



Clinical trial results:

An Uncontrolled, open-label, phase II study in subjects with Metastatic Adenocarcinoma of the colon or rectum who are Receiving first line Chemotherapy with mFOLFOX6 (oxaliplatin/ folinic acid/5-fluorouracil [5-FU]) in combination with regorafenib

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-020121-41 |
| Trial protocol | GB DE BE ES IT |
| Global end of trial date | 30 June 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 12 July 2016 |
| First version publication date | 26 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY73-4506/11728 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01289821 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bayer HealthCare AG |
| Sponsor organisation address | Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com |
| Scientific contact | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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 | 30 June 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- Objective tumor response rate (ORR), centrally assessed

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 (ICH) guideline E6: Good Clinical Practice. Before entering the study, the ICF was read by and explained to all subjects or their legally authorized representative. 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:

mFOLFOX6: On Day 1, subjects received 85 milligram per square meter (mg/m^2) oxaliplatin as a 2 hour intravenous (IV) infusion and folinic acid (either 400 mg/m^2 D/L folinic acid or 200 mg/m^2 L folinic acid) as a 2 hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Days 15 to 17.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 07 February 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 40 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | United States: 4 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Spain: 14 |
| Worldwide total number of subjects | 54 |
| EEA total number of subjects | 50 |

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) | 33 |
| From 65 to 84 years | 21 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Male or female subjects with histological or cytological documentation of metastatic adenocarcinoma of the colon or rectum that was unresectable or unlikely of becoming resectable, who were at least 18 years of age and were suitable to receive mFOLFOX6 regimen as first line treatment could participate in this study at 16 centers in 7 countries.

Pre-assignment

Screening details:

Of 66 enrolled subjects, 54 received study medication, 4 withdrew consent during screening, and 8 were screen failures due to no measurable lesion, not suitable to receive mFOLFOX as 1st line regimen (2), uncontrolled hypertension, symptoms/signs/history of brain metastases, glomerular filtration rate too low (2), and protein in spot urine.

Period 1

| | |
|------------------------------|------------------|
| Period 1 title | Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|--|
| Arm title | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|------------------|--|

Arm description:

On Day 1, subjects received 85 milligram per square meter (mg/m²) oxaliplatin as a 2-hour intravenous (IV) infusion and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m² IV bolus injection immediately followed by a 5-FU 2400 mg/m² IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

| | |
|--|--------------|
| 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:

Subjects received regorafenib 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. If regorafenib was administered as a monotherapy during the study, 160 mg once daily was administered for 3 weeks on/1 week off. Doses were self-administered as four 40 mg tablets taken with 8 ounces of fluid after a low-fat breakfast.

| | |
|--|---|
| Investigational medicinal product name | mFOLFOX6 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous bolus use , Intravenous use |

Dosage and administration details:

On Day 1, subjects were administered 85 mg/m² oxaliplatin and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion (sequential or concurrent administration was possible). Once the initial infusion was complete, subjects received a 5-FU 400 mg/m² IV bolus injection immediately followed by 5-FU 2400 mg/m² IV for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17.

| Number of subjects in period 1 | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|--|--|
| Started | 54 |
| Subjects Received Regorafenib | 54 |
| Completed | 0 |
| Not completed | 54 |
| Progressive disease - Radiological progression | 43 |
| Consent withdrawn by subject | 1 |
| Physician decision | 3 |
| Progressive disease - Clinical progression | 2 |
| Adverse event | 4 |
| Therapeutic procedure required | 1 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Safety Follow-up Period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|--|
| Arm title | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|------------------|--|

Arm description:

On Day 1, subjects received 85 mg/m² oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m² IV bolus injection immediately followed by a 5-FU 2400 mg/m² IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Subjects who had not started another anti-tumor treatment within 30 days after the last dose of study treatment, a safety follow-up visit was performed after 30 days after the last dose of study treatment.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | mFOLFOX6 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous bolus use , Intravenous use |

Dosage and administration details:

On Day 1, subjects were administered 85 mg/m² oxaliplatin and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion (sequential or concurrent administration was possible). Once the initial infusion was complete, subjects received a 5-FU 400 mg/m² IV bolus injection immediately followed by 5-FU 2400 mg/m² IV for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17.

| | |
|--|-------------|
| 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:

Subjects received Regorafenib 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. If Regorafenib was administered as a monotherapy during the study, 160 mg orally was administered for 3 weeks on/1 week off. Doses were self-administered as four 40 mg tablets taken with 8 ounces of fluid after a low-fat breakfast.

| Number of subjects in period 2 | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|---------------------------------------|--|
| Started | 54 |
| Completed | 49 |
| Not completed | 5 |
| Consent withdrawn by subject | 1 |
| Protocol violation | 3 |
| Unspecified reason | 1 |

Period 3

| | |
|------------------------------|---------------------------|
| Period 3 title | Survival Follow-up Period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|--|
| Arm title | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|------------------|--|

Arm description:

On Day 1, subjects received 85 mg/m² oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m² IV bolus injection immediately followed by a 5-FU 2400 mg/m² IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Subjects were evaluated bimonthly to determine their survival status up to data cut off date 30 June 2014.

| | |
|--|--------------|
| 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:

Subjects received regorafenib 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. If regorafenib was administered as a monotherapy during the study, 160 mg once daily was administered for 3 weeks on/1 week off. Doses were self-administered as four 40 mg tablets taken with 8 ounces of fluid after a low-fat breakfast.

| | |
|--|---|
| Investigational medicinal product name | mFOLFOX6 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous bolus use , Intravenous use |

Dosage and administration details:

On Day 1, subjects were administered 85 mg/m² oxaliplatin and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion (sequential or concurrent administration was possible). Once the initial infusion was complete, subjects received a 5-FU 400 mg/m² IV bolus injection immediately followed by 5-FU 2400 mg/m² IV for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17.

| Number of subjects in period 3 | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|---------------------------------------|--|
| Started | 52 |
| Completed | 0 |
| Not completed | 52 |
| Lost to follow up | 1 |
| Clinical endpoint reached | 16 |
| Protocol violation | 1 |
| Death | 34 |

Baseline characteristics

Reporting groups

| Reporting group title | Treatment Period |
|--|------------------|
| Reporting group description: | |
| On Day 1, subjects received 85 mg/m ² oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m ² D/L-folinic acid or 200 mg/m ² L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m ² IV bolus injection immediately followed by a 5-FU 2400 mg/m ² IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days. | |

| Reporting group values | Treatment Period | Total | |
|---|------------------|-------|--|
| Number of subjects | 54 | 54 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.6 | | |
| standard deviation | ± 10.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 26 | 26 | |
| Male | 28 | 28 | |
| Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at study entry | | | |
| The ECOG PS required for the study was 0 (fully active) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature). | | | |
| Units: Subjects | | | |
| Zero | 35 | 35 | |
| One | 19 | 19 | |
| Stage at Initial Diagnosis | | | |
| The TNM classification of malignant tumors (TNM) is a cancer staging system that describes the extent of a person's cancer. T describes the size of the original (primary) tumor and whether it has invaded nearby tissue, N describes nearby (regional) lymph nodes that are involved, M describes distant metastasis. For colon carcinoma, this is translated into stages I-IV. Stages II-IV can be further subdivided in subgroups (for example A, B, or C). | | | |
| Units: Subjects | | | |
| Stage: 1 | 1 | 1 | |
| Stage: 2A | 5 | 5 | |
| Stage: 3B | 3 | 3 | |
| Stage: 3C | 4 | 4 | |
| Stage: 4 | 41 | 41 | |
| Race | | | |
| Units: Subjects | | | |
| Caucasian | 54 | 54 | |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|-----------------------|--|

Reporting group description:

On Day 1, subjects received 85 milligram per square meter (mg/m²) oxaliplatin as a 2-hour intravenous (IV) infusion and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m² IV bolus injection immediately followed by a 5-FU 2400 mg/m² IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

| | |
|-----------------------|--|
| Reporting group title | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|-----------------------|--|

Reporting group description:

On Day 1, subjects received 85 mg/m² oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m² IV bolus injection immediately followed by a 5-FU 2400 mg/m² IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Subjects who had not started another anti-tumor treatment within 30 days after the last dose of study treatment, a safety follow-up visit was performed after 30 days after the last dose of study treatment.

| | |
|-----------------------|--|
| Reporting group title | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|-----------------------|--|

Reporting group description:

On Day 1, subjects received 85 mg/m² oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m² D/L-folinic acid or 200 mg/m² L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m² IV bolus injection immediately followed by a 5-FU 2400 mg/m² IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Subjects were evaluated bimonthly to determine their survival status up to data cut off date 30 June 2014.

| | |
|----------------------------|------------------------|
| Subject analysis set title | Per Protocol Set (PPS) |
|----------------------------|------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

PPS (N=48) included all FAS subjects with no major protocol deviations affecting tumor evaluation. At least one post-baseline tumor assessment was required in order to consider the subject evaluable. Subjects who were not evaluable for tumor response and who discontinued due to a drug-related toxicity, progression by clinical judgment before disease was re-evaluated, or death were also to be considered evaluable.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
|----------------------------|-------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

FAS (N=54) included all subjects who received treatment.

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Primary Analysis Set (PAS) |
|----------------------------|----------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

PAS (N=41) was a subset of the PPS and included the first 41 subjects, who were assigned to treatment.

Primary: Objective Response (OR)

| | |
|-----------------|--|
| End point title | Objective Response (OR) ^[1] |
|-----------------|--|

End point description:

OR was defined as the best tumor response (confirmed complete response [CR] or partial response [PR]) observed by magnetic resonance imaging (MRI) or computed tomography (CT) scan assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1. CR and PR were confirmed not earlier than 4 weeks following the initial detection of response. CR = Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non target) must have a reduction in short axis to less than (<) 10 millimeter

(mm). PR = At least a 30 percent (%) 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.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: EudraCT database does not allow to report only one treatment group in statistical analyses section. Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[2] | | | |
| Units: Proportion of Subjects | | | | |
| number (not applicable) | 43.9 | | | |

Notes:

[2] - PAS

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Statistical analysis_Primary_Objective |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was calculated as the time from first date of receiving study treatment to date of death due to any cause. Subjects alive at the time of analysis were censored at their last date of follow-up.

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

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 ^[3] | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 772 (646 to 1089) | | | |

Notes:

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

| | |
|-----------------|---------------------------------|
| End point title | Progression-free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS was defined as time from the date of start of study treatment to the date of first observed disease progression (radiological according to central assessment or clinical), or death due to any cause, if death occurred before progression was documented. PFS for subjects without disease progression or death at the date of database cutoff were right-censored at the last date of tumor assessment. Subjects who had no tumor evaluation after baseline and no clinical progression post baseline and who did not die were censored at Day 1 in the analysis. PD = At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute PD.

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

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 ^[4] | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 258 (222 to 334) | | | |

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (DC)

| | |
|-----------------|----------------------|
| End point title | Disease Control (DC) |
|-----------------|----------------------|

End point description:

DC was defined as the proportion of subjects who had a best response rating of CR, PR, or stable disease (SD) according to RECIST criteria that was achieved during treatment or within 30 days after termination of study treatment. CR and PR were confirmed not earlier than 4 weeks following the initial detection of response. A minimum of 8 weeks (allowing a minus 7-day time window) between start of study treatment and the first follow-up tumor assessment with SD as response was required to assign SD as best overall response.

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

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 ^[5] | | | |
| Units: Proportion of Subjects | | | | |
| number (not applicable) | 85.37 | | | |

Notes:

[5] - PAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

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

End point description:

DOR was defined as the time from the date of first documented objective response of PR or CR, whichever was noted earlier, to first subsequent disease progression or death (if death occurred before progression was documented). DOR was defined for responders only (that is, subjects with CR or PR). DOR for subjects without disease progression or death before progression was right censored at the date of their last tumor assessment.

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

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 ^[6] | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 257 (176 to 349) | | | |

Notes:

[6] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable Disease (DOSD)

| | |
|-----------------|-----------------------------------|
| End point title | Duration of Stable Disease (DOSD) |
|-----------------|-----------------------------------|

End point description:

DOSD was only evaluated in subjects failing to achieve a best response of CR or PR, but who achieved SD. DOSR was defined as the time (in days) from date of start of study treatment to the date at which disease progression or death (if death occurred before progression was first documented). The date the tumor scan was performed was used for this calculation. DOSD for subjects without disease progression or death before progression at the time of analysis were censored at the date of their last tumor assessment.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks | |

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 ^[7] | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 231 (167 to 259) | | | |

Notes:

[7] - PPS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment until 4 weeks following the last dose of study treatment

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

Dictionary used

| | |
|-----------------|-----------|
| Dictionary name | NCI_CTCAE |
|-----------------|-----------|

| | |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) |
|-----------------------|--|

Reporting group description:

On Day 1, participants received 85 mg/m2 oxaliplatin as a 2-hour intravenous (IV) infusion and folinic acid (either 400 mg/m2 D/L folinic acid or 200 mg/m2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, participants received 5-FU 400 mg/m2 IV bolus injection immediately followed by a 5-FU 2400 mg/m2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Participants received Regorafenib (Stivarga, BAY73-4506) 160 mg orally (po) once daily (qd) on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

| Serious adverse events | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 53 (47.17%) | | |
| number of deaths (all causes) | 34 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectosigmoid cancer | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to spleen | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colorectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Resection of rectum | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stoma care | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sigmoidectomy | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Therapeutic embolisation | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cancer surgery | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Electrocardiogram abnormal | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorder postoperative | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retroperitoneal lymphadenopathy | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal sepsis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colonic abscess | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|--|--|
| Dehydration | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6) | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 53 / 53 (100.00%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | | |
| occurrences (all) | 9 | | |
| Hypertension | | | |
| subjects affected / exposed | 28 / 53 (52.83%) | | |
| occurrences (all) | 118 | | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 53 (9.43%) | | |
| occurrences (all) | 5 | | |
| Phlebitis | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | | |
| occurrences (all) | 3 | | |
| Prehypertension | | | |
| subjects affected / exposed | 7 / 53 (13.21%) | | |
| occurrences (all) | 16 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 22 / 53 (41.51%) | | |
| occurrences (all) | 70 | | |

| | | | |
|---|--|--|--|
| <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>14 / 53 (26.42%)</p> <p>20</p> | | |
| <p>Mucosal inflammation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>11 / 53 (20.75%)</p> <p>34</p> | | |
| <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>9 / 53 (16.98%)</p> <p>16</p> | | |
| <p>Immune system disorders</p> <p>Drug hypersensitivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 53 (9.43%)</p> <p>5</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 53 (9.43%)</p> <p>8</p> <p>18 / 53 (33.96%)</p> <p>35</p> <p>7 / 53 (13.21%)</p> <p>12</p> <p>5 / 53 (9.43%)</p> <p>6</p> | | |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 53 (9.43%)</p> <p>5</p> | | |
| <p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Amylase increased</p> | <p>10 / 53 (18.87%)</p> <p>27</p> | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 5 / 53 (9.43%) | | |
| occurrences (all) | 8 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 7 / 53 (13.21%) | | |
| occurrences (all) | 12 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 12 / 53 (22.64%) | | |
| occurrences (all) | 29 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 8 / 53 (15.09%) | | |
| occurrences (all) | 17 | | |
| Lipase increased | | | |
| subjects affected / exposed | 13 / 53 (24.53%) | | |
| occurrences (all) | 18 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 12 / 53 (22.64%) | | |
| occurrences (all) | 28 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 13 / 53 (24.53%) | | |
| occurrences (all) | 24 | | |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 53 (9.43%) | | |
| occurrences (all) | 7 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | | |
| occurrences (all) | 3 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | | |
| occurrences (all) | 3 | | |
| Injury, poisoning and procedural complications | | | |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | | |
| occurrences (all) | 3 | | |
| Nervous system disorders | | | |

| | | | |
|--------------------------------------|------------------|--|--|
| Aphonia | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | | |
| occurrences (all) | 10 | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | | |
| occurrences (all) | 6 | | |
| Dysaesthesia | | | |
| subjects affected / exposed | 10 / 53 (18.87%) | | |
| occurrences (all) | 27 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 16 / 53 (30.19%) | | |
| occurrences (all) | 18 | | |
| Headache | | | |
| subjects affected / exposed | 8 / 53 (15.09%) | | |
| occurrences (all) | 12 | | |
| Lethargy | | | |
| subjects affected / exposed | 10 / 53 (18.87%) | | |
| occurrences (all) | 30 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 8 / 53 (15.09%) | | |
| occurrences (all) | 12 | | |
| Neurotoxicity | | | |
| subjects affected / exposed | 11 / 53 (20.75%) | | |
| occurrences (all) | 16 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 28 / 53 (52.83%) | | |
| occurrences (all) | 66 | | |
| Polyneuropathy | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | | |
| occurrences (all) | 6 | | |
| Somnolence | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | | |
| occurrences (all) | 4 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 12 / 53 (22.64%) | | |
| occurrences (all) | 22 | | |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | | |
| occurrences (all) | 5 | | |
| Neutropenia | | | |
| subjects affected / exposed | 28 / 53 (52.83%) | | |
| occurrences (all) | 60 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 16 / 53 (30.19%) | | |
| occurrences (all) | 37 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 24 / 53 (45.28%) | | |
| occurrences (all) | 38 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 9 / 53 (16.98%) | | |
| occurrences (all) | 11 | | |
| Constipation | | | |
| subjects affected / exposed | 17 / 53 (32.08%) | | |
| occurrences (all) | 26 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 37 / 53 (69.81%) | | |
| occurrences (all) | 124 | | |
| Nausea | | | |
| subjects affected / exposed | 28 / 53 (52.83%) | | |
| occurrences (all) | 70 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | | |
| occurrences (all) | 7 | | |
| Proctalgia | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | | |
| occurrences (all) | 3 | | |
| Stomatitis | | | |
| subjects affected / exposed | 17 / 53 (32.08%) | | |
| occurrences (all) | 29 | | |

| | | | |
|--|------------------------|--|--|
| Vomiting subjects affected / exposed occurrences (all) | 16 / 53 (30.19%) 29 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 15 / 53 (28.30%) 15 | | |
| Dry skin subjects affected / exposed occurrences (all) | 5 / 53 (9.43%) 6 | | |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 18 / 53 (33.96%) 43 | | |
| Pruritus subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 4 | | |
| Rash subjects affected / exposed occurrences (all) | 10 / 53 (18.87%) 15 | | |
| Renal and urinary disorders | | | |
| Haematuria subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 4 | | |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 5 / 53 (9.43%) 7 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 4 | | |
| Back pain subjects affected / exposed occurrences (all) | 11 / 53 (20.75%) 17 | | |
| Myalgia | | | |

| | | | |
|--|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 4 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 53 (7.55%) 4 | | |
| Pain in jaw subjects affected / exposed occurrences (all) | 5 / 53 (9.43%) 5 | | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 4 | | |
| Device related infection subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 5 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 53 (9.43%) 7 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 6 / 53 (11.32%) 10 | | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 6 / 53 (11.32%) 7 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 6 / 53 (11.32%) 9 | | |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 4 / 53 (7.55%) | | |
| occurrences (all) | 4 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 13 / 53 (24.53%) | | |
| occurrences (all) | 33 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 21 / 53 (39.62%) | | |
| occurrences (all) | 42 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 25 July 2011 | <p>Amendment 1 was instituted to:</p> <ul style="list-style-type: none">- Require additional monitoring of liver function (weekly monitoring of aspartate transaminase, alanine transaminase, and bilirubin during the first 2 cycles of regorafenib dosing was added) and to include a dose modification/interruption table specific to changes of liver function tests under treatment in accordance with the Safety Report for Health Authorities and Ethics Committees, dated 13 July 2011- Add 2 inclusion criteria that ensured that subjects with adequate pancreatic and renal function were enrolled- Revise the description of withdrawal of subjects from study treatment to add clinical progression to radiological progression as a condition of disease progression- Add rules for the replacement of non-evaluable subjects for the primary endpoint- Clarify that the administration of oxaliplatin and folinic acid could be concurrent or sequential- Add a description of the reporting of adverse event of special interest- Revise the definition of the FAS population to align with the intent-to-treat principle- Rename the population analysis set to per-protocol analysis set- Change the display of population characteristics to reflect the FAS only- Provide miscellaneous corrections and clarifications to improved consistency throughout the document. |
| 25 February 2014 | <p>Amendment 2 was instituted to specify that OS data collection would be halted as of 30 June 2014.</p> |

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.

'99999' in the posting indicates that data were not calculated. Decimal places were automatically truncated if last decimal equals zero.

Notes: