



Clinical trial results:

A Multicentre Randomized Phase II Study to Assess the Safety and Resectability in Patients With Initially Unresectable Liver Metastases Secondary to Colorectal Cancer Receiving First-Line Treatment Either With mFOLFOX-6 Plus Bevacizumab or FOLFOXIRI Plus Bevacizumab (OLIVIA)

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2007-007863-26 |
| Trial protocol | AT GB FR ES |
| Global end of trial date | 21 October 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 20 April 2016 |
| First version publication date | 07 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MO18725 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00778102 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche Ltd, 41 616878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche Ltd, 41 616878333, global.trial_information@roche.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 | 28 April 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This multicenter, randomized, Phase II study was designed to assess the safety and resectability in participants with initially unresectable liver metastases secondary to colorectal cancer receiving first-line treatment with bevacizumab plus 1 of 2 fluoropyrimidine/oxaliplatin-based chemotherapy regimens.

Protection of trial subjects:

The Investigator has ensured that this study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in Guideline for Good Clinical Practice International Conference on Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it affords greater protection to the participant.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 23 October 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | Austria: 15 |
| Country: Number of subjects enrolled | France: 24 |
| Worldwide total number of subjects | 80 |
| EEA total number of subjects | 80 |

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) | 51 |
| From 65 to 84 years | 29 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After informed consent was obtained, a 2-part Screening/Baseline investigation was carried out. During the first part (Day -28 to Day 1), investigations largely involved demography, physical examination, and other noninvasive measurements. The second part (Day -7 to Day 1) involved collection of clinical laboratory data.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

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

| | |
|------------------|-------------------------|
| Arm title | Bevacizumab + mFOLFOX-6 |
|------------------|-------------------------|

Arm description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (mFOLFOX-6). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 milligrams per kilogram (mg/kg) via intravenous (IV) infusion; oxaliplatin 85 milligrams per meter-squared (mg/m²) via IV infusion; leucovorin 400 mg/m² via IV infusion; 5-FU 400 mg/m² via IV bolus; and 5-FU 2400 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, progressive disease (PD), unacceptable toxicity, or participant refusal.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Bevacizumab was administered on Day 1 of each cycle and repeated every 2 weeks: 5 mg/kg via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| | |
|--|-----------------------|
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Oxaliplatin was administered on Day 1 of each cycle and repeated every 2 weeks: 85 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal. Following completion of 12 cycles, participants could discontinue oxaliplatin.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Leucovorin was administered on Day 1 of each cycle and repeated every 2 weeks: 200 or 400 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant

refusal.

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

5-FU was administered on Day 1 of each cycle and repeated every 2 weeks. Dosing was based upon treatment assignment. Participants could have received either: 400 mg/m² via IV bolus and 2400 mg/m² via continuous 46-hour IV infusion, or (without bolus) 3200 mg/m² via continuous 46-hour IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| | |
|------------------|-------------------------|
| Arm title | Bevacizumab + FOLFOXIRI |
|------------------|-------------------------|

Arm description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, irinotecan, leucovorin, and 5-FU (FOLFOXIRI). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; irinotecan 165 mg/m² via IV infusion; leucovorin 200 mg/m² via IV infusion; and 5-FU 3200 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Bevacizumab was administered on Day 1 of each cycle and repeated every 2 weeks: 5 mg/kg via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| | |
|--|-----------------------|
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Oxaliplatin was administered on Day 1 of each cycle and repeated every 2 weeks: 85 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal. Following completion of 12 cycles, participants could discontinue oxaliplatin.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Leucovorin was administered on Day 1 of each cycle and repeated every 2 weeks: 200 or 400 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| | |
|--|-----------------------|
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

5-FU was administered on Day 1 of each cycle and repeated every 2 weeks. Dosing was based upon treatment assignment. Participants could have received either: 400 mg/m² via IV bolus and 2400 mg/m² via continuous 46-hour IV infusion, or (without bolus) 3200 mg/m² via continuous 46-hour

IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| | |
|--|-----------------------|
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Irinotecan was administered on Day 1 of each cycle and repeated every 2 weeks: 165 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal. Following completion of 12 cycles, participants could discontinue irinotecan.

| Number of subjects in period 1 | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI |
|---------------------------------------|----------------------------|----------------------------|
| Started | 39 | 41 |
| Completed | 18 | 19 |
| Not completed | 21 | 22 |
| Consent withdrawn by subject | 1 | 1 |
| Death | 1 | 1 |
| Refused treatment | 2 | 3 |
| Violation of selection criteria | 1 | 1 |
| Adverse event | 8 | 5 |
| Lost to follow-up | 1 | - |
| Administrative reason | 7 | 10 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Bevacizumab + mFOLFOX-6 |
|-----------------------|-------------------------|

Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (mFOLFOX-6). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 milligrams per kilogram (mg/kg) via intravenous (IV) infusion; oxaliplatin 85 milligrams per meter-squared (mg/m²) via IV infusion; leucovorin 400 mg/m² via IV infusion; 5-FU 400 mg/m² via IV bolus; and 5-FU 2400 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, progressive disease (PD), unacceptable toxicity, or participant refusal.

| | |
|-----------------------|-------------------------|
| Reporting group title | Bevacizumab + FOLFOXIRI |
|-----------------------|-------------------------|

Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, irinotecan, leucovorin, and 5-FU (FOLFOXIRI). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; irinotecan 165 mg/m² via IV infusion; leucovorin 200 mg/m² via IV infusion; and 5-FU 3200 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| Reporting group values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | Total |
|------------------------|-------------------------|-------------------------|-------|
| Number of subjects | 39 | 41 | 80 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|---------|---------|----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.1 | 61.8 | |
| standard deviation | ± 10.32 | ± 11.02 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 21 | 12 | 33 |
| Male | 18 | 29 | 47 |

End points

End points reporting groups

| | |
|--|-------------------------|
| Reporting group title | Bevacizumab + mFOLFOX-6 |
| Reporting group description: Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (mFOLFOX-6). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 milligrams per kilogram (mg/kg) via intravenous (IV) infusion; oxaliplatin 85 milligrams per meter-squared (mg/m ²) via IV infusion; leucovorin 400 mg/m ² via IV infusion; 5-FU 400 mg/m ² via IV bolus; and 5-FU 2400 mg/m ² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, progressive disease (PD), unacceptable toxicity, or participant refusal. | |
| Reporting group title | Bevacizumab + FOLFOXIRI |
| Reporting group description: Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, irinotecan, leucovorin, and 5-FU (FOLFOXIRI). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m ² via IV infusion; irinotecan 165 mg/m ² via IV infusion; leucovorin 200 mg/m ² via IV infusion; and 5-FU 3200 mg/m ² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal. | |

Primary: Percentage of Participants With Complete Resection or Residual (Microscopic or Macroscopic) Tumor

| | |
|--|---|
| End point title | Percentage of Participants With Complete Resection or Residual (Microscopic or Macroscopic) Tumor |
| End point description: Following resective surgery, participants were evaluated for complete resection (R0) or the presence of microscopic (R1) or macroscopic (R2) residual tumor. The percentage of participants within each residual tumor classification was calculated as [number of participants with R0, R1, and/or R2 divided by the total number of participants] multiplied by 100. Associated 95% confidence intervals were calculated for one-sample binomial using the Clopper-Pearson method. Intent-to-Treat (ITT) Population: All randomized participants. Participants were analyzed according to which treatment group they were randomized, regardless of the treatment actually received. | |
| End point type | Primary |
| End point timeframe: Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; and at time of/after surgery) | |

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| R0, R1, or R2 | 48.7 (32.4 to 65.2) | 61 (44.5 to 75.8) | | |
| R0 or R1 | 33.3 (19.1 to 50.2) | 51.2 (35.1 to 67.1) | | |
| R0 | 23.1 (11.1 to 39.3) | 48.8 (32.9 to 64.9) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Difference in resection rate (R0, R1, R2) |
| Statistical analysis description: | |
| Difference between groups in the collective percentage of participants with R0, R1, or R2. | |
| Comparison groups | Bevacizumab + mFOLFOX-6 v Bevacizumab + FOLFOXIRI |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2707 |
| Method | Chi-squared |
| Parameter estimate | Difference in resection rate |
| Point estimate | 12.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11 |
| upper limit | 35.5 |

Secondary: Time to Resection

| | |
|---|-------------------|
| End point title | Time to Resection |
| End point description: | |
| Time to resection was defined as the time from randomization to the date of first resective surgery. For participants who did not undergo resective surgery, time to resection was censored at Day 1. Time to resection was estimated by Kaplan-Meier analysis. ITT Population. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years (at Screening; prior to each cycle, and within 7 days prior to surgery; and at time of surgery) | |

| | | | | |
|----------------------------------|-------------------------|-------------------------|--|--|
| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.4 (4.1 to 5.8) | 4.3 (3.9 to 5.5) | | |

Statistical analyses

Secondary: Percentage of Participants With Histopathological Response

| | |
|--|--|
| End point title | Percentage of Participants With Histopathological Response |
| End point description: | |
| At the time of resective surgery, participants were evaluated for histopathological response as defined through pathologist review of the resected metastatic lesions, including assessment of margin status and tumor cell viability. Histopathological response classification was based upon the percentage of viable tumor cells, where 'Complete response' was considered for those with 0 percent (%) viable tumor cells, 'Major response' for those with 1% to 49% viable tumor cells, 'Minor response' for 50% to 99% viable tumor cells, and 'No response' for 100% viable tumor cells. The response could not be determined in some cases and was documented as 'Unknown.' The percentage of participants within each response category was calculated as [number of participants with a given response divided by the number of participants who completed the assessment] multiplied by 100. ITT Population. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; and at time of/after surgery) | |

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 ^[1] | 21 ^[2] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Complete response | 0 | 4.8 | | |
| Major response | 57.1 | 47.6 | | |
| Minor response | 28.6 | 33.3 | | |
| No response | 0 | 0 | | |
| Unknown | 14.3 | 14.3 | | |

Notes:

[1] - Only participants with histopathological assessment after first resective surgery were considered.

[2] - Only participants with histopathological assessment after first resective surgery were considered.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete or Major Histopathological Response

| | |
|---|--|
| End point title | Percentage of Participants With Complete or Major Histopathological Response |
| End point description: | |
| At the time of resective surgery, participants were evaluated for histopathological response as defined through pathologist review of the resected metastatic lesions, including assessment of margin status and tumor cell viability. Histopathological response classification was based upon the percentage of viable tumor cells, as described previously. The collective percentage of participants assessed as having a complete or major response was calculated as [number of participants with complete or major response divided by the number of participants who completed the assessment] multiplied by 100. Associated 95% confidence intervals were calculated for one-sample binomial using the Clopper-Pearson method. ITT Population. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; and at time of/after surgery) | |

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 ^[3] | 21 ^[4] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 57.1 (28.9 to 82.3) | 52.4 (29.8 to 74.3) | | |

Notes:

[3] - Only participants with histopathological assessment after first resective surgery were included.

[4] - Only participants with histopathological assessment after first resective surgery were included.

Statistical analyses

| Statistical analysis title | Difference in response rate |
|---|---|
| Statistical analysis description: | |
| Difference between groups in the collective percentage of participants with complete or major histopathological response. | |
| Comparison groups | Bevacizumab + mFOLFOX-6 v Bevacizumab + FOLFOXIRI |
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7817 |
| Method | Chi-squared |
| Parameter estimate | Difference in response rate |
| Point estimate | -4.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -43 |
| upper limit | 33.5 |

Secondary: Percentage of Participants Experiencing Relapse Following Curative Resection

| End point title | Percentage of Participants Experiencing Relapse Following Curative Resection |
|---|--|
| End point description: | |
| Among participants with curative resection (complete resection [R0] or microscopic residual tumor [R1]), relapse was defined as the first new occurrence of cancer or death. The percentage of participants who experienced relapse was calculated as [number of participants with a relapse event divided by the number of participants initially classified as R0 or R1 following resective surgery] multiplied by 100. ITT Population. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually) | |

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 ^[5] | 21 ^[6] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 76.9 | 57.1 | | |

Notes:

[5] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

[6] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-Free Survival (RFS)

| | |
|-----------------|-----------------------------|
| End point title | Relapse-Free Survival (RFS) |
|-----------------|-----------------------------|

End point description:

RFS was defined as the time from curative resection (complete resection [R0] or microscopic residual tumor [R1]) to the date of first diagnosis of relapse. For participants with curative resection and without relapse, RFS was censored at the last known relapse-free assessment. RFS was estimated by Kaplan-Meier analysis. ITT Population. (99999 = not estimable due to insufficient follow-up.)

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

End point timeframe:

Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 ^[7] | 21 ^[8] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.1 (3.8 to 11.7) | 17.1 (12.3 to 99999) | | |

Notes:

[7] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

[8] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Death or Disease Progression

| | |
|-----------------|--|
| End point title | Percentage of Participants Experiencing Death or Disease Progression |
|-----------------|--|

End point description:

PD was defined, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, as at least a 20% increase in the sum of the longest diameter of target lesions, or the appearance of one or more new lesions. The percentage of participants experiencing PD or death was calculated as [number of participants with event divided by the number of participants analyzed] multiplied by 100. ITT

Population.

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

End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 89.7 | 68.3 | | |

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, using RECIST version 1.0, as the time from randomization to the date of first documented PD or death from any cause. PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, or the appearance of one or more new lesions. For participants without documented PD or death, PFS was censored at the time of last tumor assessment. PFS was estimated by Kaplan-Meier analysis. ITT Population.

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

End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.5 (9.6 to 13.6) | 18.6 (12.9 to 22.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

| | |
|---|-------------------------------------|
| End point title | Percentage of Participants Who Died |
| End point description: ITT Population. | |
| End point type | Secondary |
| End point timeframe: Up to 5 years (prior to each cycle, and within 7 days prior to surgery; at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually) | |

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 48.7 | 19.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: OS was defined as the time from randomization to death from any cause. For participants without an event of death, OS was censored at the last-known alive date. OS was estimated by Kaplan-Meier analysis. ITT Population. (99999 = not estimable due to insufficient follow-up.) | |
| End point type | Secondary |
| End point timeframe: Up to 5 years (prior to each cycle, and within 7 days prior to surgery; at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually) | |

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 32.2 (21.5 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

Secondary: Percentage of Participants With a Confirmed Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.0

| | |
|-----------------|--|
| End point title | Percentage of Participants With a Confirmed Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.0 |
|-----------------|--|

End point description:

Using RECIST version 1.0, participants were considered to have achieved CR upon the disappearance of all target and non-target lesions. Participants who achieved PR demonstrated at least a 30% decrease in the sum of the largest diameter of target lesions, taking as reference the Screening sum largest diameter. Responses were confirmed by repeat assessments no less than 4 weeks after criteria for response were first met. The collective percentage of participants with confirmed best overall response of CR or PR was calculated as [number of participants meeting RECIST criteria for CR or PR divided by the number of participants analyzed] multiplied by 100. Associated 95% confidence intervals were calculated for one-sample binomial using the Clopper-Pearson method. ITT Population.

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

End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 61.5 (44.6 to 76.6) | 80.5 (65.1 to 91.2) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Difference in response rate (CR or PR) |
|----------------------------|--|

Statistical analysis description:

Difference between groups in the collective percentage of participants with confirmed best overall response of CR or PR.

| | |
|---|---|
| Comparison groups | Bevacizumab + mFOLFOX-6 v Bevacizumab + FOLFOXIRI |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0612 |
| Method | Chi-squared |
| Parameter estimate | Difference in response rate |
| Point estimate | 18.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 40 |

Secondary: Time to Response

| | |
|-----------------|------------------|
| End point title | Time to Response |
|-----------------|------------------|

End point description:

Time to response according to RECIST version 1.0 was defined as the time from randomization to the date of first documented CR or PR. Participants were considered to have achieved CR upon the disappearance of all target and non-target lesions. Participants who achieved PR demonstrated at least a 30% decrease in the sum of the largest diameter of target lesions, taking as reference the Screening sum largest diameter. Responses were confirmed by repeat assessments no less than 4 weeks after criteria for response were first met. For participants who did not complete a confirmatory tumor assessment, time to response was censored at the date of last tumor assessment, or if unavailable, at the date of first dose. Time to response was estimated by Kaplan-Meier analysis. ITT Population.

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

End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 41 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.1 (2.7 to 8.6) | 3.1 (1.9 to 3.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complications Related to First Resective Surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With Complications Related to First Resective Surgery |
|-----------------|--|

End point description:

Complications related to the first resective surgery were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0, and classified according to severity. The NCI-CTCAE severity classification criteria are as follows: Grade 5 equals (=) resulting in death; Grade 4 = life-threatening; Grade 3 = severe; Grade 2 = moderate; and Grade 1 = mild. The percentage of participants experiencing a given adverse event (AE) by severity grade was calculated as [number of participants with an AE divided by the number of participants who underwent first resective surgery] multiplied by 100. Safety Population (First Surgery Subpopulation): All participants who underwent a first resective surgery and who received at least one dose of trial medication, whether prematurely withdrawn or not. Participants were analyzed according to the actual treatment they received.

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

End point timeframe:

Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|---|----------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 25 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Any complication, Total | 73.7 | 52 | | |
| Any complication, Grade 1 | 15.8 | 4 | | |
| Any complication, Grade 2 | 36.8 | 12 | | |
| Any complication, Grade 3 | 10.5 | 24 | | |
| Any complication, Grade 4 | 0 | 12 | | |
| Any complication, Grade 5 | 10.5 | 0 | | |
| Bleeding, Total | 15.8 | 8 | | |
| Bleeding, Grade 1 | 5.3 | 0 | | |
| Bleeding, Grade 2 | 5.3 | 4 | | |
| Bleeding, Grade 3 | 5.3 | 4 | | |
| Cardiovascular, Total | 10.5 | 4 | | |
| Cardiovascular, Grade 2 | 0 | 4 | | |
| Cardiovascular, Grade 3 | 5.3 | 0 | | |
| Cardiovascular, Grade 4 | 5.3 | 0 | | |
| Infections, Total | 26.3 | 32 | | |
| Infections, Grade 1 | 10.5 | 12 | | |
| Infections, Grade 2 | 5.3 | 0 | | |
| Infections, Grade 3 | 5.3 | 16 | | |
| Infections, Grade 4 | 5.3 | 4 | | |
| Liver insufficiency, Total | 10.5 | 0 | | |
| Liver insufficiency, Grade 5 | 10.5 | 0 | | |
| Neural disorder, Total | 5.3 | 0 | | |
| Neural disorder, Grade 2 | 5.3 | 0 | | |
| Noninfected perihepatic fluid collections, Total | 0 | 4 | | |
| Noninfected perihepatic fluid collections, Grade 2 | 0 | 4 | | |
| Other complication, Total | 52.6 | 28 | | |
| Other complication, Grade 1 | 26.3 | 8 | | |
| Other complication, Grade 2 | 21.1 | 8 | | |
| Other complication, Grade 3 | 0 | 12 | | |
| Other complication, Grade 4 | 5.3 | 0 | | |
| Pulmonary, Total | 5.3 | 4 | | |
| Pulmonary, Grade 3 | 5.3 | 4 | | |
| Renal impairment, Total | 10.5 | 4 | | |
| Renal impairment, Grade 2 | 5.3 | 4 | | |
| Renal impairment, Grade 4 | 5.3 | 0 | | |
| Wound healing, Total | 5.3 | 12 | | |
| Wound healing, Grade 1 | 5.3 | 0 | | |
| Wound healing, Grade 3 | 0 | 4 | | |
| Wound healing, Grade 4 | 0 | 8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complications Related to Second Resective Surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With Complications Related to Second Resective Surgery |
|-----------------|---|

End point description:

Complications related to the second resective surgery were evaluated using the NCI-CTCAE version 3.0, and classified according to severity. The NCI-CTCAE severity classification criteria are as follows: Grade 5 = resulting in death; Grade 4 = life-threatening; Grade 3 = severe; Grade 2 = moderate; and Grade 1 = mild. The percentage of participants experiencing a given AE by severity grade was calculated as [number of participants with an AE divided by the number of participants who underwent second resective surgery] multiplied by 100. Safety Population (Second Surgery Subpopulation): All participants who underwent a second resective surgery and who received at least one dose of trial medication, whether prematurely withdrawn or not. Participants were analyzed according to the actual treatment they received.

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

End point timeframe:

Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

| End point values | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | | |
|-----------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 3 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Any complication, Total | 100 | 66.7 | | |
| Any complication, Grade 1 | 0 | 33.3 | | |
| Any complication, Grade 2 | 66.7 | 0 | | |
| Any complication, Grade 3 | 0 | 33.3 | | |
| Any complication, Grade 3a | 33.3 | 0 | | |
| Bleeding, Total | 33.3 | 33.3 | | |
| Bleeding, Grade 1 | 0 | 33.3 | | |
| Bleeding, Grade 2 | 33.3 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 years (at Screening; prior to each cycle, and within 7 days prior to surgery; at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Bevacizumab + mFOLFOX-6 |
|-----------------------|-------------------------|

Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus mFOLFOX-6. Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; leucovorin 400 mg/m² via IV infusion; 5-FU 400 mg/m² via IV bolus; and 5-FU 2400 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| | |
|-----------------------|-------------------------|
| Reporting group title | Bevacizumab + FOLFOXIRI |
|-----------------------|-------------------------|

Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus FOLFOXIRI. Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; irinotecan 165 mg/m² via IV infusion; leucovorin 200 mg/m² via IV infusion; and 5-FU 3200 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

| Serious adverse events | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | |
|--|-------------------------|-------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 37 (64.86%) | 24 / 40 (60.00%) | |
| number of deaths (all causes) | 19 | 8 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 40 (5.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|----------------|----------------|--|
| Pyrexia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 40 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Pelvic fluid collection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Endoscopic retrograde cholangiopancreatography | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 40 (7.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to anastomose | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (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 | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 6 / 40 (15.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 4 / 40 (10.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 6 / 40 (15.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised intraabdominal fluid collection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal haemorrhage | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (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 | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal disorder | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (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 Peritonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 37 (0.00%) 0 / 0 0 / 0 | 2 / 40 (5.00%) 0 / 2 0 / 0 | |
| Bacterial sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 37 (2.70%) 1 / 1 0 / 0 | 0 / 40 (0.00%) 0 / 0 0 / 0 | |
| Campylobacter infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 37 (0.00%) 0 / 0 0 / 0 | 1 / 40 (2.50%) 1 / 1 0 / 0 | |
| Cholecystitis infective subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 37 (0.00%) 0 / 0 0 / 0 | 1 / 40 (2.50%) 0 / 1 0 / 0 | |
| Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 37 (2.70%) 1 / 1 0 / 0 | 0 / 40 (0.00%) 0 / 0 0 / 0 | |
| Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 37 (0.00%) 0 / 0 0 / 0 | 1 / 40 (2.50%) 0 / 1 0 / 0 | |
| Liver abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 37 (2.70%) 0 / 1 0 / 0 | 0 / 40 (0.00%) 0 / 0 0 / 0 | |
| Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 37 (0.00%) 0 / 0 0 / 0 | 1 / 40 (2.50%) 1 / 1 0 / 0 | |
| Lung infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 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 | Bevacizumab + mFOLFOX-6 | Bevacizumab + FOLFOXIRI | |
|---|-------------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 37 (97.30%) | 40 / 40 (100.00%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | 5 / 40 (12.50%) | |
| occurrences (all) | 12 | 5 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 14 / 37 (37.84%) | 16 / 40 (40.00%) | |
| occurrences (all) | 35 | 40 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 20 / 37 (54.05%) | 17 / 40 (42.50%) | |
| occurrences (all) | 37 | 31 | |
| Fatigue | | | |
| subjects affected / exposed | 10 / 37 (27.03%) | 12 / 40 (30.00%) | |
| occurrences (all) | 27 | 35 | |
| Pyrexia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 7 / 37 (18.92%) | 12 / 40 (30.00%) | |
| occurrences (all) | 15 | 15 | |
| Catheter site pain | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Pain | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 3 / 40 (7.50%) | |
| occurrences (all) | 4 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 13 / 37 (35.14%) | 16 / 40 (40.00%) | |
| occurrences (all) | 17 | 26 | |
| Cough | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 5 / 40 (12.50%) | |
| occurrences (all) | 5 | 6 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 3 / 40 (7.50%) | |
| occurrences (all) | 6 | 4 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 2 / 40 (5.00%) | |
| occurrences (all) | 4 | 2 | |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 3 | |
| Dyspnoea exertional | | | |

| | | | |
|---|-----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 2 / 40 (5.00%) 2 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 4 / 40 (10.00%) 4 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 2 / 40 (5.00%) 2 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 7 / 37 (18.92%) 8 | 2 / 40 (5.00%) 2 | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 1 / 40 (2.50%) 1 | |
| Investigations | | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 5 / 37 (13.51%) 12 | 3 / 40 (7.50%) 5 | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 10 | 2 / 40 (5.00%) 3 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 1 / 40 (2.50%) 6 | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 6 | 1 / 40 (2.50%) 1 | |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 5 | 0 / 40 (0.00%) 0 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 1 / 40 (2.50%) 2 | |
| Aspartate aminotransferase increased | | | |

| | | | |
|---|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 1 / 40 (2.50%) 1 | |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 1 / 40 (2.50%) 2 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 0 / 40 (0.00%) 0 | |
| Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 2 | 3 / 40 (7.50%) 3 | |
| Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all) | 22 / 37 (59.46%) 63 | 19 / 40 (47.50%) 56 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 12 / 37 (32.43%) 26 | 7 / 40 (17.50%) 12 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 4 / 37 (10.81%) 22 | 4 / 40 (10.00%) 10 | |
| Headache subjects affected / exposed occurrences (all) | 9 / 37 (24.32%) 15 | 7 / 40 (17.50%) 8 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 5 / 37 (13.51%) 8 | 10 / 40 (25.00%) 13 | |
| Lethargy subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 8 | 2 / 40 (5.00%) 12 | |
| Dysaesthesia subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 5 | 2 / 40 (5.00%) 3 | |
| Dizziness | | | |

| | | | |
|---|------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 3 | 1 / 40 (2.50%) 1 | |
| Polyneuropathy subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 3 | 1 / 40 (2.50%) 1 | |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 20 / 37 (54.05%) 33 | 26 / 40 (65.00%) 75 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 37 (10.81%) 8 | 8 / 40 (20.00%) 16 | |
| Anaemia subjects affected / exposed occurrences (all) | 4 / 37 (10.81%) 4 | 6 / 40 (15.00%) 8 | |
| Leukopenia subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 4 / 40 (10.00%) 6 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 4 | 0 / 40 (0.00%) 0 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 2 / 40 (5.00%) 5 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 20 / 37 (54.05%) 39 | 33 / 40 (82.50%) 103 | |
| Nausea subjects affected / exposed occurrences (all) | 23 / 37 (62.16%) 64 | 21 / 40 (52.50%) 66 | |
| Vomiting subjects affected / exposed occurrences (all) | 14 / 37 (37.84%) 19 | 25 / 40 (62.50%) 56 | |
| Constipation | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 18 / 37 (48.65%) | 15 / 40 (37.50%) | |
| occurrences (all) | 31 | 25 | |
| Abdominal pain | | | |
| subjects affected / exposed | 15 / 37 (40.54%) | 15 / 40 (37.50%) | |
| occurrences (all) | 20 | 28 | |
| Dry mouth | | | |
| subjects affected / exposed | 7 / 37 (18.92%) | 8 / 40 (20.00%) | |
| occurrences (all) | 13 | 11 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | 5 / 40 (12.50%) | |
| occurrences (all) | 11 | 8 | |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 3 / 40 (7.50%) | |
| occurrences (all) | 5 | 6 | |
| Toothache | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 2 / 40 (5.00%) | |
| occurrences (all) | 6 | 3 | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Flatulence | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 12 / 40 (30.00%) | |
| occurrences (all) | 2 | 13 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 3 / 40 (7.50%) | |
| occurrences (all) | 5 | 3 | |

| | | | |
|---|-----------------|-----------------|--|
| Rash | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 2 / 40 (5.00%) | |
| occurrences (all) | 6 | 2 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 3 / 40 (7.50%) | |
| occurrences (all) | 2 | 5 | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Skin lesion | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 4 / 40 (10.00%) | |
| occurrences (all) | 2 | 4 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | 7 / 40 (17.50%) | |
| occurrences (all) | 8 | 7 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 4 / 40 (10.00%) | |
| occurrences (all) | 4 | 9 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 6 / 40 (15.00%) | |
| occurrences (all) | 6 | 6 | |
| Neck pain | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 1 / 40 (2.50%) | |
| occurrences (all) | 5 | 1 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 4 / 40 (10.00%) | |
| occurrences (all) | 0 | 4 | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 3 | |
| Myalgia | | | |

| | | | |
|------------------------------------|-----------------|------------------|--|
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 4 / 40 (10.00%) | |
| occurrences (all) | 5 | 4 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 1 / 40 (2.50%) | |
| occurrences (all) | 5 | 1 | |
| Oral herpes | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 3 / 40 (7.50%) | |
| occurrences (all) | 3 | 3 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 3 | |
| Device related infection | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 40 (7.50%) | |
| occurrences (all) | 0 | 3 | |
| Candida infection | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | 13 / 40 (32.50%) | |
| occurrences (all) | 16 | 19 | |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 2 / 37 (5.41%) | 6 / 40 (15.00%) | |
| occurrences (all) | 2 | 7 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 40 (7.50%) | |
| occurrences (all) | 0 | 3 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 February 2009 | The protocol was amended to remove an eligible age upper limit and to allow all participants at least 18 years of age. Select prior intervention-related exclusion criteria were omitted based upon new safety findings. Additional guidance was provided for the maximum duration (12 cycles) of the full regimen of FOLFOXIRI, and dosing criteria were updated to reflect the most current bevacizumab safety and dose modification guidance. Tumor tissue collection methods were modified, and the schedule of objective tumor assessments was changed from a 6-month to a 3-month frequency to ensure timely capturing of relapse data. A new action plan for the management of several specific AEs was added, and guidance for the assessment of causality for clinical AEs was updated. Further, AEs caused by underlying disease were not to be reported as AEs in accordance with common oncology practice. |
| 30 August 2011 | The protocol was amended to exclude participants with a diagnosis of metastatic disease for more than 3 months prior to study entry and to allow participants who received prior therapy for a primary tumor in the case of synchronous metastatic rectal cancer, as well as to clarify additional eligibility criteria. Participants with R1 residual tumor classification were considered as having achieved complete resection. The analysis of AEs was also expanded and clarified, and the Schedule of Assessments was updated to include several missing assessments previously specified elsewhere in the protocol. Study treatment was updated, so that participants with complete resection (R0 or R1) could continue to receive the original randomized treatment post-surgery. Discontinuation of oxaliplatin was allowed in the Bevacizumab + mFOLFOX-6 arm, and the protocol-required discontinuation of at least one cytotoxic agent in the Bevacizumab + FOLFOXIRI arm was clarified. Resumption of treatment and second resective surgery was permitted, at the discretion of the investigator, among participants who relapsed after a previous complete resection. Further, participants with PD were to discontinue treatment and enter a follow-up period. |
| 30 April 2013 | The protocol was amended to shorten the treatment period to 2 years, resulting in an expected length of study approximately 5 years. The procedure for reporting and managing serious AEs was updated and clarified. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported