



Clinical trial results:

A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild-type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Summary

EudraCT number	2008-004752-77
Trial protocol	DE FR ES IT BE
Global end of trial date	22 July 2013

Results information

Result version number	v1
This version publication date	01 July 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	20070820
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00891930
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	22 July 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1:

To determine if acquired resistance to panitumumab therapy in subjects with KRAS wildtype metastatic colorectal cancer (mCRC) correlates with emergence of mutant KRAS tumors. (Acquired resistance is defined as disease progression on panitumumab and irinotecan that occurs after a period of disease response or stable disease on treatment with this regimen is observed and radiographically-confirmed.)

Part 2:

To determine if inhibition of the insulin-like growth factor-1 receptor (IGF-1R) pathway with ganitumab can overcome resistance to panitumumab therapy, as demonstrated by the objective response rate (ORR) to panitumumab and ganitumab following disease progression on panitumumab and irinotecan.

Protection of trial subjects:

This study was conducted in accordance with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines.

The protocol, amendments, proposed informed consent form (ICF), other written subject information, and any proposed advertising material were reviewed and approved by an Institutional Review Board (IRB) before any subjects were recruited into the study and before investigational product (IP) was shipped to the study site.

All subjects provided written informed consent before undergoing any study-related procedures, including protocol-specific screening procedures or administration of study medication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 May 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 14
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	42
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 100 subjects were screened, of which 76 subjects were enrolled in part 1 of this study.

Period 1

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

Arms

Arm title	Panitumumab + Irinotecan
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Arm description:

Subjects received panitumumab (6 mg/kg starting dose) with irinotecan (starting dose of 180 mg/m²) every 2 weeks (Q2W).

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

Dosage and administration details:

Panitumumab was administered at a starting dose of 6 mg/kg Q2W administered intravenously (IV) by an infusion pump through a peripheral line or indwelling catheter.

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

Dosage and administration details:

Irinotecan was administered IV at a starting dose of 180 mg/m² on Day 1 of each cycle in Part 1 after completion of the panitumumab infusion.

Number of subjects in period 1	Panitumumab + Irinotecan
Started	76
Received Treatment	74
Completed	36
Not completed	40
Consent withdrawn by subject	1
Death	36
Did not receive study drug	2
Lost to follow-up	1

Period 2

Period 2 title	Part 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Panitumumab + Ganitumab
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Arm description:

Subjects who responded (complete or partial response) or had stable disease in Part 1 proceeded to Part 2 of the study and received treatment with panitumumab (6 mg/kg starting dose) and ganitumab (12 mg/kg starting dose) Q2W.

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

Dosage and administration details:

Panitumumab was administered at a starting dose of 6 mg/kg Q2W administered intravenously (IV) by an infusion pump through a peripheral line or indwelling catheter.

Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganitumab was administered at a starting dose of 12 mg/mL administered IV by an infusion pump through a peripheral line or indwelling catheter.

Number of subjects in period 2	Panitumumab + Ganitumab
Started	36
Completed	5
Not completed	31
Consent withdrawn by subject	1
Death	30

Baseline characteristics

Reporting groups

Reporting group title	Panitumumab + Irinotecan
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Reporting group description:

Subjects received panitumumab (6 mg/kg starting dose) with irinotecan (starting dose of 180 mg/m²) every 2 weeks (Q2W).

Reporting group values	Panitumumab + Irinotecan	Total	
Number of subjects	76	76	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	62.4 ± 9.9	-	
Gender categorical Units: Subjects			
Female	28	28	
Male	48	48	
Race Units: Subjects			
White or Caucasian	75	75	
Other	1	1	
Primary diagnosis Units: Subjects			
Colon Cancer	49	49	
Rectal Cancer	27	27	

End points

End points reporting groups

Reporting group title	Panitumumab + Irinotecan
Reporting group description: Subjects received panitumumab (6 mg/kg starting dose) with irinotecan (starting dose of 180 mg/m ² every 2 weeks (Q2W)).	
Reporting group title	Panitumumab + Ganitumab
Reporting group description: Subjects who responded (complete or partial response) or had stable disease in Part 1 proceeded to Part 2 of the study and received treatment with panitumumab (6 mg/kg starting dose) and ganitumab (12 mg/kg starting dose) Q2W.	

