



Clinical trial results:

A Randomized, Multicenter, Phase 2 Study to Compare the Efficacy of Panitumumab in Combination With mFOLFOX6 to the Efficacy of Bevacizumab in Combination With mFOLFOX6 in Patients With Previously Untreated, KRAS Wild-Type, Unresectable, Metastatic Colorectal Cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2008-004281-71 |
| Trial protocol | DE BE ES IT |
| Global end of trial date | 07 July 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 08 July 2017 |
| First version publication date | 08 July 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20070509 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00819780 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---------------------------------------------------------------------------------------|
| Sponsor organisation name | Amgen Inc |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 | 11 February 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to estimate the treatment effect on progression-free survival (PFS) of panitumumab relative to bevacizumab in combination with mFOLFOX6 chemotherapy as first-line therapy for metastatic colorectal cancer (mCRC) in patients with tumors expressing wild-type Kirsten Rat Sarcoma-2 Virus (KRAS).

Protection of trial subjects:

This study was conducted in accordance with Food and Drug Administration and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 24 April 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 36 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 36 |
| Country: Number of subjects enrolled | United States: 88 |
| Country: Number of subjects enrolled | Belgium: 20 |
| Country: Number of subjects enrolled | Germany: 57 |
| Country: Number of subjects enrolled | Italy: 23 |
| Country: Number of subjects enrolled | Spain: 61 |
| Worldwide total number of subjects | 285 |
| EEA total number of subjects | 161 |

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) | 170 |
| From 65 to 84 years | 115 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 60 centers in North America and Europe. The first participant was enrolled on 24 April 2009 and the last participant was enrolled on 09 December 2011.

Pre-assignment

Screening details:

Six hundred and fifty-eight patients were screened and 285 enrolled in the study. Randomization was stratified by prior adjuvant oxaliplatin therapy (yes vs no).

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 | Panitumumab Plus mFOLFOX6 |

Arm description:

Participants received 6 mg/kg panitumumab administered by intravenous (IV) infusion and modified FOLFOX6 (mFOLFOX6) chemotherapy regimen consisting of oxaliplatin (85 mg/m²), leucovorin (400 mg/m²) and 5-fluorouracil (5-FU; 2400 mg/m²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death.

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

Dosage and administration details:

Panitumumab was administered by intravenous (IV) infusion at a dose of 6 mg/kg on day 1 of every 14-day cycle, before the administration of chemotherapy.

| | |
|------------------|---------------------------|
| Arm title | Bevacizumab Plus mFOLFOX6 |
|------------------|---------------------------|

Arm description:

Participants received 5 mg/kg bevacizumab administered by IV infusion and the mFOLFOX6 regimen consisting of oxaliplatin (85 mg/m²), leucovorin (400 mg/m²), followed by 5-FU (2400 mg/m²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death.

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

Dosage and administration details:

Bevacizumab was administered by IV infusion at a dose of 5 mg/kg on day 1 of every 14-day cycle, before the administration of chemotherapy.

| Number of subjects in period 1 | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 |
|---------------------------------------|------------------------------|------------------------------|
| Started | 142 | 143 |
| Received Treatment | 139 | 139 |
| Completed | 139 | 139 |
| Not completed | 3 | 4 |
| Did not receive study drug | 3 | 4 |

Baseline characteristics

Reporting groups

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Reporting group title | Panitumumab Plus mFOLFOX6 |
| Reporting group description: Participants received 6 mg/kg panitumumab administered by intravenous (IV) infusion and modified FOLFOX6 (mFOLFOX6) chemotherapy regimen consisting of oxaliplatin (85 mg/m ²), leucovorin (400 mg/m ²) and 5-fluorouracil (5-FU; 2400 mg/m ²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death. | |
| Reporting group title | Bevacizumab Plus mFOLFOX6 |
| Reporting group description: Participants received 5 mg/kg bevacizumab administered by IV infusion and the mFOLFOX6 regimen consisting of oxaliplatin (85 mg/m ²), leucovorin (400 mg/m ²), followed by 5-FU (2400 mg/m ²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death. | |

| Reporting group values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | Total |
|-------------------------------------------------------|---------------------------|---------------------------|-------|
| Number of subjects | 142 | 143 | 285 |
| Age Categorical Units: Subjects | | | |
| < 65 years | 80 | 90 | 170 |
| ≥ 65 years | 62 | 53 | 115 |
| Age Continuous Units: years | | | |
| arithmetic mean | 61.6 | 60.5 | |
| standard deviation | ± 10.4 | ± 9.8 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 56 | 47 | 103 |
| Male | 86 | 96 | 182 |
| Race/Ethnicity Units: Subjects | | | |
| White or Caucasian | 131 | 127 | 258 |
| Black or African American | 9 | 6 | 15 |
| Hispanic or Latino | 2 | 5 | 7 |
| Asian | 0 | 4 | 4 |
| Japanese | 0 | 1 | 1 |
| Prior Adjuvant Oxaliplatin Therapy Units: Subjects | | | |
| Yes | 14 | 14 | 28 |
| No | 128 | 129 | 257 |

End points

End points reporting groups

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Reporting group title | Panitumumab Plus mFOLFOX6 |
| Reporting group description: Participants received 6 mg/kg panitumumab administered by intravenous (IV) infusion and modified FOLFOX6 (mFOLFOX6) chemotherapy regimen consisting of oxaliplatin (85 mg/m ²), leucovorin (400 mg/m ²) and 5-fluorouracil (5-FU; 2400 mg/m ²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death. | |
| Reporting group title | Bevacizumab Plus mFOLFOX6 |
| Reporting group description: Participants received 5 mg/kg bevacizumab administered by IV infusion and the mFOLFOX6 regimen consisting of oxaliplatin (85 mg/m ²), leucovorin (400 mg/m ²), followed by 5-FU (2400 mg/m ²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death. | |

Primary: Progression-free Survival (PFS)

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title | Progression-free Survival (PFS) |
| End point description: PFS was defined as the time from the date of randomization to the date of first disease progression, or death within 60 days after the last evaluable tumor assessment or randomization date (whichever was later). Participants not meeting the criteria by the cutoff date were censored at the last evaluable tumor assessment date. Tumor response was evaluated by the investigator per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 every 8 weeks until radiographic disease progression. Progression is defined as at least a 20% increase in the size of target lesions, unequivocal progression of existing non-target lesions, or any new lesions. PFS was analyzed in the intent-to-treat (ITT) analysis set, which includes all randomized participants. | |
| End point type | Primary |
| End point timeframe: From randomization until the data cutoff date of 11 February 2015; median follow-up time was 103 weeks. | |

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 142 | 143 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.9 (9.4 to 12.8) | 10.1 (9 to 12.6) | | |

Statistical analyses

| | |
|----------------------------|-------------------------------------------------------|
| Statistical analysis title | Primary Analysis of Progression-free Survival Time |
| Comparison groups | Bevacizumab Plus mFOLFOX6 v Panitumumab Plus mFOLFOX6 |

| | |
|-----------------------------------------|-------------------------------------|
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2924 ^[1] |
| Method | Stratified Cox proportional hazards |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.868 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.667 |
| upper limit | 1.13 |

Notes:

[1] - The Cox proportional hazard model is stratified by prior adjuvant oxaliplatin therapy

Secondary: Overall Survival

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall survival was defined as the time from randomization to the date of death, with participants alive or lost to follow-up at the analysis data cutoff date censored at their last contact date. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until the data cutoff date of 11 February 2015; median follow-up time was 103 weeks. | |

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 142 | 143 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 31.6 (24.3 to 41.2) | 23.9 (20.9 to 29) | | |

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------------|
| Statistical analysis title | Primary Analysis of Survival Time |
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0385 ^[2] |
| Method | Stratified Cox proportional hazards |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.742 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.559 |
| upper limit | 0.984 |

Notes:

[2] - The Cox proportional hazard model is stratified by prior adjuvant oxaliplatin therapy

Secondary: Percentage of Participants With an Objective Response

| | |
|-----------------|-------------------------------------------------------|
| End point title | Percentage of Participants With an Objective Response |
|-----------------|-------------------------------------------------------|

End point description:

Objective response was defined as having a confirmed complete response (CR) or partial response (PR) during first-line treatment, based on the investigator's review of scans using a modified-RECIST v1.0. A complete or partial response was confirmed no less than 4-weeks after the criteria for response were first met. Complete Response: Disappearance of all target and non-target lesions and no new lesions. Partial Response: At least a 30% decrease in the sum of the longest diameter (SLD) of target lesions and no progression of non-target lesions and no new lesions, or the disappearance of all target lesions with persistence of one or more non-target lesion(s) not qualifying for either CR or progressive disease and no new lesions.

Response was analyzed in the Evaluable for Local Tumor Response Analysis Set, defined as the subset of participants in the ITT Analysis Set who had at least 1 unidimensionally measurable lesion per modified RECIST 1.0 per the local investigator.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 103 weeks.

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|-----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 142 ^[3] | 142 ^[4] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 59.15 (50.6 to 67.32) | 52.11 (43.58 to 60.56) | | |

Notes:

[3] - Evaluable for Local Tumor Response Analysis Set

[4] - Evaluable for Local Tumor Response Analysis Set

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------------|
| Statistical analysis title | Analysis of Objective Response |
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 284 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2804 ^[5] |
| Method | Stratified exact test |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.33 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 2.2 |

Notes:

[5] - Stratified by prior adjuvant oxaliplatin therapy

Secondary: Duration of Response

| | |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

For participants with a confirmed objective response, the time from first confirmed objective response to radiologic disease progression per modified RECIST 1.0 criteria or death. For participants who responded and did not progress or die, duration of response was censored at their last evaluable disease assessment date.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 103 weeks.

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 ^[6] | 74 ^[7] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.1 (8.8 to 13.2) | 9.2 (7.5 to 10.2) | | |

Notes:

[6] - Evaluable for Local Tumor Response Analysis Set: Responders

[7] - Evaluable for Local Tumor Response Analysis Set: Responders

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

| | |
|-----------------|-----------------------------|
| End point title | Time to Disease Progression |
|-----------------|-----------------------------|

End point description:

Time to progression (TTP) is defined as the time from randomization to the date of radiologic disease progression per modified RECIST 1.0 criteria. Participants not meeting criteria for disease progression by the analysis data cutoff date were censored at their last evaluable disease assessment date. Progression is defined as at least a 20% increase in the size of target lesions, unequivocal progression of existing non-target lesions, or any new lesions.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 103 weeks.

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 142 | 143 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.2 (9.8 to 13.1) | 11.1 (9.3 to 12.7) | | |

Statistical analyses

| Statistical analysis title | Analysis of Time to Disease Progression |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3164 [8] |
| Method | Stratified Cox proportional hazards |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.662 |
| upper limit | 1.143 |

Notes:

[8] - The Cox proportional hazard model is stratified by prior adjuvant oxaliplatin therapy

Secondary: Time to Initial Objective Response

| End point title | Time to Initial Objective Response |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point description: | For participants with a confirmed objective response, the time from randomization to the date of first confirmed objective response. Assessments are based on the investigator's review of scans using a modified-RECIST v1.0. An objective response is defined as a best tumor response of complete or partial response. A complete or partial response was confirmed no less than 4-weeks after the criteria for response were first met. |
| End point type | Secondary |
| End point timeframe: | From randomization until the data cutoff date of 11 February 2015; median follow-up time was 103 weeks. |

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|---------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 ^[9] | 74 ^[10] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 1.84 (1.69 to 2.3) | 1.84 (1.71 to 3.65) | | |

Notes:

[9] - Evaluable for Local Tumor Response Analysis Set: Responders

[10] - Evaluable for Local Tumor Response Analysis Set: Responders

Statistical analyses

No statistical analyses for this end point

Secondary: Resection Rate

| | |
|-----------------|----------------|
| End point title | Resection Rate |
|-----------------|----------------|

End point description:

The resection rate was defined as the percentage of participants with a surgical procedure that resulted in partial reduction or complete eradication of all metastatic disease.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 103 weeks.

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|-----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 142 | 143 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 13.38 (8.25 to 20.1) | 11.19 (6.53 to 17.53) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) in Participants With Wild-type Rat Sarcoma Viral Oncogene Homolog (RAS)

| | |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Progression-free Survival (PFS) in Participants With Wild-type Rat Sarcoma Viral Oncogene Homolog (RAS) |
|-----------------|---------------------------------------------------------------------------------------------------------|

End point description:

PFS was defined as the time from the date of randomization to the date of first disease progression, or death within 60 days after the last evaluable tumor assessment or randomization date (whichever was later). Participants not meeting the criteria by the cutoff date were censored at the last evaluable tumor assessment date. Tumor response was evaluated by the investigator per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 every 8 weeks until radiographic disease progression. Progression is defined as at least a 20% increase in the size of target lesions, unequivocal progression of existing non-target lesions, or any new lesions.

The Wild-type RAS Efficacy Analysis Set was defined as a subset of Wild-type KRAS Exon 2 Efficacy Analysis Set including all randomized participants with wild-type KRAS exon 2, 3, 4, NRAS exon 2, 3, and 4.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 126 weeks.

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 ^[11] | 82 ^[12] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.8 (10.7 to 15.1) | 10.1 (9 to 12.7) | | |

Notes:

[11] - Wild-type RAS Efficacy Analysis Set

[12] - Wild-type RAS Efficacy Analysis Set

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------------|
| Statistical analysis title | Analysis of Progression-free Survival Time |
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0292 ^[13] |
| Method | Stratified Cox proportional hazards |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.679 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 0.962 |

Notes:

[13] - The Cox proportional hazard model is stratified by prior adjuvant oxaliplatin therapy

Secondary: Progression-free Survival (PFS) in Participants With Wild-type RAS / V-raf Murine Sarcoma Viral Oncogene Homolog B1 (BRAF)

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Progression-free Survival (PFS) in Participants With Wild-type RAS / V-raf Murine Sarcoma Viral Oncogene Homolog B1 (BRAF) |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|

End point description:

PFS was defined as the time from the date of randomization to the date of first disease progression, or death within 60 days after the last evaluable tumor assessment or randomization date (whichever was later). Participants not meeting the criteria by the cutoff date were censored at the last evaluable tumor assessment date. Tumor response was evaluated by the investigator per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 every 8 weeks until radiographic disease progression. Progression is defined as at least a 20% increase in the size of target lesions, unequivocal progression of existing non-target lesions, or any new lesions.

The Wild-type RAS/BRAF Efficacy Analysis Set was defined as a subset of Wild-type KRAS Exon 2 Efficacy Analysis Set with wild-type KRAS exon 2, 3, and 4, NRAS exon 2, 3, 4, and BRAF exon 15.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 135

weeks.

| | | | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 77 ^[14] | 79 ^[15] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 13.1 (11.6 to 16.2) | 10.1 (9 to 12.7) | | |

Notes:

[14] - Wild-type RAS/BRAF Efficacy Analysis Set

[15] - Wild-type RAS/BRAF Efficacy Analysis Set

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------------|
| Statistical analysis title | Analysis of Progression-free Survival Time |
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0075 ^[16] |
| Method | Stratified Cox proportional hazards |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.607 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.421 |
| upper limit | 0.875 |

Notes:

[16] - The Cox proportional hazard model is stratified by prior adjuvant oxaliplatin therapy

Secondary: Overall Survival in Participants With Wild-type RAS

| | |
|-----------------|-----------------------------------------------------|
| End point title | Overall Survival in Participants With Wild-type RAS |
|-----------------|-----------------------------------------------------|

End point description:

Overall survival was defined as the time from randomization to the date of death, with participants alive or lost to follow-up at the analysis data cutoff date censored at their last contact date.

The Wild-type RAS Efficacy Analysis Set was defined as a subset of Wild-type KRAS Exon 2 Efficacy Analysis Set including all randomized participants with wild-type KRAS exon 2, 3, 4, NRAS exon 2, 3, and 4.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 126 weeks.

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 ^[17] | 82 ^[18] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 36.9 (27.9 to 46.1) | 28.9 (23.3 to 32) | | |

Notes:

[17] - Wild-type RAS Efficacy Analysis Set

[18] - Wild-type RAS Efficacy Analysis Set

Statistical analyses

| Statistical analysis title | Analysis of Survival Time |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1541 ^[19] |
| Method | Stratified Cox proportional hazards |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.763 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.526 |
| upper limit | 1.107 |

Notes:

[19] - The Cox proportional hazard model is stratified by prior adjuvant Oxaliplatin therapy

Secondary: Overall Survival in Participants With Wild-type RAS / BRAF

| | |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Overall Survival in Participants With Wild-type RAS / BRAF |
| End point description: | Overall survival was defined as the time from randomization to the date of death, with participants alive or lost to follow-up at the analysis data cutoff date censored at their last contact date. The Wild-type RAS/BRAF Efficacy Analysis Set was defined as a subset of Wild-type KRAS Exon 2 Efficacy Analysis Set with wild-type KRAS exon 2, 3, and 4, NRAS exon 2, 3, 4, and BRAF exon 15. |
| End point type | Secondary |
| End point timeframe: | From randomization until the data cutoff date of 11 February 2015; median follow-up time was 135 weeks. |

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 77 ^[20] | 79 ^[21] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 41.3 (31.6 to 46.7) | 28.9 (23.9 to 33.1) | | |

Notes:

[20] - Wild-type RAS/BRAF Efficacy Analysis Set

[21] - Wild-type RAS/BRAF Efficacy Analysis Set

Statistical analyses

| | |
|-----------------------------------------|-------------------------------------------------------|
| Statistical analysis title | Analysis of Survival Time |
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0809 [22] |
| Method | Stratified Cox proportional hazards |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.704 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.475 |
| upper limit | 1.044 |

Notes:

[22] - The Cox proportional hazard model is stratified by prior adjuvant oxaliplatin therapy

Secondary: Percentage of Participants With an Objective Response for Participants With Wild-type RAS

| | |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With an Objective Response for Participants With Wild-type RAS |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

Objective response was defined as having a confirmed complete response (CR) or partial response (PR) during first-line treatment, based on the investigator's review of scans using a modified-RECIST v1.0. A complete or partial response was confirmed no less than 4-weeks after the criteria for response were first met.

Complete Response: Disappearance of all target and non-target lesions and no new lesions. Partial Response: At least a 30% decrease in the sum of the longest diameter (SLD) of target lesions and no progression of non-target lesions and no new lesions, or the disappearance of all target lesions with persistence of one or more non-target lesion(s) not qualifying for either CR or progressive disease and no new lesions.

The Wild-type RAS Investigator Tumor Response Analysis Set was defined as the subset of participants in the Wild-type RAS Efficacy Analysis Set who had at least 1 unidimensionally measurable lesion per modified RECIST 1.0 per the local investigator.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 126 weeks

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|-----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 ^[23] | 81 ^[24] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 63.64 (52.69 to 73.63) | 58.02 (46.54 to 68.91) | | |

Notes:

[23] - Wild-type RAS Investigator Tumor Response Analysis Set

[24] - Wild-type RAS Investigator Tumor Response Analysis Set

Statistical analyses

| Statistical analysis title | Analysis of Objective Response |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7088 ^[25] |
| Method | Stratified exact test |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 2.34 |

Notes:

[25] - Stratified by prior exposure to oxaliplatin

Secondary: Percentage of Participants With an Objective Response for Participants With Wild-type RAS / BRAF

| | |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With an Objective Response for Participants With Wild-type RAS / BRAF |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

Objective response was defined as having a confirmed complete response (CR) or partial response (PR) during first-line treatment, based on the investigator's review of scans using a modified-RECIST v1.0. A complete or partial response was confirmed no less than 4-weeks after the criteria for response were first met. Complete Response: Disappearance of all target and non-target lesions and no new lesions. Partial Response: At least a 30% decrease in the sum of the longest diameter (SLD) of target lesions and no progression of non-target lesions and no new lesions, or the disappearance of all target lesions with persistence of one or more non-target lesion(s) not qualifying for either CR or progressive disease and no new lesions.

The Wild-type RAS/BRAF Investigator Tumor Response Analysis Set was defined as the subset of participants in the Wild-type RAS/BRAF Efficacy Analysis Set who had at least 1 unidimensionally measurable lesion per modified RECIST 1.0 per the local investigator.

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

End point timeframe:

From randomization until the data cutoff date of 11 February 2015; median follow-up time was 135 weeks

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|-----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 77 ^[26] | 78 ^[27] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 63.64 (51.88 to 74.3) | 58.97 (47.25 to 69.99) | | |

Notes:

[26] - Wild-type RAS/BRAF Investigator Tumor Response Analysis Set

[27] - Wild-type RAS/BRAF Investigator Tumor Response Analysis Set

Statistical analyses

| Statistical analysis title | Analysis of Objective Response |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Panitumumab Plus mFOLFOX6 v Bevacizumab Plus mFOLFOX6 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7613 ^[28] |
| Method | Stratified exact test |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 2.38 |

Notes:

[28] - Stratified by prior exposure to oxaliplatin

Secondary: Number of Participants With Adverse Events (AEs)

| End point title | Number of Participants With Adverse Events (AEs) |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point description: | Severity was graded using Common Terminology Criteria for Adverse Events (CTCAE) v3.0, with the exception of some dermatology/skin adverse events that were graded using CTCAE v3.0 with modifications. Fatal adverse events are classified as grade 5. Serious adverse events include any event that is fatal, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other significant medical hazard. Treatment-related AEs were those that the investigator considered a reasonable possibility that might have been caused by study drug. |
| End point type | Secondary |
| End point timeframe: | The time frame for adverse event reporting is from the first dose date to 30 days since the last dose date. The median time frame is 8.0 months for Panitumumab plus mFOLFOX6 arm and 7.3 months for Bevacizumab plus mFOLFOX6 arm. |

| End point values | Panitumumab Plus mFOLFOX6 | Bevacizumab Plus mFOLFOX6 | | |
|--------------------------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 139 ^[29] | 139 ^[30] | | |
| Units: participants | | | | |
| Any adverse event (AE) | 139 | 139 | | |
| AE with worst grade of 3 | 88 | 79 | | |
| AE with worst grade of 4 | 31 | 28 | | |
| AE with worst grade of 5 | 7 | 9 | | |
| Serious adverse event (SAE) | 62 | 54 | | |
| AE leading to discontinuation of study drug | 41 | 37 | | |
| Any treatment-related adverse event (TRAE) | 138 | 136 | | |
| Treatment-related AE with worst grade of 3 | 92 | 77 | | |
| Treatment-related AE with worst grade of 4 | 24 | 25 | | |
| Treatment-related AE with worst grade of 5 | 3 | 2 | | |
| Serious treatment-related adverse event | 37 | 28 | | |
| TRAE leading to discontinuation of study drug | 30 | 30 | | |

Notes:

[29] - Safety Analysis Set

[30] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time frame for adverse event reporting is from the first dose date to 30 days since the last dose date. The median time frame is 8.0 months for Panitumumab plus mFOLFOX6 arm and 7.3 months for Bevacizumab plus mFOLFOX6 arm.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Bevacizumab Plus mFOLFOX6 |
|-----------------------|---------------------------|

Reporting group description:

Participants received 5 mg/kg bevacizumab administered by IV infusion and the mFOLFOX6 regimen consisting of oxaliplatin (85 mg/m²), leucovorin (400 mg/m²), followed by 5-FU (2400 mg/m²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death.

| | |
|-----------------------|---------------------------|
| Reporting group title | Panitumumab Plus mFOLFOX6 |
|-----------------------|---------------------------|

Reporting group description:

Participants received 6 mg/kg panitumumab administered by intravenous (IV) infusion and modified FOLFOX6 (mFOLFOX6) chemotherapy regimen consisting of oxaliplatin (85 mg/m²), leucovorin (400 mg/m²) and 5-fluorouracil (5-FU; 2400 mg/m²) administered on Day 1 of every 14-day cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death.

