects affected / exposed | 27 / 190 (14.21%) | 17 / 75 (22.67%) | |
| occurrences (all) | 41 | 28 | |
| Pain of skin | | | |
| subjects affected / exposed | 9 / 190 (4.74%) | 6 / 75 (8.00%) | |
| occurrences (all) | 39 | 36 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 126 / 190 (66.32%) | 58 / 75 (77.33%) | |
| occurrences (all) | 666 | 455 | |
| Pruritus | | | |
| subjects affected / exposed | 20 / 190 (10.53%) | 10 / 75 (13.33%) | |
| occurrences (all) | 27 | 15 | |
| Rash acneiform | | | |
| subjects affected / exposed | 12 / 190 (6.32%) | 7 / 75 (9.33%) | |
| occurrences (all) | 12 | 7 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 32 / 190 (16.84%) | 16 / 75 (21.33%) | |
| occurrences (all) | 71 | 26 | |
| Renal and urinary disorders | | | |
| Hematuria | | | |
| subjects affected / exposed | 7 / 190 (3.68%) | 3 / 75 (4.00%) | |
| occurrences (all) | 9 | 3 | |
| Renal and urinary disorders - Other | | | |
| subjects affected / exposed | 10 / 190 (5.26%) | 4 / 75 (5.33%) | |
| occurrences (all) | 12 | 5 | |
| Proteinuria | | | |
| subjects affected / exposed | 23 / 190 (12.11%) | 9 / 75 (12.00%) | |
| occurrences (all) | 58 | 21 | |
| Urinary frequency | | | |
| subjects affected / exposed | 7 / 190 (3.68%) | 4 / 75 (5.33%) | |
| occurrences (all) | 8 | 5 | |
| Endocrine disorders | | | |

| | | | |
|--|-------------------------|------------------------|--|
| Hypothyroidism subjects affected / exposed occurrences (all) | 39 / 190 (20.53%) 50 | 25 / 75 (33.33%) 32 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 14 / 190 (7.37%) 20 | 8 / 75 (10.67%) 14 | |
| Back pain subjects affected / exposed occurrences (all) | 21 / 190 (11.05%) 29 | 14 / 75 (18.67%) 20 | |
| Bone pain subjects affected / exposed occurrences (all) | 5 / 190 (2.63%) 9 | 5 / 75 (6.67%) 9 | |
| Flank pain subjects affected / exposed occurrences (all) | 5 / 190 (2.63%) 5 | 4 / 75 (5.33%) 4 | |
| Generalized muscle weakness subjects affected / exposed occurrences (all) | 6 / 190 (3.16%) 14 | 3 / 75 (4.00%) 11 | |
| Myalgia subjects affected / exposed occurrences (all) | 34 / 190 (17.89%) 76 | 17 / 75 (22.67%) 49 | |
| Neck pain subjects affected / exposed occurrences (all) | 2 / 190 (1.05%) 2 | 1 / 75 (1.33%) 1 | |
| Musculoskeletal and connective tissue disorder - Other subjects affected / exposed occurrences (all) | 14 / 190 (7.37%) 17 | 10 / 75 (13.33%) 12 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 28 / 190 (14.74%) 51 | 17 / 75 (22.67%) 37 | |
| Infections and infestations | | | |
| Bronchial infection subjects affected / exposed occurrences (all) | 11 / 190 (5.79%) 12 | 9 / 75 (12.00%) 10 | |
| Infections and infestations - Other | | | |

| | | | |
|------------------------------------|-------------------|------------------|--|
| subjects affected / exposed | 21 / 190 (11.05%) | 13 / 75 (17.33%) | |
| occurrences (all) | 39 | 26 | |
| Rash pustular | | | |
| subjects affected / exposed | 13 / 190 (6.84%) | 10 / 75 (13.33%) | |
| occurrences (all) | 49 | 42 | |
| Sinusitis | | | |
| subjects affected / exposed | 6 / 190 (3.16%) | 5 / 75 (6.67%) | |
| occurrences (all) | 6 | 5 | |
| Skin infection | | | |
| subjects affected / exposed | 6 / 190 (3.16%) | 4 / 75 (5.33%) | |
| occurrences (all) | 7 | 4 | |
| Tooth infection | | | |
| subjects affected / exposed | 6 / 190 (3.16%) | 5 / 75 (6.67%) | |
| occurrences (all) | 6 | 5 | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 26 / 190 (13.68%) | 21 / 75 (28.00%) | |
| occurrences (all) | 41 | 36 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 190 (6.32%) | 6 / 75 (8.00%) | |
| occurrences (all) | 17 | 9 | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 77 / 190 (40.53%) | 32 / 75 (42.67%) | |
| occurrences (all) | 134 | 72 | |
| Dehydration | | | |
| subjects affected / exposed | 6 / 190 (3.16%) | 4 / 75 (5.33%) | |
| occurrences (all) | 8 | 6 | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 9 / 190 (4.74%) | 2 / 75 (2.67%) | |
| occurrences (all) | 10 | 2 | |
| Hypocalcemia | | | |
| subjects affected / exposed | 9 / 190 (4.74%) | 4 / 75 (5.33%) | |
| occurrences (all) | 15 | 4 | |
| Hypokalemia | | | |
| subjects affected / exposed | 20 / 190 (10.53%) | 13 / 75 (17.33%) | |
| occurrences (all) | 31 | 22 | |

| | | | |
|-----------------------------|------------------|-----------------|--|
| Hyponatremia | | | |
| subjects affected / exposed | 8 / 190 (4.21%) | 2 / 75 (2.67%) | |
| occurrences (all) | 11 | 2 | |
| Hypophosphatemia | | | |
| subjects affected / exposed | 10 / 190 (5.26%) | 5 / 75 (6.67%) | |
| occurrences (all) | 13 | 7 | |
| Hypercalcemia | | | |
| subjects affected / exposed | 4 / 190 (2.11%) | 4 / 75 (5.33%) | |
| occurrences (all) | 4 | 4 | |
| Hyperglycemia | | | |
| subjects affected / exposed | 13 / 190 (6.84%) | 9 / 75 (12.00%) | |
| occurrences (all) | 18 | 10 | |
| Hyperuricemia | | | |
| subjects affected / exposed | 7 / 190 (3.68%) | 2 / 75 (2.67%) | |
| occurrences (all) | 7 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 09 February 2011 | a global amendment, was to modify and clarify RECIST v1.1 for GIST tumor evaluation, give patients who were screen failures one more opportunity to be screened for potential study enrollment, implement clarifications (primarily in study procedures) and to correct minor errors or omissions. |
| 26 July 2011 | provided specific procedures that must be followed to monitor liver function; changed the frequency of safety assessments during Cycle 5 and Cycle 6; implemented clarifications; and corrected minor errors or omissions. |
| 27 September 2011 | a global amendment increased the number of PFS events required for analysis of the primary efficacy endpoint, and indicated that because of the increased current number of randomized patients, the number of survival events for final analysis would also be increased (by the same ratio as the number of PFS events) due to the over recruitment. Also, if the study results supported a positive benefit/risk assessment for regorafenib following primary endpoint analysis, Amendment 3 offered those patients currently on placebo the opportunity to receive regorafenib through open label treatment on this study. In addition, editorial changes and corrections were made. |
| 30 September 2014 | a global amendment, was to revise and clarify the study procedures to be performed after data cutoff for the final OS analysis, since efficacy assessments were no longer necessary, but subjects who are benefiting from treatment will have continuing access to study drug. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Overall survival results are confounded by the fact that 85% of the participants initially randomized to placebo switched to open-label regorafenib.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23177515>

<http://www.ncbi.nlm.nih.gov/pubmed/24957256>

<http://www.ncbi.nlm.nih.gov/pubmed/25655899>