Primary: Part 1: Emergence of Mutant KRAS

End point title	Part 1: Emergence of Mutant KRAS ^[1]
End point description: Mutation in Kirsten rat sarcoma-2 virus oncogene (KRAS) status was determined by examining KRAS exons 2, 3, and 4. The emergence of mutant KRAS was defined as KRAS mutation status changed from wild-type at Baseline in KRAS exons 2, 3, and 4 to mutant in any of KRAS exons 2, 3, and 4 at the time of the second biopsy following the radiographic evidence of acquired resistance to panitumumab given in combination with irinotecan. This analysis was performed in the KRAS analysis set which includes treated subjects with known KRAS status at both Baseline and at the 2nd biopsy.	
End point type	Primary
End point timeframe: From first dose of study drug until the 2nd biopsy at the time of disease progression	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This is a single-arm study; the EudraCT system does not accept statistics for single arm analyses.	

End point values	Panitumumab + Irinotecan			
Subject group type	Reporting group			
Number of subjects analysed	25 ^[2]			
Units: percentage of subjects				
number (confidence interval 95%)	8 (0.98 to 26.03)			

Notes:
[2] - KRAS Analysis Set with wild-type KRAS at Baseline

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Objective Response Rate

End point title	Part 2: Objective Response Rate ^[3]
End point description: Objective response rate (ORR) is defined as the incidence of either a confirmed complete response (CR) or partial response (PR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria during the treatment period. This analysis was performed in the Tumor Response Evaluable Analysis Set, defined as all subjects who	

had radiographically confirmed disease progression on panitumumab and irinotecan in Part 1, who received at least 1 dose of panitumumab and/or ganitumab in Part 2, with at least one Baseline uni-dimensionally measurable lesion per the RECIST version 1.0 based on investigators' review.

End point type	Primary
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End point timeframe:

From the first dose of study drug in Part 2 until the end of treatment in Part 2; median duration of treatment in Part 2 was 8 weeks.

Notes:

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

Justification: This is a single-arm study; the EudraCT system does not accept statistics for single arm analyses.

End point values	Panitumumab + Ganitumab			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 9.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Objective Response Rate

End point title	Part 1: Objective Response Rate
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End point description:

ORR is defined as the incidence of either a confirmed complete response (CR) or partial response (PR) per modified RECIST version 1.0 criteria during the treatment period.

This endpoint was analyzed in the Tumor Response Evaluable Analysis Set – Part 1: all subjects who had known wild-type KRAS tumors from archival tumor sample and who received at least 1 dose of panitumumab and/or irinotecan in Part 1 and with at least one Baseline uni-dimensionally measurable lesion per the RECIST version 1.0 based on investigators' review.

End point type	Secondary
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End point timeframe:

From first dose of study drug until the end of treatment in Part 1; median duration of treatment was 16 weeks.

End point values	Panitumumab + Irinotecan			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percentage of subjects				
number (confidence interval 95%)	21.62 (12.89 to 38.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival
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End point description:

Progression-free survival was defined as the interval in days from the first dose of study therapy to the earlier date of disease progression (per modified RECIST version 1.0) or death prior to the analysis data cutoff date, initiating a new line of anti-tumor therapy, and receiving study treatment in part 2 where applicable. Subjects who had not progressed or died during this period were censored at their last evaluable disease assessment date.

This endpoint was analyzed in the Primary Analysis Set, for Part 1 defined as all subjects who had known wild-type KRAS tumors from archival tumor sample and who received at least 1 dose of panitumumab and/or irinotecan in Part 1, and for Part 2 as all subjects who had radiographically confirmed disease progression on panitumumab and irinotecan in Part 1 and received at least 1 dose of panitumumab and/or ganitumab in Part 2.

End point type	Secondary
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End point timeframe:

From the first dose of study drug until the data cut-off date of 30 July 2013. Median time on study follow-up was 48.5 weeks for Part 1 and 32 weeks in Part 2.

End point values	Panitumumab + Irinotecan	Panitumumab + Ganitumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	36		
Units: months				
median (confidence interval 95%)	4.6 (3.7 to 6.9)	1.7 (1.6 to 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival was defined as the time from the first dose of study therapy of part 1 or part 2 to the date of death. Subjects who had not died by the analysis data cutoff date were censored at their last contact date.

This endpoint was analyzed in the Primary Analysis Set.

End point type	Secondary
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End point timeframe:

From the first dose of study drug until the data cut-off date of 30 July 2013. Median time on study follow-up was 48.5 weeks for Part 1 and 32 weeks in Part 2.

End point values	Panitumumab + Irinotecan	Panitumumab + Ganitumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	36		
Units: months				
number (confidence interval 95%)	11.6 (7.8 to 12.9)	7.6 (5.6 to 12.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response

End point title	Time to Objective Response
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End point description:

Time to objective response was defined as time from first dose of study drug to the first confirmed objective response. An objective response is defined as a confirmed complete response or partial response per modified RECIST v1.0 criteria during the treatment period. This endpoint was analyzed in the Tumor Response Evaluable Analysis Set, defined as subset of subjects in the Primary Analysis Set with at least one baseline uni-dimensionally measurable lesion per the RECIST version 1.0 based on investigators' review.

End point type	Secondary
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End point timeframe:

From the first dose of study drug until the end of treatment; median duration of treatment was 16 weeks in Part 1 and 8 weeks in Part 2.

End point values	Panitumumab + Irinotecan	Panitumumab + Ganitumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16 ^[4]	0 ^[5]		
Units: Months				
median (full range (min-max))	1.8 (1.6 to 3)	(to)		

Notes:

[4] - Subjects with an objective response in Part 1

[5] - Subjects with an objective response In Part 2

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response
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End point description:

Duration of response is defined as the time from the first confirmed objective response to the earlier date of disease progression or death.

An objective response is defined as a confirmed complete response or partial response per modified RECIST v1.0 criteria during the treatment period. This endpoint was analyzed in the Tumor Response Evaluable Analysis Set.

End point type	Secondary
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End point timeframe:

From the first dose of study drug until the data cut-off date of 30 July 2013. Median time on study follow-up was 48.5 weeks for Part 1 and 32 weeks in Part 2.

End point values	Panitumumab + Irinotecan	Panitumumab + Ganitumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16 ^[6]	0 ^[7]		
Units: months				
median (confidence interval 95%)	7.7 (6.7 to 9.1)	(to)		

Notes:

[6] - Subjects with an objective response in Part 1

[7] - Subjects with an objective response in Part 2

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Developed Antibodies to Panitumumab

End point title	Number of Subjects Who Developed Antibodies to Panitumumab
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End point description:

Two screening immunoassays, an acid-dissociation enzyme-linked immunosorbent assay (ELISA) and a Biacore-based biosensor assay, were used to detect antibodies capable of binding to panitumumab. Positive samples were further tested for neutralizing antibodies in a cell-based epidermal growth factor receptor (EGFR) phosphorylation bioassay.

End point type	Secondary
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End point timeframe:

From first dose of study drug until 30 days after the last dose; median duration of treatment was 16 weeks in Part 1 and 8 weeks in Part 2.

End point values	Panitumumab + Irinotecan			
Subject group type	Reporting group			
Number of subjects analysed	25 ^[8]			
Units: subjects				
Binding antibody positive	0			
Neutralizing antibody positive	0			

Notes:

[8] - Subjects with at least 1 post-baseline immunoassay result

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Developed Antibodies to Ganitumab

End point title	Number of Subjects Who Developed Antibodies to Ganitumab
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End point description:

Two validated assays were used to detect the presence of anti-ganitumab antibodies. First, an electrochemiluminescent bridging immunoassay was used to detect binding antibodies (screening assay) and confirm antibodies (confirmatory assay) capable of binding ganitumab. Second, a cell-based bioassay was used to test positive binding antibody samples for neutralizing activity against ganitumab.

End point type	Secondary
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End point timeframe:

From first dose of ganitumab until 30 days after last dose; median duration of treatment was 8 weeks in Part 2.

End point values	Panitumumab + Ganitumab			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[9]			
Units: subjects				
Binding antibody positive	0			
Neutralizing antibody positive	0			

Notes:

[9] - Subjects with at least 1 immunoassay result in Part 2

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events
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End point description:

Severity was graded using the National Cancer Institute Common Toxicity Criteria version 3.0, with the exception of skin or nail toxicities that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

Treatment-related adverse events were those events the investigator considered there to be a reasonable possibility that the event may have been caused by panitumumab (Part 1) and by panitumumab and/or ganitumab (Part 2).

End point type	Secondary
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End point timeframe:

From first dose of study drug through 30 days after the last dose; median duration of treatment was 16 weeks in Part 1 and 8 weeks in Part 2.

End point values	Panitumumab + Irinotecan	Panitumumab + Ganitumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	36		
Units: subjects				
Any adverse event (AE)	74	35		
Worst grade of 3	43	17		
Worst grade of 4	6	1		
Worst grade of 5	6	2		
Worst grade of 5 excluding progressive disease	1	0		

Serious adverse event (SAE)	26	8		
AE leading to discontinuation	3	1		
SAE leading to discontinuation	8	1		
Any treatment-related adverse event (TRAE)	70	33		
TRAE worst grade of 3	34	7		
TRAE worst grade of 4	3	1		
TRAE worst grade of 5	0	0		
TRAE worst grade 5 excluding progressive disease	0	0		
Treatment-related SAE	7	1		
TRAE leading to discontinuation	0	1		
Serious TRAE leading to discontinuation	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worst Post-baseline Grade 3 or Higher Laboratory Toxicities

End point title	Number of Subjects With Worst Post-baseline Grade 3 or Higher Laboratory Toxicities
End point description:	The severity of laboratory toxicities was graded using CTCAE v3.0.
End point type	Secondary
End point timeframe:	From the first dose of study drug through 30 days after the last dose; median duration of treatment was 16 weeks in Part 1 and 8 weeks in Part 2.

End point values	Panitumumab + Irinotecan	Panitumumab + Ganitumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	36		
Units: subjects				
Decreased absolute neutrophil count	3	0		
Decreased hemoglobin	3	0		
Decreased lymphocytes	3	0		
Decreased total neutrophils	2	0		
Decreased white blood cells	2	0		
Decreased albumin	1	0		
Increased alkaline phosphatase	5	2		
Increased aspartate aminotransferase	1	1		
Decreased calcium	4	1		
Increased creatinine	1	0		
Decreased glucose	2	0		
Increased glucose	1	2		
Decreased magnesium	9	2		

Increased magnesium	2	2		
Decreased phosphorus	2	1		
Decreased potassium	7	0		
Increased potassium	3	0		
Decreased sodium	7	0		
Increased total bilirubin	3	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through 30 days after the last dose; median duration of treatment was 16 weeks in Part 1 and 8 weeks in Part 2.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Part1: Panitumumab + Irinotecan
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Reporting group description:

Subjects received panitumumab (6 mg/kg starting dose) with irinotecan (starting dose of 180 mg/m²) every 2 weeks (Q2W).

Reporting group title	Part2: Panitumumab + Ganitumab
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Reporting group description:

Subjects who responded (complete or partial response) or had stable disease in Part 1 proceeded to Part 2 of the study and received treatment with panitumumab (6 mg/kg starting dose) and ganitumab (12 mg/kg starting dose) Q2W.

Serious adverse events	Part1: Panitumumab + Irinotecan	Part2: Panitumumab + Ganitumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 74 (35.14%)	8 / 36 (22.22%)	
number of deaths (all causes)	6	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer			
subjects affected / exposed	1 / 74 (1.35%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Metastases to peritoneum			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (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			
Asthenia			

subjects affected / exposed	3 / 74 (4.05%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 74 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	5 / 74 (6.76%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 74 (1.35%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 74 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Paresis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 74 (8.11%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (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 / 74 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 74 (4.05%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	2 / 74 (2.70%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (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			
Arthralgia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle contracture			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 74 (2.70%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (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			
Decreased appetite			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Part1: Panitumumab + Irinotecan	Part2: Panitumumab + Ganitumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 74 (100.00%)	35 / 36 (97.22%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 74 (5.41%)	1 / 36 (2.78%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 74 (52.70%)	12 / 36 (33.33%)	
occurrences (all)	109	22	
Chest pain			
subjects affected / exposed	4 / 74 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Chills			

subjects affected / exposed	2 / 74 (2.70%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Fatigue			
subjects affected / exposed	12 / 74 (16.22%)	5 / 36 (13.89%)	
occurrences (all)	26	8	
General physical health deterioration			
subjects affected / exposed	6 / 74 (8.11%)	1 / 36 (2.78%)	
occurrences (all)	6	1	
Mucosal inflammation			
subjects affected / exposed	25 / 74 (33.78%)	4 / 36 (11.11%)	
occurrences (all)	71	5	
Oedema peripheral			
subjects affected / exposed	5 / 74 (6.76%)	4 / 36 (11.11%)	
occurrences (all)	7	5	
Pyrexia			
subjects affected / exposed	12 / 74 (16.22%)	4 / 36 (11.11%)	
occurrences (all)	15	5	
Xerosis			
subjects affected / exposed	7 / 74 (9.46%)	2 / 36 (5.56%)	
occurrences (all)	9	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 74 (10.81%)	2 / 36 (5.56%)	
occurrences (all)	10	2	
Dysphonia			
subjects affected / exposed	4 / 74 (5.41%)	1 / 36 (2.78%)	
occurrences (all)	4	1	
Dyspnoea			
subjects affected / exposed	7 / 74 (9.46%)	2 / 36 (5.56%)	
occurrences (all)	9	2	
Epistaxis			
subjects affected / exposed	2 / 74 (2.70%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5	1 / 36 (2.78%) 1	
Productive cough subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5	0 / 36 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 9	0 / 36 (0.00%) 0	
Investigations Weight decreased subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 9	1 / 36 (2.78%) 1	
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	3 / 36 (8.33%) 3	
Congenital, familial and genetic disorders Trichomegaly subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 7	0 / 36 (0.00%) 0	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	0 / 36 (0.00%) 0	
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5	2 / 36 (5.56%) 3	
Headache subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 6	0 / 36 (0.00%) 0	
Neurotoxicity subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	0 / 36 (0.00%) 0	
Paraesthesia			

subjects affected / exposed	5 / 74 (6.76%)	0 / 36 (0.00%)	
occurrences (all)	6	0	
Polyneuropathy			
subjects affected / exposed	5 / 74 (6.76%)	0 / 36 (0.00%)	
occurrences (all)	6	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 74 (14.86%)	3 / 36 (8.33%)	
occurrences (all)	24	4	
Neutropenia			
subjects affected / exposed	9 / 74 (12.16%)	2 / 36 (5.56%)	
occurrences (all)	22	3	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	9 / 74 (12.16%)	3 / 36 (8.33%)	
occurrences (all)	12	3	
Dry eye			
subjects affected / exposed	4 / 74 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 74 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	4	0	
Abdominal pain			
subjects affected / exposed	17 / 74 (22.97%)	8 / 36 (22.22%)	
occurrences (all)	25	8	
Abdominal pain upper			
subjects affected / exposed	8 / 74 (10.81%)	7 / 36 (19.44%)	
occurrences (all)	9	10	
Constipation			
subjects affected / exposed	20 / 74 (27.03%)	8 / 36 (22.22%)	
occurrences (all)	29	11	
Diarrhoea			
subjects affected / exposed	54 / 74 (72.97%)	8 / 36 (22.22%)	
occurrences (all)	241	10	
Dyspepsia			

subjects affected / exposed	6 / 74 (8.11%)	2 / 36 (5.56%)	
occurrences (all)	6	2	
Haemorrhoids			
subjects affected / exposed	4 / 74 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	6	0	
Nausea			
subjects affected / exposed	38 / 74 (51.35%)	10 / 36 (27.78%)	
occurrences (all)	91	14	
Stomatitis			
subjects affected / exposed	5 / 74 (6.76%)	2 / 36 (5.56%)	
occurrences (all)	11	2	
Vomiting			
subjects affected / exposed	28 / 74 (37.84%)	4 / 36 (11.11%)	
occurrences (all)	49	7	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	2 / 74 (2.70%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	10 / 74 (13.51%)	2 / 36 (5.56%)	
occurrences (all)	25	4	
Alopecia			
subjects affected / exposed	23 / 74 (31.08%)	1 / 36 (2.78%)	
occurrences (all)	38	1	
Dermatitis acneiform			
subjects affected / exposed	8 / 74 (10.81%)	3 / 36 (8.33%)	
occurrences (all)	21	3	
Dry skin			
subjects affected / exposed	24 / 74 (32.43%)	5 / 36 (13.89%)	
occurrences (all)	42	6	
Eczema			
subjects affected / exposed	1 / 74 (1.35%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Erythema			

subjects affected / exposed	5 / 74 (6.76%)	1 / 36 (2.78%)	
occurrences (all)	9	1	
Nail bed inflammation			
subjects affected / exposed	0 / 74 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	4	
Nail toxicity			
subjects affected / exposed	4 / 74 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	12	0	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 74 (1.35%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Pruritus			
subjects affected / exposed	13 / 74 (17.57%)	2 / 36 (5.56%)	
occurrences (all)	20	2	
Rash			
subjects affected / exposed	39 / 74 (52.70%)	15 / 36 (41.67%)	
occurrences (all)	145	38	
Skin fissures			
subjects affected / exposed	19 / 74 (25.68%)	3 / 36 (8.33%)	
occurrences (all)	37	5	
Skin toxicity			
subjects affected / exposed	14 / 74 (18.92%)	3 / 36 (8.33%)	
occurrences (all)	55	6	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 74 (5.41%)	2 / 36 (5.56%)	
occurrences (all)	5	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 74 (5.41%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Back pain			
subjects affected / exposed	9 / 74 (12.16%)	3 / 36 (8.33%)	
occurrences (all)	11	3	
Musculoskeletal chest pain			

subjects affected / exposed	1 / 74 (1.35%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Musculoskeletal pain			
subjects affected / exposed	6 / 74 (8.11%)	4 / 36 (11.11%)	
occurrences (all)	7	4	
Infections and infestations			
Folliculitis			
subjects affected / exposed	6 / 74 (8.11%)	2 / 36 (5.56%)	
occurrences (all)	12	4	
Infection			
subjects affected / exposed	0 / 74 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	4 / 74 (5.41%)	1 / 36 (2.78%)	
occurrences (all)	4	1	
Paronychia			
subjects affected / exposed	18 / 74 (24.32%)	7 / 36 (19.44%)	
occurrences (all)	40	10	
Urinary tract infection			
subjects affected / exposed	5 / 74 (6.76%)	3 / 36 (8.33%)	
occurrences (all)	5	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 74 (37.84%)	5 / 36 (13.89%)	
occurrences (all)	40	6	
Hypokalaemia			
subjects affected / exposed	6 / 74 (8.11%)	0 / 36 (0.00%)	
occurrences (all)	8	0	
Hypomagnesaemia			
subjects affected / exposed	22 / 74 (29.73%)	5 / 36 (13.89%)	
occurrences (all)	59	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2009	- Inclusion criteria were updated to allow the use of other experienced laboratories to confirm wild-type KRAS tumor status of archival tumor tissue using a validated test method per local regulatory guidelines, in addition to Amgen approved central laboratory. - Screening procedures were updated to include various methods of obtaining KRAS tumor status determination by an Amgen approved central laboratory or an experienced laboratory (local laboratory) per local regulatory guidelines using a validated test method. - Inclusion/exclusion criteria, dose adjustment, and discontinuation criteria were updated based on new requirements for ganitumab. - The section on long-term follow-up was updated to include the procedure for assessment of anti-panitumumab and antiganitumab antibodies. - Reporting procedures for all adverse events were updated with specific timelines to report any adverse event. - The version of Response Evaluation Criteria in Solid Tumors (RECIST) utilized in this study was updated to 1.0. - The drug storage and handling information for panitumumab and ganitumab was updated in the pharmacy guide.
27 May 2011	- To address a potential risk of formation of particles in vials of ganitumab that has been exposed to temperatures < - 30°C, a requirement was added to use an in-line, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron filter when administering ganitumab. - Reporting procedures for all adverse events were updated to clarify the reporting procedures for non-serious adverse events. Additionally, serious adverse event reporting procedures were updated to include reporting methods other than fax, eg, electronic reporting. - Secondary endpoints were updated in line with the statistical analysis plan.
14 November 2012	- The duration of the long term follow-up for survival was shortened and the primary analysis and final analysis were combined into a single analysis because the majority of enrolled subjects (75 out of the 76 [99%]) had already ended the study treatment and safety follow-up, and it was expected that at least 66 out of the 76 enrolled subjects [87%] would end the long term follow-up and the study due to death by the time of the analysis data cut-off date. - The period of long term follow-up for survival was modified to end approximately 2 years ($\pm$ 2 months) after the last subject is enrolled in part 1. - The definition of the end of study for a subject was updated to include the date the subject completes the 30-day safety follow-up visit. - The criterion for end of study was revised to include flexibility of $\pm$ 2 months at 2 years after the last subject is enrolled in part 1. - A new section was added to limit data collection from subjects who remained on treatment after all planned study analyses were completed to investigational product administration and serious adverse event reporting through 30 days after the last dose of study treatment. - The serious adverse event reporting timeline was changed from 1 working day to 24 hours. - A new section was added on pregnancy and lactation reporting procedures. - The timing of the final analysis was updated to occur after a minimum potential follow-up of 2 years ($\pm$ 2 months) after the last subject is enrolled in part 1. - Pregnancy Notification Worksheet was updated and the Lactation Notification Worksheet was included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported