



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
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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
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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 standard deviation	61.6 ± 10.4	60.5 ± 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
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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
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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
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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
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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
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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
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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
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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
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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)
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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
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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)
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Bevacizumab Plus mFOLFOX6
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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
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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