| Serious adverse events | Bevacizumab Plus mFOLFOX6 | Panitumumab Plus mFOLFOX6 | |
|---------------------------------------------------------------------|---------------------------|---------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 54 / 139 (38.85%) | 62 / 139 (44.60%) | |
| number of deaths (all causes) | 9 | 7 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 139 (2.88%) | 4 / 139 (2.88%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal haematoma | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 139 (2.88%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 2 / 7 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 6 / 139 (4.32%) | 7 / 139 (5.04%) | |
| occurrences causally related to treatment / all | 4 / 6 | 5 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary venous thrombosis | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Psychiatric disorders | | | |
| Mood altered | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|----------------------------------------------------------------|-----------------|-----------------|--|
| Substance abuse | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (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 | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Face injury | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound haemorrhage | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 4 / 139 (2.88%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 139 (2.16%) | 3 / 139 (2.16%) | |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 9 / 139 (6.47%) | |
| occurrences causally related to treatment / all | 1 / 1 | 10 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 3 / 139 (2.16%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Large intestinal obstruction | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nail bed inflammation | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Groin pain | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Spinal pain | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trismus | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster oticus | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion site infection | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningoencephalitis herpetic | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 139 (2.16%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 3 / 139 (2.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 2 / 139 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 3 / 139 (2.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 0 / 139 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 1 / 139 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Bevacizumab Plus mFOLFOX6 | Panitumumab Plus mFOLFOX6 | |
|-------------------------------------------------------|------------------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 139 / 139 (100.00%) | 139 / 139 (100.00%) | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 11 / 139 (7.91%) | 5 / 139 (3.60%) | |
| occurrences (all) | 12 | 6 | |
| Hypertension | | | |
| subjects affected / exposed | 36 / 139 (25.90%) | 7 / 139 (5.04%) | |
| occurrences (all) | 50 | 9 | |
| Haematoma | | | |
| subjects affected / exposed | 7 / 139 (5.04%) | 1 / 139 (0.72%) | |
| occurrences (all) | 7 | 2 | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 139 (4.32%) | 7 / 139 (5.04%) | |
| occurrences (all) | 7 | 9 | |

| | | | |
|------------------------------------------------------|-------------------|-------------------|--|
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 12 / 139 (8.63%) | 11 / 139 (7.91%) | |
| occurrences (all) | 16 | 12 | |
| Asthenia | | | |
| subjects affected / exposed | 44 / 139 (31.65%) | 50 / 139 (35.97%) | |
| occurrences (all) | 101 | 107 | |
| Fatigue | | | |
| subjects affected / exposed | 66 / 139 (47.48%) | 50 / 139 (35.97%) | |
| occurrences (all) | 158 | 164 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 21 / 139 (15.11%) | 50 / 139 (35.97%) | |
| occurrences (all) | 32 | 113 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 9 / 139 (6.47%) | 19 / 139 (13.67%) | |
| occurrences (all) | 9 | 22 | |
| Pyrexia | | | |
| subjects affected / exposed | 30 / 139 (21.58%) | 21 / 139 (15.11%) | |
| occurrences (all) | 53 | 24 | |
| Temperature intolerance | | | |
| subjects affected / exposed | 11 / 139 (7.91%) | 7 / 139 (5.04%) | |
| occurrences (all) | 14 | 8 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 19 / 139 (13.67%) | 16 / 139 (11.51%) | |
| occurrences (all) | 25 | 24 | |
| Dysphonia | | | |
| subjects affected / exposed | 8 / 139 (5.76%) | 4 / 139 (2.88%) | |
| occurrences (all) | 8 | 4 | |
| Cough | | | |
| subjects affected / exposed | 13 / 139 (9.35%) | 18 / 139 (12.95%) | |
| occurrences (all) | 15 | 21 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 6 / 139 (4.32%) | 7 / 139 (5.04%) | |
| occurrences (all) | 6 | 8 | |
| Epistaxis | | | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 32 / 139 (23.02%) 43 | 29 / 139 (20.86%) 42 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 12 / 139 (8.63%) 15 | 4 / 139 (2.88%) 4 | |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 8 / 139 (5.76%) 8 | 7 / 139 (5.04%) 7 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 13 / 139 (9.35%) 16 | 4 / 139 (2.88%) 4 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 8 / 139 (5.76%) 8 | 10 / 139 (7.19%) 10 | |
| Insomnia subjects affected / exposed occurrences (all) | 20 / 139 (14.39%) 22 | 15 / 139 (10.79%) 16 | |
| Investigations Platelet count decreased subjects affected / exposed occurrences (all) | 5 / 139 (3.60%) 9 | 10 / 139 (7.19%) 12 | |
| Weight decreased subjects affected / exposed occurrences (all) | 16 / 139 (11.51%) 19 | 32 / 139 (23.02%) 67 | |
| Weight increased subjects affected / exposed occurrences (all) | 2 / 139 (1.44%) 2 | 8 / 139 (5.76%) 11 | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 6 / 139 (4.32%) 8 | 10 / 139 (7.19%) 15 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 18 / 139 (12.95%) 22 | 17 / 139 (12.23%) 25 | |

| | | | |
|--------------------------------------|-------------------|-------------------|--|
| Dysaesthesia | | | |
| subjects affected / exposed | 23 / 139 (16.55%) | 13 / 139 (9.35%) | |
| occurrences (all) | 88 | 32 | |
| Dysgeusia | | | |
| subjects affected / exposed | 27 / 139 (19.42%) | 31 / 139 (22.30%) | |
| occurrences (all) | 29 | 40 | |
| Headache | | | |
| subjects affected / exposed | 17 / 139 (12.23%) | 13 / 139 (9.35%) | |
| occurrences (all) | 28 | 15 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 46 / 139 (33.09%) | 46 / 139 (33.09%) | |
| occurrences (all) | 133 | 172 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 12 / 139 (8.63%) | 12 / 139 (8.63%) | |
| occurrences (all) | 31 | 35 | |
| Paraesthesia | | | |
| subjects affected / exposed | 31 / 139 (22.30%) | 26 / 139 (18.71%) | |
| occurrences (all) | 86 | 64 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 24 / 139 (17.27%) | 25 / 139 (17.99%) | |
| occurrences (all) | 53 | 93 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 16 / 139 (11.51%) | 18 / 139 (12.95%) | |
| occurrences (all) | 38 | 33 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 66 / 139 (47.48%) | 63 / 139 (45.32%) | |
| occurrences (all) | 145 | 171 | |
| Leukopenia | | | |
| subjects affected / exposed | 10 / 139 (7.19%) | 10 / 139 (7.19%) | |
| occurrences (all) | 12 | 19 | |
| Anaemia | | | |
| subjects affected / exposed | 20 / 139 (14.39%) | 25 / 139 (17.99%) | |
| occurrences (all) | 31 | 44 | |
| Thrombocytopenia | | | |

| | | | |
|---------------------------------------------------------------------------|--------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 17 / 139 (12.23%) 59 | 34 / 139 (24.46%) 94 | |
| Eye disorders | | | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 6 / 139 (4.32%) 6 | 8 / 139 (5.76%) 9 | |
| Vision blurred subjects affected / exposed occurrences (all) | 3 / 139 (2.16%) 4 | 8 / 139 (5.76%) 8 | |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 6 / 139 (4.32%) 6 | 8 / 139 (5.76%) 8 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 30 / 139 (21.58%) 40 | 26 / 139 (18.71%) 33 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 12 / 139 (8.63%) 13 | 11 / 139 (7.91%) 13 | |
| Ascites subjects affected / exposed occurrences (all) | 7 / 139 (5.04%) 7 | 0 / 139 (0.00%) 0 | |
| Cheilitis subjects affected / exposed occurrences (all) | 0 / 139 (0.00%) 0 | 8 / 139 (5.76%) 10 | |
| Constipation subjects affected / exposed occurrences (all) | 46 / 139 (33.09%) 59 | 44 / 139 (31.65%) 65 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 85 / 139 (61.15%) 205 | 84 / 139 (60.43%) 232 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 16 / 139 (11.51%) 18 | 15 / 139 (10.79%) 20 | |
| Haemorrhoids | | | |

| | | | |
|----------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 8 / 139 (5.76%) | 4 / 139 (2.88%) | |
| occurrences (all) | 11 | 4 | |
| Nausea | | | |
| subjects affected / exposed | 85 / 139 (61.15%) | 76 / 139 (54.68%) | |
| occurrences (all) | 165 | 145 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 6 / 139 (4.32%) | 8 / 139 (5.76%) | |
| occurrences (all) | 6 | 8 | |
| Stomatitis | | | |
| subjects affected / exposed | 31 / 139 (22.30%) | 47 / 139 (33.81%) | |
| occurrences (all) | 65 | 117 | |
| Vomiting | | | |
| subjects affected / exposed | 38 / 139 (27.34%) | 44 / 139 (31.65%) | |
| occurrences (all) | 68 | 75 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 35 / 139 (25.18%) | |
| occurrences (all) | 1 | 193 | |
| Alopecia | | | |
| subjects affected / exposed | 21 / 139 (15.11%) | 26 / 139 (18.71%) | |
| occurrences (all) | 23 | 29 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 27 / 139 (19.42%) | |
| occurrences (all) | 2 | 54 | |
| Dry skin | | | |
| subjects affected / exposed | 12 / 139 (8.63%) | 56 / 139 (40.29%) | |
| occurrences (all) | 14 | 100 | |
| Erythema | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 12 / 139 (8.63%) | |
| occurrences (all) | 2 | 17 | |
| Exfoliative rash | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 11 / 139 (7.91%) | |
| occurrences (all) | 4 | 23 | |
| Hypertrichosis | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 9 / 139 (6.47%) | |
| occurrences (all) | 0 | 9 | |

| | | | |
|-------------------------------------------------|-------------------|-------------------|--|
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 14 / 139 (10.07%) | 22 / 139 (15.83%) | |
| occurrences (all) | 29 | 31 | |
| Nail disorder | | | |
| subjects affected / exposed | 6 / 139 (4.32%) | 13 / 139 (9.35%) | |
| occurrences (all) | 6 | 42 | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 139 (2.88%) | 16 / 139 (11.51%) | |
| occurrences (all) | 5 | 25 | |
| Rash | | | |
| subjects affected / exposed | 9 / 139 (6.47%) | 87 / 139 (62.59%) | |
| occurrences (all) | 11 | 274 | |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 139 (0.72%) | 31 / 139 (22.30%) | |
| occurrences (all) | 5 | 60 | |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 139 (0.00%) | 10 / 139 (7.19%) | |
| occurrences (all) | 0 | 21 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 2 / 139 (1.44%) | 7 / 139 (5.04%) | |
| occurrences (all) | 2 | 9 | |
| Proteinuria | | | |
| subjects affected / exposed | 11 / 139 (7.91%) | 16 / 139 (11.51%) | |
| occurrences (all) | 19 | 33 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 14 / 139 (10.07%) | 8 / 139 (5.76%) | |
| occurrences (all) | 16 | 10 | |
| Back pain | | | |
| subjects affected / exposed | 14 / 139 (10.07%) | 13 / 139 (9.35%) | |
| occurrences (all) | 18 | 17 | |
| Muscular weakness | | | |
| subjects affected / exposed | 7 / 139 (5.04%) | 3 / 139 (2.16%) | |
| occurrences (all) | 8 | 5 | |
| Neck pain | | | |

| | | | |
|---------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 139 (5.04%) 7 | 2 / 139 (1.44%) 2 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 10 / 139 (7.19%) 12 | 9 / 139 (6.47%) 11 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 7 / 139 (5.04%) 7 | 3 / 139 (2.16%) 4 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 18 / 139 (12.95%) 28 | 12 / 139 (8.63%) 13 | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 8 / 139 (5.76%) 10 | 4 / 139 (2.88%) 5 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 139 (5.76%) 9 | 8 / 139 (5.76%) 8 | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 4 / 139 (2.88%) 16 | 17 / 139 (12.23%) 31 | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 139 (4.32%) 9 | 9 / 139 (6.47%) 10 | |
| Paronychia subjects affected / exposed occurrences (all) | 2 / 139 (1.44%) 3 | 25 / 139 (17.99%) 44 | |
| Rhinitis subjects affected / exposed occurrences (all) | 5 / 139 (3.60%) 5 | 9 / 139 (6.47%) 11 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 9 / 139 (6.47%) 9 | 6 / 139 (4.32%) 8 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 9 / 139 (6.47%) 13 | 11 / 139 (7.91%) 29 | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 44 / 139 (31.65%) | 56 / 139 (40.29%) | |
| occurrences (all) | 56 | 111 | |
| Dehydration | | | |
| subjects affected / exposed | 10 / 139 (7.19%) | 18 / 139 (12.95%) | |
| occurrences (all) | 14 | 27 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 5 / 139 (3.60%) | 12 / 139 (8.63%) | |
| occurrences (all) | 5 | 23 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 7 / 139 (5.04%) | 3 / 139 (2.16%) | |
| occurrences (all) | 17 | 7 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 17 / 139 (12.23%) | 38 / 139 (27.34%) | |
| occurrences (all) | 27 | 90 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 9 / 139 (6.47%) | 58 / 139 (41.73%) | |
| occurrences (all) | 10 | 192 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 January 2010 | <ul style="list-style-type: none">• Allowed local KRAS testing by other experienced laboratories using a validated test method per local regulatory guidelines• Updated inclusion/exclusion, dose adjustment, withholding, and discontinuation criteria to reflect recent changes in clinical practice• Clarified the exclusion criteria regarding the use of contraception during the study to be consistent with contraception use instructions described in the Risk and Discomfort section of panitumumab informed consent template and bevacizumab prescribing information• Updated the panitumumab background information to incorporate the latest information for the two large phase 3 studies, 20050203 and 20050181, of panitumumab in combination with first- and second-line chemotherapy, respectively, that were conducted in patients with mCRC• Clarified collection of antibody samples• Specified RECIST version utilized in this study as version 1.0• Clarified adverse event reporting timelines• Deleted the main and the optional pharmacogenetic informed consent form templates from the appendix section of the protocol. The ICF templates were provided to the investigative sites separately. |
| 23 February 2012 | <ul style="list-style-type: none">• Prospectively prespecified the study and analysis of a wider array of potentially prognostic and predictive biomarkers within the RAS/BRAF family oncogenes for efficacy and safety• Revised the definition of PFS, changing from "the time from the date of randomization to the date of progression or the date of death (any cause)" to "the time from randomization to the date of first disease progression, or death within 60 days after the last evaluable tumor assessment or randomization date (whichever is later). Subjects not meeting the criteria by the cutoff date are censored at the last evaluable tumor assessment date."• Addition of a sensitivity analysis using the original PFS definition• Modification of the anti-panitumumab antibody follow-up instructions to clarify that, if a subject tests positive at the safety follow-up visit, additional serum samples would continue to be collected during the long term follow-up regardless of the baseline antibody test results• Clarified that data collection for subjects who remained on protocol-specified treatment following the completion of all planned study analyses was limited to treatment administration and serious adverse events up to and including the 30-day safety follow-up visit• Revised Section 8.1 to permit obtainment of survival data from public records for any subject for whom the survival status was not known even if a subject withdrew full consent per the FDA guidelines and local regional regulatory agencies• Revised the reasons for removal from study in Section 8.1 to differentiate between removal from treatment phase and removal from long-term follow-up observation phase• Revised the "Reporting Procedures for SAE" to allow for reporting other than by fax (eg, electronic reporting) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported