Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-label Trial to Evaluate the Survival Benefit of Panitumumab and Best Supportive Care, Compared to Best Supportive Care Alone, in Subjects With Chemorefractory Wild-type KRAS Metastatic Colorectal Cancer

Summary

EudraCT number	2010-022951-49
Trial protocol	GR EE LV LT
Global end of trial date	11 November 2016

Results information

Result version number	v1 (current)
This version publication date	23 November 2017
First version publication date	23 November 2017

Trial information

Trial identification

Sponsor protocol code	20100007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01412957
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	24 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the benefit of panitumumab in addition to best supportive care compared to best supportive care alone in patients with chemorefractory wild-type KRAS (Kirsten rat sarcoma viral oncogene homolog) metastatic colorectal cancer.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP. 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	08 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 34
Country: Number of subjects enrolled	India: 23
Country: Number of subjects enrolled	Korea, Republic of: 79
Country: Number of subjects enrolled	Malaysia: 16
Country: Number of subjects enrolled	Philippines: 10
Country: Number of subjects enrolled	Croatia: 59
Country: Number of subjects enrolled	Estonia: 27
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Latvia: 11
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Romania: 48
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Canada: 7

Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Mexico: 16
Worldwide total number of subjects	377
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)	241
From 65 to 84 years	136
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 377 participants were randomized at 66 centers in Europe, Asia, North and South America from 8 November 2011 until 30 July 2013. Results are reported as of the final analysis data cut-off date of 24 July 2015.

Pre-assignment

Screening details:

Participants were stratified according to geographic region (Europe vs Asia vs rest of the world) and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2) and randomized (1:1 ratio) to 1 of 2 treatment groups.

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 + BSC

Arm description:

Participants received panitumumab administered intravenously 6 mg/kg every 14 days plus best supportive care (BSC) until disease progression, withdrawal of consent, death, or intolerance of study drug.

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:

The starting panitumumab dose was 6 mg/kg; panitumumab was administered by intravenous infusion on day 1 of every 14-day cycle.

Arm title	BSC Alone

Arm description:

Participants received best supportive care until disease progression, withdrawal of consent, or death.

Arm type	Best Supportive Care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Panitumumab + BSC	BSC Alone
Started	189	188
Completed	189	188

Baseline characteristics

Reporting groups	
Reporting group title	Panitumumab + BSC
Reporting group description:	
Participants received panitumumab administered intravenously 6 mg/kg every 14 days plus best supportive care (BSC) until disease progression, withdrawal of consent, death, or intolerance of study drug.	
Reporting group title	BSC Alone
Reporting group description:	
Participants received best supportive care until disease progression, withdrawal of consent, or death.	

Reporting group values	Panitumumab + BSC	BSC Alone	Total
Number of subjects	189	188	377
Age categorical Units: Subjects			
Adults (18-64 years)	114	127	241
From 65-84 years	75	61	136
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.2	58.7	
standard deviation	± 10.7	± 11.1	-
Gender, Male/Female Units: Subjects			
Female	82	79	161
Male	107	109	216
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	23	22	45
Not Hispanic or Latino	166	166	332
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	3	3
Asian	79	82	161
White	107	102	209
Other	3	1	4
Geographic Region Units: Subjects			
Europe	86	85	171
Asia	80	82	162
Rest of world	23	21	44
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self care, unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	71	65	136

Grade 1	100	107	207
Grade 2	18	16	34
Location of Primary Tumor Units: Subjects			
Colon	108	106	214
Rectum	81	81	162
Missing	0	1	1

End points

End points reporting groups

Reporting group title	Panitumumab + BSC

Reporting group description:

Participants received panitumumab administered intravenously 6 mg/kg every 14 days plus best supportive care (BSC) until disease progression, withdrawal of consent, death, or intolerance of study drug.

Reporting group title	BSC Alone

Reporting group description:

Participants received best supportive care until disease progression, withdrawal of consent, or death.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from the randomization date to the date of death. Participants who had not died by the analysis data cut-off date were censored at their last contact date and participants with survival data obtained after the planned analysis data cut-off date had survival censored at the cut-off date. The Intent to Treat (ITT) Analysis Set included all randomized participants; participants in the ITT Analysis Set were required to have wild-type KRAS exon 2 (codons 12 and 13, alleles G12A, G12D, G12R, G12C, G12S, G12V, or G13D) per protocol.

End point type	Primary

End point timeframe:

From randomization to the last on-study or long-term follow-up visit, as of the data cut-off date of 24 July 2015. The median follow-up time was 34.4 weeks (panitumumab plus BSC: 40.3 weeks; BSC alone: 25.3 weeks).

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	10.0 (8.7 to 11.3)	7.4 (5.8 to 9.3)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The primary hypothesis was that panitumumab plus BSC would improve overall survival compared to BSC alone. A comparison between treatments was performed using the log-rank test stratified by the randomization factors at a 5% significance level.

Comparison groups	Panitumumab + BSC v BSC Alone

Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0086 [1]
Method	Logrank

Notes:

[1] - Log-rank test stratified by randomization factors: geographic region (Europe vs Asia vs rest of world) and ECOG performance status (0 or 1 vs 2).

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) was defined as the time from the randomization date to the date of disease progression per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 or death. Progressive disease (PD): At least a 20% increase in the size of target lesions compared with the smallest size since treatment started and an absolute increase of at least 5 mm, any new lesions or an increase in size of non-target lesions thought be ≥ 20% and an absolute increase of at least 5 mm, or significant increase in pleural effusions, ascites or other fluid collections with cytologic proof of malignancy. Participants who were alive and did not meet the criteria for progression by the analysis data cut-off date were censored at their last evaluable disease assessment date.

End point type	Secondary

End point timeframe:

From randomization to the last on-study or long-term follow-up visit, as of the data cut-off date of 24 July 2015. The median follow-up time was 34.4 weeks (panitumumab plus BSC: 40.3 weeks; BSC alone: 25.3 weeks).

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	3.6 (3.4 to 5.3)	1.7 (1.6 to 1.9)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

PFS in the ITT Analysis Set was tested at a significance level of 5% conditional on a significant treatment effect on overall survival in the ITT Analysis Set.

Comparison groups	Panitumumab + BSC v BSC Alone
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Logrank

Notes:

[2] - Log-rank test stratified by randomization factors: geographic region (Europe vs Asia vs rest of world) and ECOG performance status (0 or 1 vs 2).

Secondary: Overall Survival in Participants with Wild-type RAS

End point title	Overall Survival in Participants with Wild-type RAS

End point description:

A secondary efficacy endpoint was overall survival in participants with wild-type rat sarcoma viral oncogene homolog (RAS) (without mutation in exons 2 [codons 12 and 13], 3 [codons 59 and 61], and 4 [codons 117 and 146] of KRAS and neuroblastoma RAS viral oncogene (NRAS)). In participants with wild-type RAS, RAS mutation status was defined by KRAS exon 2 mutation status per clinical trial assay testing and mutation status of KRAS exon 3 and 4 and NRAS exons 2, 3 and 4 per Sanger bi-directional sequencing. Overall survival was defined as the time from the randomization date to the date of death. Participants who had not died by the analysis data cut-off date were censored at their last contact date and participants with survival data obtained after the planned analysis data cut-off date had survival censored at the cut-off date.

End point type	Secondary

End point timeframe:

From randomization to the last on-study or long-term follow-up visit, as of the data cut-off date of 24 July 2015. The median follow-up time was 36.1 weeks (panitumumab plus BSC: 43.7 weeks; BSC alone: 23.6 weeks).

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	128		
Units: months				
median (confidence interval 95%)	10.0 (8.7 to 11.6)	6.9 (5.2 to 7.9)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Overall survival in the Wild-type RAS Efficacy Analysis Set was compared at a significance level of 5% conditional on a significant treatment effect for progression-free survival in the ITT Analysis Set.

Comparison groups	Panitumumab + BSC v BSC Alone
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0152 [3]
Method	Logrank

Notes:

[3] - Log-rank test stratified by randomization factors: geographic region (Europe vs Asia vs rest of world) and ECOG performance status (0 or 1 vs 2).

Secondary: Progression Free Survival (PFS) in Participants with Wild-type RAS

End point title	Progression Free Survival (PFS) in Participants with Wild-type RAS

End point description:

PFS was defined as the time from the randomization date to the date of disease progression per RECIST version 1.1 or death. Progressive disease (PD): At least a 20% increase in the size of target lesions compared with the smallest size since treatment started and an absolute increase of at least 5 mm, any new lesions, or an increase in size of non-target lesions thought be ≥ 20% with an absolute increase of at least 5 mm, or significant increase in pleural effusions, ascites or other fluid collections with cytologic proof of malignancy. Participants who were alive and did not meet the criteria for progression by the analysis data cut-off date were censored at their last evaluable disease assessment date. The Wild-type RAS Efficacy Analysis Set consists of a subset of participants in the ITT Analysis Set without mutation in

exon 2, 3, and 4 of KRAS or NRAS).

End point type	Secondary

End point timeframe:

From randomization to the last on-study or long-term follow-up visit, as of the data cut-off date of 24 July 2015. The median follow-up time was 36.1 weeks (panitumumab plus BSC: 43.7 weeks; BSC alone: 23.6 weeks).

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	128		
Units: months				
median (confidence interval 95%)	5.2 (3.5 to 5.3)	1.7 (1.6 to 2.2)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

PFS in the Wild-type RAS Efficacy Analysis Set was to be compared at a significance level of 5% if overall survival in the wild-type RAS Efficacy Anaysis Set demonstrated a significant treatment effect.

Comparison groups	Panitumumab + BSC v BSC Alone
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Logrank

Notes:

[4] - Log-rank test stratified by randomization factors: geographic region (Europe vs Asia vs rest of world) and ECOG performance status (0 or 1 vs 2).

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate (ORR) is defined as the percentage of participants with either a complete response (CR) or partial response (PR) per RECIST version 1.1. Radiographic tumor assessments and investigator's assessment of response were performed at Week 4, Week 8, and then every 8 weeks until disease progression (radiographic or clinical progression). CR: Disappearance of all target and non-target lesions and no new lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR: At least a 30% decrease in the size of target lesions with 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 lesions not qualifying for either CR or PD and no new lesions.

End point type	Secondary

End point timeframe:

Response was assessed at Week 4, Week 8, and then every 8 weeks until the data cut-off date of 24 July 2015. The median follow-up time was 34.4 weeks (panitumumab plus BSC: 40.3 weeks; BSC alone: 25.3 weeks).

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: percentage of participants				
number (confidence interval 95%)	26.98 (20.80 to 33.91)	1.60 (0.33 to 4.59)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

ORR was not formally tested and the p-values are descriptive only. An exact test was used to test the hypothesis that the common odds ratio for panitumumab plus BSC relative to BSC alone for the objective response is equal to 1.0 stratified by the randomization factors.

Comparison groups	Panitumumab + BSC v BSC Alone
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Stratified exact test
Parameter estimate	Odds ratio (OR)
Point estimate	24.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.47
upper limit	123.77

Notes:

[5] - Stratified by randomization factors: geographic region (Europe vs Asia vs rest of world) and ECOG performance status (0 or 1 vs 2).

Secondary: Objective Response Rate in Participants with Wild-type RAS

End point title	Objective Response Rate in Participants with Wild-type RAS

End point description:

Objective response rate is defined as the percentage of participants with either a complete response (CR) or partial response (PR) per RECIST version 1.1. Radiographic tumor assessments and investigator's assessment of response were performed at Week 4, Week 8, and then every 8 weeks until disease progression (radiographic or clinical progression). CR: Disappearance of all target and non-target lesions and no new lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR: At least a 30% decrease in the size of target lesions with 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 lesions not qualifying for either CR or PD and no new lesions. The Wild-type RAS Efficacy Analysis Set was used for the analysis.

End point type	Secondary

End point timeframe:

Response was assessed at Week 4, Week 8, and then every 8 weeks until the data cut-off date of 24 July 2015. The median follow-up time was 36.1 weeks (panitumumab plus BSC: 43.7 weeks; BSC alone: 23.6 weeks).

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	128		
Units: percentage of participants				
number (confidence interval 95%)	30.99 (23.50 to 39.28)	2.34 (0.49 to 6.70)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

ORR was not formally tested and the p-values are descriptive only. An exact test was used to test the hypothesis that the common odds ratio for panitumumab plus BSC relative to BSC alone for the objective response is equal to 1.0 stratified by the randomization factors.

Comparison groups	Panitumumab + BSC v BSC Alone
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Stratified exact test
Parameter estimate	Odds ratio (OR)
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.89
upper limit	101.62

Notes:

[6] - Stratified by randomization factors: geographic region (Europe vs Asia vs rest of world) and ECOG performance status (0 or 1 vs 2).

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

The severity of each AE was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Grade 1 = Mild; 2 = Moderate (discomfort enough to cause interference with usual activity); 3 = Severe (incapacitating with inability to work or do usual activity); 4 = Life-threatening and 5 = Fatal), with the exception of the skin-or nail-related AEs which were graded using a CTCAE version 3.0 with modifications. A serious AE was defined as an AE that met at least 1 of the following criteria:
• fatal,
• life-threatening,
• required in-patient hospitalization or prolongation of existing hospitalization, • resulted in persistent or significant disability/incapacity,
• congenital anomaly/birth defect, and/or
• other medically important serious event.
Treatment-related AEs (TRAEs) are those the investigator considered there was reasonable possibility that the event might have been caused by study drug.

End point type	Secondary

End point timeframe:

From first dose until 30 days after last dose; median safety reporting periods were 4.2 months and 2.2 months for panitumumab plus BSC arm and BSC alone arm, respectively.

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: participants				
Any adverse event (AE)|	184	115		
AE with worst grade of 3|	71	30		
AE with worst grade of 4|	17	5		
AE with worst grade of 5|	8	15		
Serious adverse event (SAE)|	48	37		
AE leading to discontinuation of panitumumab|	19	0		
Treatment-related adverse event (TRAE)|	166	7		
Treatment-related AE with worst grade of 3|	42	1		
Treatment-related AE with worst grade of 4|	4	1		
Treatment-related AE with worst grade of 5|	0	1		
Serious treatment-related AE|	2	3		
TRAE leading to discontinuation of panitumumab|	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Post-baseline Change from Baseline in Corrected QT (QTc) Interval

End point title	Maximum Post-baseline Change from Baseline in Corrected QT (QTc) Interval

End point description:

QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by electrocardiogram (ECG). QTc is the QT interval corrected for heart rate. ECGs were collected at the following time points from participants randomized to panitumumab arm at a limited number of sites: Week 1 prior to first panitumumab infusion (Baseline) and within 30 minutes following the end of the first infusion of panitumumab (Cmax), Week 7 after 3 doses of panitumumab (steady state), and the safety follow-up visit. ECGs were submitted for independent central review to calculate the reported QTc interval using both the Bazett correction (QTcB) and the Fridericia correction (QTcF). The QTc Analysis Set consists of a subset of participants in the Safety Analysis Set who received at least one panitumumab dose and were enrolled at one of the sites participating in QTc evaluation and had baseline and at least 1 post-baseline QTc assessment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose), Week 1 and Week 7 (post-dose) and 4 weeks after the last dose (Safety Follow-up visit)

End point values	Panitumumab + BSC	BSC Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	0[7]		
Units: msec				
arithmetic mean (standard deviation)				
QTcF	14.58 (± 13.60)	()		
QTcB	12.57 (± 12.15)	()		

Notes:

[7] - QTC was only analyzed in participants who received panitumumab

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose until 30 days after last dose; median safety reporting periods were 4.2 months and 2.2 months for panitumumab plus BSC arm and BSC alone arm, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Panitumumab + BSC

Reporting group description:

Participants received panitumumab administered intravenously 6 mg/kg every 14 days plus best supportive care (BSC) until disease progression, withdrawal of consent, death, or intolerance of study drug.

Reporting group title	BSC Alone

Reporting group description:

Participants received best supportive care until disease progression, withdrawal of consent, or death.

Serious adverse events	Panitumumab + BSC	BSC Alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 189 (25.40%)	37 / 188 (19.68%)	
number of deaths (all causes)	8	15	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	3 / 189 (1.59%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 3	
Colorectal cancer			
subjects affected / exposed	1 / 189 (0.53%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 3	
Colorectal cancer metastatic			
subjects affected / exposed	2 / 189 (1.06%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Colorectal cancer recurrent			

subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	2 / 189 (1.06%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 189 (0.53%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	0 / 189 (0.00%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 189 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (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 myocardial infarction			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			

subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (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			
Brain oedema			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 189 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lateral medullary syndrome			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 189 (1.06%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 189 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 189 (0.53%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow toxicity			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 189 (1.59%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 189 (1.59%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	3 / 189 (1.59%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			

subjects affected / exposed	1 / 189 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 189 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 189 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (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			
Acne			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 189 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			

subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract inflammation			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
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	2 / 189 (1.06%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Panitumumab + BSC	BSC Alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	174 / 189 (92.06%)	75 / 188 (39.89%)	
Investigations			
Weight decreased			
subjects affected / exposed	13 / 189 (6.88%)	5 / 188 (2.66%)	
occurrences (all)	19	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 189 (7.41%)	16 / 188 (8.51%)	
occurrences (all)	28	21	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 189 (14.81%)	14 / 188 (7.45%)	
occurrences (all)	42	20	
Pyrexia			

subjects affected / exposed	16 / 189 (8.47%)	9 / 188 (4.79%)	
occurrences (all)	21	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	29 / 189 (15.34%)	18 / 188 (9.57%)	
occurrences (all)	38	24	
Constipation			
subjects affected / exposed	16 / 189 (8.47%)	12 / 188 (6.38%)	
occurrences (all)	17	13	
Diarrhoea			
subjects affected / exposed	25 / 189 (13.23%)	7 / 188 (3.72%)	
occurrences (all)	44	7	
Dyspepsia			
subjects affected / exposed	10 / 189 (5.29%)	2 / 188 (1.06%)	
occurrences (all)	10	2	
Nausea			
subjects affected / exposed	11 / 189 (5.82%)	10 / 188 (5.32%)	
occurrences (all)	18	13	
Stomatitis			
subjects affected / exposed	12 / 189 (6.35%)	0 / 188 (0.00%)	
occurrences (all)	15	0	
Vomiting			
subjects affected / exposed	12 / 189 (6.35%)	7 / 188 (3.72%)	
occurrences (all)	12	8	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	54 / 189 (28.57%)	0 / 188 (0.00%)	
occurrences (all)	105	0	
Acne			
subjects affected / exposed	26 / 189 (13.76%)	0 / 188 (0.00%)	
occurrences (all)	49	0	
Dry skin			
subjects affected / exposed	29 / 189 (15.34%)	1 / 188 (0.53%)	
occurrences (all)	40	1	
Erythema			

subjects affected / exposed	23 / 189 (12.17%)	0 / 188 (0.00%)	
occurrences (all)	35	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	20 / 189 (10.58%)	0 / 188 (0.00%)	
occurrences (all)	25	0	
Pruritus			
subjects affected / exposed	47 / 189 (24.87%)	0 / 188 (0.00%)	
occurrences (all)	80	0	
Rash			
subjects affected / exposed	73 / 189 (38.62%)	2 / 188 (1.06%)	
occurrences (all)	142	2	
Rash maculo-papular			
subjects affected / exposed	10 / 189 (5.29%)	0 / 188 (0.00%)	
occurrences (all)	35	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	14 / 189 (7.41%)	10 / 188 (5.32%)	
occurrences (all)	20	11	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	12 / 189 (6.35%)	0 / 188 (0.00%)	
occurrences (all)	28	0	
Paronychia			
subjects affected / exposed	27 / 189 (14.29%)	0 / 188 (0.00%)	
occurrences (all)	56	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 189 (9.52%)	16 / 188 (8.51%)	
occurrences (all)	25	16	
Hypoalbuminaemia			
subjects affected / exposed	10 / 189 (5.29%)	3 / 188 (1.60%)	
occurrences (all)	16	3	
Hypocalcaemia			
subjects affected / exposed	14 / 189 (7.41%)	1 / 188 (0.53%)	
occurrences (all)	23	1	
Hypokalaemia			

subjects affected / exposed	11 / 189 (5.82%)	1 / 188 (0.53%)	
occurrences (all)	17	1	
Hypomagnesaemia			
subjects affected / exposed	53 / 189 (28.04%)	2 / 188 (1.06%)	
occurrences (all)	112	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2012	• Clarified that the investigator's assessment of response will be used to determine tumor response and progression for the purposes of management of a subject and for the analysis of PFS and ORR endpoints. Tumor imaging studies will be submitted to a central repository location. • Specified that tumor radiographic imaging scans performed according to the Schedule of Assessments must be submitted to the central imaging vendor. • Specified additional collection of blood for biomarker development: blood collection for exploratory biomarker development (at study day 1 [prior to the panitumumab administration for subjects randomized to panitumumab plus BSC arm]), at time of each scheduled radiographic tumor imaging assessment (ie, at week 4 [+ 1 week], week 8 [± 1 week] and then every 8 weeks [± 1 week]) until disease progression, and at the safety follow-up visit. • Clarified that in case Amgen elects to have scans reviewed by an independent centralized radiology vendor, additional available imaging data may be requested from subjects who discontinue the treatment phase due to assessment of disease progression by the investigator that is not subsequently confirmed by the central radiology review. • Clarified that for the purposes of the PFS and ORR analyses, the determination of objective disease progression will be based on investigator's assessments. In the case Amgen elects to have scans reviewed by an independent centralized radiology vendor, additional analyses of PFS and ORR will be provided based on the central review of the scans.
25 July 2013	• Expanded the codons examined in subjects with wild-type RAS to include exons 2 [codons 12 and 13], 3 [codons 59 and 61], and 4 [codons 117 and 146] of KRAS; specify that the NRAS gene will be examined; and specify that exon 2 (codons 12 and 13) will be examined in subjects with wild-type KRAS tumors. • Updated the background and rationale sections to provide the justification for incorporating additional RAS mutations into the study objectives • Corrected Section 7 and Schedule of Assessment to ensure biomarker blood samples are collected from both arms • Updated the planned method of statistical analyses to include an alternative definition for progression-free survival by excluding deaths occurring more than 60 days after the last evaluable tumor assessment or randomization date (whichever is later) as events which will also be considered as part of planned PFS analyses. • Added language to inform the investigator to report a serious adverse event that occurs outside the protocol-specified reporting period per EU CT-3 Guidance • Added pregnancy and lactation reporting procedures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported