Clinical trial results:
A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects With Wild-Type KRAS Metastatic Colorectal Cancer

Summary

EudraCT number	2008-001751-21
Trial protocol	ES BE AT IT FR GB
Global end of trial date	31 October 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	20060447

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00788957
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	08 February 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of part 1 of this study was to identify a tolerable dose of rilotumumab in combination with panitumumab based on the incidence of dose-limiting toxicities (DLTs).

The primary objective of part 2 of this study was to evaluate the efficacy, as assessed by the overall objective response rate (ORR), of rilotumumab (at the tolerable dose selected in Part 1) in combination with panitumumab and the efficacy of ganitumab in combination with panitumumab compared with that of panitumumab alone.

Protection of trial subjects:

This study was conducted in accordance with US Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The study protocol, amendments to the protocol, subject information, and informed consent forms were reviewed and approved by the independent ethics committee or institutional review board of each study center.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 October 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	153
EEA total number of subjects	84

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)	102
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject enrolled 27 October 2008; last subject enrolled 05 February 2010. In Part 1, subjects with wild-type KRAS metastatic colorectal cancer received open-label rilotumumab and panitumumab to identify a tolerable dose of rilotumumab for Part 2 of the study. Participants enrolled in Part 1 were not eligible for randomization in Part 2.

Pre-assignment

Screening details:

In Part 2 subjects were randomized in a 1:1:1 ratio to 1 of the 3 double-blinded treatment arms. In Part 3, subjects randomized to Panitumumab Alone in Part 2 and with disease progression or intolerability were re-randomized 1:1 into 2 double-blind groups. Participants completed a safety follow-up visit 30 days after the last dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

In Part 1 subjects received open-label rilotumumab in combination with panitumumab with the purpose of identifying a tolerable dose of rilotumumab for the Part 2 portion of the study. In Part 2, panitumumab was administered open-label and rilotumumab and ganitumab were double-blinded. Part 3 was double-blinded for both rilotumumab and ganitumab. Part 3 was double-blinded for both rilotumumab and ganitumab.

Arms

Are arms mutually exclusive?	No
Arm title	Part 1: Panitumumab + Rilotumumab

Arm description:

Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Arm type	Experimental
Investigational medicinal product name	Panitumumab
Investigational medicinal product code	AMG 954
Other name	Vectibix®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg by intravenous infusion once every 2 weeks

Investigational medicinal product name	Rilotumumab
Investigational medicinal product code	AMG 102
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg by intravenous infusion once every 2 weeks

Arm title	Part 2: Panitumumab Alone

Arm description:

Participants received panitumumab 6 mg/kg and placebo by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Arm type	Active comparator

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	AMG 954
Other name	Vectibix®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg by intravenous infusion once every 2 weeks

Arm title	Part 2: Panitumumab + Rilotumumab

Arm description:

Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Arm type	Experimental
Investigational medicinal product name	Panitumumab
Investigational medicinal product code	AMG 954
Other name	Vectibix®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg by intravenous infusion once every 2 weeks

Investigational medicinal product name	Rilotumumab
Investigational medicinal product code	AMG 102
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg by intravenous infusion once every 2 weeks

Arm title	Part 2: Panitumumab + Ganitumab

Arm description:

Participants received panitumumab 6 mg/kg and ganitumab 12 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Arm type	Experimental
Investigational medicinal product name	Panitumumab
Investigational medicinal product code	AMG 954
Other name	Vectibix®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg by intravenous infusion once every 2 weeks

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

Dosage and administration details:

12 mg/kg by intravenous infusion once every 2 weeks

Arm title	Part 3: Rilotumumab

Arm description:

Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive rilotumumab 10 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.

Arm type	Experimental

Investigational medicinal product name	Rilotumumab
Investigational medicinal product code	AMG 102
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg by intravenous infusion once every 2 weeks

Arm title	Part 3: Ganitumab

Arm description:

Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive ganitumab 12 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.

Arm type	Experimental
Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg/kg by intravenous infusion once every 2 weeks

Number of subjects in period 1	Part 1: Panitumumab + Rilotumumab	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab
Started	11	48	48
Completed	2	6	4
Not completed	9	42	44
Consent withdrawn by subject	-	9	5
Death	8	32	35
Lost to follow-up	1	-	3
On-study at time of data cut-off	-	1	1

Number of subjects in period 1	Part 2: Panitumumab + Ganitumab	Part 3: Rilotumumab	Part 3: Ganitumab
Started	46	13	11
Completed	5	4	1
Not completed	41	9	10
Consent withdrawn by subject	3	-	2
Death	37	8	8
Lost to follow-up	-	-	-
On-study at time of data cut-off	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Panitumumab + Rilotumumab
Reporting group description:	
Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 2: Panitumumab Alone
Reporting group description:	
Participants received panitumumab 6 mg/kg and placebo by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 2: Panitumumab + Rilotumumab
Reporting group description:	
Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 2: Panitumumab + Ganitumab
Reporting group description:	
Participants received panitumumab 6 mg/kg and ganitumab 12 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 3: Rilotumumab
Reporting group description:	
Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive rilotumumab 10 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.	
Reporting group title	Part 3: Ganitumab
Reporting group description:	
Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive ganitumab 12 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.	

Reporting group values	Part 1: Panitumumab + Rilotumumab	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab
Number of subjects	11	48	48
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	56.5	55	62.1
standard deviation	± 13.8	± 12.5	± 7.5
Gender, Male/Female Units: participants			
Female	6	20	19
Male	5	28	29
Race/Ethnicity Units: Subjects			
White or Caucasian	11	45	47
Black or African American	0	0	1
Hispanic or Latino	0	1	0
Asian	0	1	0
Other	0	1	0

Primary Tumor Type Units: Subjects			
Colon cancer	6	31	33
Rectal cancer	5	17	15
Adenocarcinoma differential of primary tumor Units: Subjects			
Well differentiated	0	8	7
Moderately differentiated	6	27	27
Poorly differentiated	5	9	6
Undifferentiated	0	0	0
Unknown	0	4	8
Months since primary diagnosis			
Data available for 9, 46, 46, 45, 13 and 10 subjects in each treatment group respectively			
Units: months			
arithmetic mean	41.7	30.3	36.2
standard deviation	± 29.7	± 18.5	± 31.8
Months since metastatic disease diagnosis Units: months			
arithmetic mean	29.7	21.8	25.8
standard deviation	± 27.6	± 12.6	± 27

Reporting group values	Part 2: Panitumumab + Ganitumab	Part 3: Rilotumumab	Part 3: Ganitumab
Number of subjects	46	13	11
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	62	54.8	52
standard deviation	± 9.7	± 13.9	± 11.3
Gender, Male/Female Units: participants			
Female	21	3	6
Male	25	10	5
Race/Ethnicity Units: Subjects			
White or Caucasian	45	13	10
Black or African American	1	0	0
Hispanic or Latino	0	0	0
Asian	0	0	0
Other	0	0	1
Primary Tumor Type Units: Subjects			
Colon cancer	28	8	8
Rectal cancer	18	5	3
Adenocarcinoma differential of primary tumor Units: Subjects			
Well differentiated	6	1	2

Moderately differentiated	25	8	6
Poorly differentiated	11	1	3
Undifferentiated	1	0	0
Unknown	3	3	0
Months since primary diagnosis			
Data available for 9, 46, 46, 45, 13 and 10 subjects in each treatment group respectively			
Units: months			
arithmetic mean	34.7	37.8	34.7
standard deviation	± 28.7	± 24.8	± 17.7
Months since metastatic disease diagnosis			
Units: months			
arithmetic mean	21.1	27.3	28.6
standard deviation	± 16	± 13.8	± 15.8

Reporting group values	Total		
Number of subjects	153		
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: participants			
Female	66		
Male	87		
Race/Ethnicity			
Units: Subjects			
White or Caucasian	148		
Black or African American	2		
Hispanic or Latino	1		
Asian	1		
Other	1		
Primary Tumor Type			
Units: Subjects			
Colon cancer	98		
Rectal cancer	55		
Adenocarcinoma differential of primary tumor			
Units: Subjects			
Well differentiated	21		
Moderately differentiated	85		
Poorly differentiated	31		
Undifferentiated	1		
Unknown	15		
Months since primary diagnosis			
Data available for 9, 46, 46, 45, 13 and 10 subjects in each treatment group respectively			
Units: months			
arithmetic mean			
standard deviation	-		

Months since metastatic disease diagnosis Units: months arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Part 1: Panitumumab + Rilotumumab
Reporting group description:	
Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 2: Panitumumab Alone
Reporting group description:	
Participants received panitumumab 6 mg/kg and placebo by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 2: Panitumumab + Rilotumumab
Reporting group description:	
Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 2: Panitumumab + Ganitumab
Reporting group description:	
Participants received panitumumab 6 mg/kg and ganitumab 12 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Reporting group title	Part 3: Rilotumumab
Reporting group description:	
Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive rilotumumab 10 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.	
Reporting group title	Part 3: Ganitumab
Reporting group description:	
Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive ganitumab 12 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.	
Subject analysis set title	Rilotumumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Rilotumumab pharmacokinetics in participants who received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	
Subject analysis set title	Panitumumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Panitumumab pharmacokinetics in participants who received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.	

Primary: Part 1: Number of Subjects With Dose-limiting Toxicities (DLT)

End point title	Part 1: Number of Subjects With Dose-limiting Toxicities
End point description:	
A DLT is defined as any grade 3 or 4 rilotumumab-related or combination (panitumumab and rilotumumab)-related adverse event or laboratory abnormality that is deemed clinically significant by the investigator. This endpoint was analyzed in the first 6 DLT evaluable participants, which included subjects who received at least 2 doses of panitumumab and rilotumumab as scheduled (ie, Week 1 and Week 3) and had a minimum 28 days follow-up for safety, or received at least 1 dose of panitumumab and rilotumumab and had a DLT within the first 28 days on study.	
End point type	Primary
End point timeframe:	
7 weeks	

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: The primary objective of Part 1 was to identify a tolerable dose of rilotumumab in combination with panitumumab for use in Part 2, based n the number of dose-limiting toxicities. No statistical comparisons were performed in Part 1.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 1 only

End point values	Part 1: Panitumumab + Rilotumumab			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Percentage of Participants with an Objective Response

End point title	Part 2: Percentage of Participants with an Objective Response[3]

End point description:

Objective response is defined as a confirmed complete (CR) or partial response (PR) no less than 4 weeks after the criteria for response are first met, determined by the investigator considering the radiologic response of all existing target and non-target lesions, evidence of new lesions, and cytology evaluation (as appropriate) according to the Modified-Response Evaluation Criteria In Solid Tumors (RECIST) v1.0 criteria: CR: Disappearance of all target and non-target and no new lesions. PR: At least a 30% decrease in the size of target lesions with no increase in non-target lesions, or, the disappearance of all target lesions and persistence of one or more non-target lesion(s) not qualifying for either CR or progressive disease. Participants without a post-baseline assessment were considered non-responders. Tumor assessments up to the initiation of another anti-tumor therapy including the Part 3 treatment, if applicable, were used.

End point type	Primary

End point timeframe:

From the date of first dose until the data cut-off date of 23 July 2010. Median follow-up time was 30 weeks.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[4]	48[5]	46[6]	
Units: percentage of participants				
number (not applicable)	21	31	22	

Notes:

[4] - Efficacy analysis set with Baseline measureable disease

[5] - Efficacy analysis set with Baseline measureable disease

[6] - Efficacy analysis set with Baseline measureable disease

Statistical analyses

Statistical analysis title	Posterior Distribution of Objective Response Rate

Statistical analysis description:

For the primary analysis of objective response rate (ORR) for Part 2, a Beta(6.3, 33.7) and Beta(1.1, 5.9) was used as priors for panitumumab alone and combination regimens in calculating the posterior distribution of the ORR for each respective treatment group.
The posterior mean difference in ORR and the 95% credible region for the difference in the ORR between panitumumab + rilotumumab compared to panitumumab alone is reported.

Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Rilotumumab
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Posterior Mean Difference in ORR
Point estimate	10.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	26.2

Notes:

[7] - The primary endpoint of ORR was analyzed by Bayesian approaches to determine if either of the combination treatments (panitumumab plus rilotumumab or panitumumab plus ganitumab) met the pre-specified criteria for promising or not promising.

Statistical analysis title	Posterior Distribution of Objective Response Rate

Statistical analysis description:

For the primary analysis of objective response rate (ORR) for Part 2, a Beta(6.3, 33.7) and Beta(1.1, 5.9) was used as priors for panitumumab alone and combination regimens in calculating the posterior distribution of the ORR for each respective treatment group.
The posterior mean difference in ORR and the 95% credible region for the difference in the ORR between panitumumab + ganitumab compared to panitumumab alone is reported.

Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Ganitumab
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Posterior Mean Difference in ORR
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	16.4

Notes:

[8] - The primary endpoint of ORR was analyzed by Bayesian approaches to determine if either of the combination treatments (panitumumab plus rilotumumab or panitumumab plus ganitumab) met the pre-specified criteria for promising or not promising.

Statistical analysis title	Posterior Distribution of ORR - Odds Ratio

Statistical analysis description:

The posterior distribution of the odds ratio for an ORR was used to assess whether rilotumumab and/or ganitumab in combination with panitumumab has a higher ORR compared to panitumumab alone. A 95% credible region was calculated for the odds ratio.
An odds ratio value greater than 1 implies a higher ORR for the respective combination therapy relative to panitumumab alone.

Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Rilotumumab
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.9318 [10]
Method	Posterior probability of OR > 1
Parameter estimate	Posterior Mean odds ratio (OR)
Point estimate	2.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	4.243

Notes:

[9] - The primary endpoint of ORR was analyzed by Bayesian approaches to determine if either of the combination treatments (panitumumab plus rilotumumab or panitumumab plus ganitumab) met the pre-specified criteria for promising or not promising.
[10] - The posterior probability of the odds ratio being > 1 is reported as the P-value.

Statistical analysis title	Posterior Distribution of ORR - Odds Ratio

Statistical analysis description:

The posterior distribution of the odds ratio for an ORR was used to assess whether rilotumumab and/or ganitumab in combination with panitumumab has a higher ORR compared to panitumumab alone. A 95% credible region was calculated for the odds ratio. An odds ratio value greater than 1 implies a higher ORR for the respective combination therapy relative to panitumumab alone.

Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Ganitumab
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.6336 [12]
Method	Posterior probability of OR > 1
Parameter estimate	Posterior Mean odds ratio (OR)
Point estimate	1.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.478
upper limit	2.726

Notes:

[11] - The primary endpoint of ORR was analyzed by Bayesian approaches to determine if either of the combination treatments (panitumumab plus rilotumumab or panitumumab plus ganitumab) met the pre-specified criteria for promising or not promising.
[12] - The posterior probability of the odds ratio being > 1 is reported as the P-value.

Secondary: Part 2: Duration of Response

End point title	Part 2: Duration of Response[13]

End point description:

The interval from the first visit of a confirmed objective response to disease progression as defined by the modified RECIST v1.0
criteria. Participants who did not progress by the earlier of the analysis data cutoff date, initiating a new line of anti-tumor therapy, and the start of Part 3 dosing where applicable were censored at their last evaluable disease assessment date prior to the end of reporting period.
Progressive disease is defined as at least a 20% increase in the size of target lesions, or unequivocal progression of existing non-target lesions, or any new lesions.
"99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From the date of first dose until the data cut-off date of 23 July 2010. Median follow-up time was 30 weeks.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[14]	15[15]	10[16]	
Units: months				
median (confidence interval 95%)	3.7 (3.6 to 99999)	5.1 (3.7 to 5.6)	3.7 (3.6 to 5.8)	

Notes:

[14] - Efficacy analysis set; participants with an objective response of CR or PR.

[15] - Efficacy analysis set; participants with an objective response of CR or PR.

[16] - Efficacy analysis set; participants with an objective response of CR or PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to Response

End point title	Part 2: Time to Response[17]

End point description:

The interval from the first dose of study therapy to the date of the first confirmed objective response, calculated only for participants with an objective response.

End point type	Secondary

End point timeframe:

From the date of first dose until the data cut-off date of 23 July 2010. Median follow-up time was 30 weeks.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[18]	15[19]	10[20]	
Units: months				
median (confidence interval 95%)	1.8 (1.6 to 2.5)	1.6 (1.6 to 1.7)	1.7 (1.6 to 1.7)	

Notes:

[18] - Efficacy analysis set; participants with an objective response of CR or PR.

[19] - Efficacy analysis set; participants with an objective response of CR or PR.

[20] - Efficacy analysis set; participants with an objective response of CR or PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Participants with Disease Control

End point title	Part 2: Percentage of Participants with Disease Control[21]

End point description:

The percentage of participants with an overall objective response of CR, PR, or stable disease (SD). CR: Disappearance of all target and non-target and no new lesions. PR: At least a 30% decrease in the size of target lesions with no increase in non-target lesions, or, the disappearance of all target lesions and persistence of one or more non-target lesion(s) not qualifying for either CR or progressive disease (PD). SD: Neither sufficient shrinkage of target lesions to qualify for PR nor sufficient increase to qualify for PD and no progression of non-target lesions, or the persistence of one or more non-target lesion(s) not qualifying for either CR or PD.

End point type	Secondary

End point timeframe:

From the date of first dose until the data cut-off date of 23 July 2010. Median follow-up time was 30 weeks.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[22]	48[23]	46[24]	
Units: percentage of participants				
number (confidence interval 95%)	56 (41 to 71)	71 (56 to 83)	61 (45 to 75)	

Notes:

[22] - Efficacy analysis set with baseline measurable disease.

[23] - Efficacy analysis set with baseline measurable disease.

[24] - Efficacy analysis set with baseline measurable disease.

Statistical analyses

Statistical analysis title	Difference in disease control rate
Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Rilotumumab

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	34

Statistical analysis title	Difference in disease control rate
Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Ganitumab
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	25

Secondary: Part 2: Progression-free Survival (PFS)

End point title	Part 2: Progression-free Survival (PFS)[25]

End point description:

The interval from the first dose of study therapy to the earlier date of disease progression (per modified-RECIST v1.0) or death. Participants who did not progress or die by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the earlier of the analysis data cutoff date, initiating a new line of anti-tumor therapy, and receiving study treatment in part 3 where applicable. Participants enrolled into Part 3 or who started a new line of anti-tumor therapy before radiographic progression but subsequently died were considered as having an event with the event date same as the death date.

End point type	Secondary

End point timeframe:

From the date of first dose until the data cut-off date of 23 July 2010. Median follow-up time was 30 weeks.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[26]	48[27]	46[28]	
Units: months				
median (confidence interval 95%)	3.7 (2.5 to 5.3)	5.2 (3.6 to 5.4)	5.3 (2.7 to 5.7)	

Notes:

[26] - Efficacy analysis set

[27] - Efficacy analysis set

[28] - Efficacy analysis set

Statistical analyses

Statistical analysis title	Difference in progression-free survival
Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Rilotumumab
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in median time
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.8

Statistical analysis title	Difference in progression-free survival
Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Ganitumab
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in median time
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2.9

Secondary: Part 2: On-treatment Progression-free Survival

End point title	Part 2: On-treatment Progression-free Survival[29]

End point description:

An event is defined as a radiographic progression or death that occurred from the first dose to 28 days since the last dose of study therapy. Participants who did not progress or die during this period were censored at their last evaluable disease assessment before the end of the 28-day period. Participants who received Part 3 treatment before 28 days since their last dose of study drug in Part 2 and did not

have radiographic progression or die were censored at their last evaluable disease assessment prior to receiving therapy in Part 3. Radiographic progressions after start of a new anti-tumor therapy, including Part 3 treatment, or after 28 days since the last dose in Part 2 were excluded from the analysis. Participants who died with no prior radiographic disease progression during Part 3 treatment, but within the 28-day period since the last dose in Part 2 were considered as having an event.

End point type	Secondary

End point timeframe:

From the date of first dose until 28 days after the last dose until the data cut-off date of 23 July 2010. Median time on treatment was 3.7, 4.9 and 5.1 months in each treatment arm respectively.

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[30]	48[31]	46[32]	
Units: months				
median (confidence interval 95%)	3.8 (2.5 to 5.3)	5.3 (3.6 to 5.4)	5.3 (2.7 to 5.7)	

Notes:

[30] - Efficacy analysis set

[31] - Efficacy analysis set

[32] - Efficacy analysis set

Statistical analyses

Statistical analysis title	Difference in on-treatment PFS
Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Rilotumumab
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in median time
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2.8

Statistical analysis title	Difference in on-treatment PFS
Comparison groups	Part 2: Panitumumab Alone v Part 2: Panitumumab + Ganitumab
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in median time
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	2.9

Secondary: Part 2: Overall Survival

End point title	Part 2: Overall Survival[33]

End point description:

The interval from the first dose of study therapy to the date of death. Participants still alive at the analysis data cutoff date were censored at their last contact date.

End point type	Secondary

End point timeframe:

From the date of first dose until the data cut-off date of 08 February 2012. Median follow-up time was 45.5 weeks.

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[34]	48[35]	46[36]	
Units: months				
median (confidence interval 95%)	11.6 (9.8 to 18)	13.8 (11 to 17.9)	10.6 (7.3 to 14.3)	

Notes:

[34] - Efficacy analysis set

[35] - Efficacy analysis set

[36] - Efficacy analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs)

End point title	Number of Subjects with Adverse Events (AEs)[37]

End point description:

A serious adverse event (SAE) is defined as an AE that is fatal, life threatening (places the participant at immediate risk of death), requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or other significant medical hazard. AEs were graded for severity according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 3: Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Fatal. AEs were assessed by the investigator for the relationship of the AE to each one or more of the investigational products by the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?"

End point type	Secondary

End point timeframe:

From the first dose date to 30 days after the last dose of study drug, up to the data cutoff date of 08 February 2012. Median time on treatment was 5.2 months for Part 1, 2.8, 3.9 and 4.2 months for each Part 2 treatment arm respectively.

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 1 and Part 2 only

End point values	Part 1: Panitumumab + Rilotumumab	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[38]	48[39]	48[40]	46[41]
Units: participants				
number (not applicable)				
Any adverse event	11	45	48	46
Worst grade of 3	8	19	28	25
Worst grade of 4	1	3	6	4
Worst grade of 5	1	1	4	4
Serious adverse event	5	10	9	10
AE leading to study drug / study discontinuation	4	4	9	7
Treatment-related adverse event (TRAE)	10	43	47	45
TRAE worst grade of 3	7	11	26	20
TRAE worst grade of 4	0	3	6	4
TRAE worst grade of 5	0	0	0	0
Serious treatment-related adverse event	2	1	2	2
TRAE leading to study drug/study discontinuation	3	2	4	2

Notes:

[38] - Safety analysis set

[39] - Safety analysis set

[40] - Safety analysis set

[41] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Grade 3 or Higher Laboratory Toxicities

End point title	Number of Subjects with Grade 3 or Higher Laboratory Toxicities[42]

End point description:

The severity of laboratory toxicities was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 3: Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Fatal.

End point type	Secondary

End point timeframe:

From the first dose date to 30 days after the last dose of study drug, up to the data cutoff date of 08 February 2012. Median time on treatment was 5.2 months for Part 1, 2.8, 3.9 and 4.2 months for each Part 2 treatment arm respectively.

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 1 and Part 2 only

End point values	Part 1: Panitumumab + Rilotumumab	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[43]	48[44]	48[45]	46[46]
Units: participants				
number (not applicable)				
Increased Alanine Amino Transferase	0	1	0	2
Decreased albumin	0	1	3	0
Increased Alkaline Phosphatase	1	2	3	5
Increased Aspartate Amino Transferase	0	0	0	4
Decreased calcium	0	3	1	2
Increased calcium	1	0	1	2
Increased Creatinine	0	0	0	1
Decreased Glucose	0	0	0	0
Increased Glucose	1	0	2	0
Decreased Magnesium	0	1	2	8
Increased Magnesium	0	4	2	2
Decreased Phosphorus	0	1	4	1
Decreased Potassium	1	1	1	0
Increased Potassium	0	0	1	0
Decreased Sodium	0	3	2	3
Increased Sodium	0	0	1	0
Increased Total Bilirubin	0	3	0	5
Increased Uric Acid	1	1	2	1
Decreased Absolute Neutrophil Count	0	1	1	2
Decreased Hemoglobin	1	2	1	0
Decreased Lymphocytes	1	3	2	1
Decreased Platelets	0	0	0	1
Decreased Total Neutrophils	0	1	1	2
Decreased White Blood Cells	0	0	0	0

Notes:

[43] - Safety analysis set

[44] - Safety analysis set

[45] - Safety analysis set

[46] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Antibody Formation to Panitumumab, Rilotumumab or Ganitumab

End point title	Number of Subjects With Antibody Formation to Panitumumab, Rilotumumab or Ganitumab[47]

End point description:

Validated immunoassays were used to detect anti-panitumumab, anti-rilotumumab and anti-ganitumab binding antibodies.

End point type	Secondary

End point timeframe:

From the first dose date to 30 days after the last dose of study drug, up to the data cutoff date of 08 February 2012. Median time on treatment was 5.2 months for Part 1, 2.8, 3.9 and 4.2 months for each Part 2 treatment arm respectively.

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed for subjects in Part 1 and Part 2 only

End point values	Part 1: Panitumumab + Rilotumumab	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[48]	40[49]	44[50]	43[51]
Units: participants				
number (not applicable)				
Anti-panitumumab antibodies	0	3	3	4
Anti-rilotumumab antibodies	0	0	3	0
Anti-ganitumab antibodies	0	0	0	2

Notes:

[48] - Safety analysis set participants with at least one post-baseline immunoassay result.

[49] - Safety analysis set participants with at least one post-baseline immunoassay result.

[50] - Safety analysis set participants with at least one post-baseline immunoassay result.

[51] - Safety analysis set participants with at least one post-baseline immunoassay result.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Maximum Observed Drug Concentration (Cmax) and Minimum drug concentration (Cmin) for Panitumumab and Rilotumumab

End point title	Part 1: Maximum Observed Drug Concentration (Cmax) and Minimum drug concentration (Cmin) for Panitumumab and Rilotumumab

End point description:

End point type	Secondary

End point timeframe:

Week 5 (third dose) at pre-dose, 5 minutes after infusion and at 24, 48 and 96, and 168 hours post infusion.

End point values	Panitumumab	Rilotumumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: µg/ml				
arithmetic mean (standard deviation)				
Cmax (n=6, 6)	227 (± 37.23)	346 (± 88.58)		
Cmin (n=5, 4)	61.1 (± 32.93)	124 (± 35.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Area Under the Drug Concentration-time Curve During a Dosing Interval (AUCtau) for Panitumumab and Rilotumumab

End point title	Part 1: Area Under the Drug Concentration-time Curve During a Dosing Interval (AUCtau) for Panitumumab and Rilotumumab

End point description:

End point type	Secondary

End point timeframe:

Week 5 (third dose) at pre-dose, 5 minutes after infusion and at 24, 48 and 96, and 168 hours post infusion.

End point values	Panitumumab	Rilotumumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[52]	4[53]		
Units: day*µg/ml				
arithmetic mean (standard deviation)	1420 (± 386.24)	2560 (± 675.84)		

Notes:

[52] - Part 1 subjects with available intensive pharmacokinetic samples after the third dose (Week 5)

[53] - Part 1 subjects with available intensive pharmacokinetic samples after the third dose (Week 5)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Maximum Observed Drug Concentration During the Dosing Interval (Cmax) for Panitumumab

End point title	Part 2: Maximum Observed Drug Concentration During the Dosing Interval (Cmax) for Panitumumab[54]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose and 5 minutes after the completion of infusion at Weeks 1, 3, 5, 7, 13 and 23.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[55]	48[56]	46[57]	
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 1 (n=43, 42, 44)	114 (± 31.58)	124 (± 32.74)	118 (± 40.95)	
Week 3 (n=38, 37, 38)	149 (± 46.79)	154 (± 44.66)	139 (± 33.92)	

Week 5 (n=35, 35, 35)	165 (± 49.67)	172 (± 55.56)	150 (± 39.75)	
Week 7 (n=30, 35, 29)	166 (± 51.13)	180 (± 53.28)	167 (± 39.91)	
Week 13 (n=16, 17, 21)	201 (± 53.67)	199 (± 51.14)	192 (± 59.9)	
Week 23 (n=10, 10, 9)	196 (± 48.02)	207 (± 51.54)	187 (± 41.7)	

Notes:

[55] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

[56] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

[57] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Minimum Observed Drug Concentration During the Dosing Interval (Cmin) for Panitumumab

End point title	Part 2: Minimum Observed Drug Concentration During the Dosing Interval (Cmin) for Panitumumab[58]

End point description:

Concentration represents the Cmin from the previous dose (eg, Week 3 Cmin is the Cmin after the 1st dose).

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 3, 5, 7, 13 and 23.

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 only

End point values	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab	Part 2: Panitumumab + Ganitumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[59]	48[60]	46[61]	
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 3 (n=39, 36, 36)	19.8 (± 15.9)	22.8 (± 16.76)	17.2 (± 9.72)	
Week 5 (n=35, 34, 35)	34.8 (± 20.5)	37.9 (± 19.9)	29.8 (± 16.6)	
Week 7 (n=29, 32, 31)	39.9 (± 24.82)	45.2 (± 22.78)	37.4 (± 20.38)	
Week 13 (n=16, 17, 20)	63.5 (± 27.31)	63.4 (± 28.66)	51.4 (± 32.43)	
Week 23 (n=8, 9, 9)	82.1 (± 23.15)	62.1 (± 27.51)	54.8 (± 29.48)	

Notes:

[59] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

[60] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

[61] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Maximum Observed Drug Concentration During the Dosing Interval (Cmax) for Rilotumumab

End point title	Part 2: Maximum Observed Drug Concentration During the Dosing Interval (Cmax) for Rilotumumab[62]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose and 5 minutes after the completion of infusion at Weeks 1, 3, 5, 7, 13 and 23.

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 who received rilotumumab

End point values	Part 2: Panitumumab + Rilotumumab			
Subject group type	Reporting group			
Number of subjects analysed	48[63]			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 1 (n=43)	239 (± 70.03)			
Week 3 (n=37)	316 (± 89.74)			
Week 5 (n=38)	357 (± 89.25)			
Week 7 (n=37)	397 (± 98.46)			
Week 13 (n=18)	453 (± 107.36)			
Week 23 (n=17)	421 (± 109.46)			

Notes:

[63] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Minimum Observed Drug Concentration During the Dosing Interval (Cmin) for Rilotumumab

End point title	Part 2: Minimum Observed Drug Concentration During the Dosing Interval (Cmin) for Rilotumumab[64]

End point description:

Concentration represents the Cmin from the previous dose (eg, Week 3 Cmin is the Cmin after the 1st dose).

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 3, 5, 7, 13 and 23.

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 who received rilotumumab

End point values	Part 2: Panitumumab + Rilotumumab			
Subject group type	Reporting group			
Number of subjects analysed	48[65]			
Units: µg/mL				
arithmetic mean (standard deviation)				

Week 3 (n=38)	70.1 (± 28.88)			
Week 5 (n=34)	119 (± 37.84)			
Week 7 (n=33)	143 (± 39.33)			
Week 13 (n=19)	186 (± 75.7)			
Week 23 (n=17)	181 (± 65.7)			

Notes:

[65] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Maximum Observed Drug Concentration During the Dosing Interval (Cmax) for Ganitumab

End point title	Part 2: Maximum Observed Drug Concentration During the Dosing Interval (Cmax) for Ganitumab[66]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose and 5 minutes after the completion of infusion at Weeks 1, 3, 5, 7, 13 and 23.

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 who received ganitumab

End point values	Part 2: Panitumumab + Ganitumab			
Subject group type	Reporting group			
Number of subjects analysed	46[67]			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 1 (n=40)	218 (± 65.4)			
Week 3 (n=42)	240 (± 60.72)			
Week 5 (n=38)	244 (± 71.49)			
Week 7 (n=35)	279 (± 99.05)			
Week 13 (n=22)	274 (± 76.99)			
Week 23 (n=16)	276 (± 62.93)			

Notes:

[67] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Minimum Observed Drug Concentration During the Dosing Interval (Cmin) for Ganitumab

End point title	Part 2: Minimum Observed Drug Concentration During the Dosing Interval (Cmin) for Ganitumab[68]

End point description:

Concentration represents the Cmin from the previous dose (eg, Week 3 Cmin is the Cmin after the 1st

dose).

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 3, 5, 7, 13 and 23.

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed for subjects in Part 2 who received ganitumab

End point values	Part 2: Panitumumab + Ganitumab			
Subject group type	Reporting group			
Number of subjects analysed	46[69]			
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 3 (n=39)	19.8 (± 10.22)			
Week 5 (n=39)	24.4 (± 13.47)			
Week 7 (n=37)	28.9 (± 15.66)			
Week 13 (n=22)	38.8 (± 23.9)			
Week 23 (n=16)	39.7 (± 23.34)			

Notes:

[69] - Part 2 subjects with available pharmacokinetic data at each time point (indicated by n).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time frame for adverse event reporting is from the first dose date to 30 days since the last dose date in each part of the study. The median time frame is 6.1, 3.7, 4.9., 5.1, 2.4 and 2.3 months by treatment arm respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Part 1: Panitumumab + Rilotumumab

Reporting group description:

Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Reporting group title	Part 2: Panitumumab Alone

Reporting group description:

Participants received panitumumab 6 mg/kg and placebo by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Reporting group title	Part 2: Panitumumab + Rilotumumab

Reporting group description:

Participants received panitumumab 6 mg/kg and rilotumumab 10 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Reporting group title	Part 2: Panitumumab + Ganitumab

Reporting group description:

Participants received panitumumab 6 mg/kg and ganitumab 12 mg/kg by intravenous infusion once every 2 weeks until progressive disease, intolerability, withdrawal, death or sponsor decision.

Reporting group title	Part 3: Rilotumumab

Reporting group description:

Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive rilotumumab 10 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.

Reporting group title	Part 3: Ganitumab

Reporting group description:

Participants randomized to Panitumumab Alone in Part 2 who had disease progression (radiographic or clinical) or intolerability were re-randomized in Part 3 to receive ganitumab 12 mg/kg every 2 weeks until disease progression, intolerability, withdrawal, death, or sponsor decision.

Serious adverse events	Part 1: Panitumumab + Rilotumumab	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	10 / 48 (20.83%)	9 / 48 (18.75%)
number of deaths (all causes)	1	1	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CANCER PAIN			

subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLORECTAL CANCER			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	3 / 48 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
COLORECTAL CANCER METASTATIC			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
CAPILLARY LEAK SYNDROME			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENED			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
HIP FRACTURE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

ARRHYTHMIA SUPRAVENTRICULAR			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASCITES			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			

subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
HYPERBILIRUBINAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
HYDRONEPHROSIS			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
CATHETER SITE INFECTION			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOCCAL INFECTION			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPERCREATININAEMIA			

subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Panitumumab + Ganitumab	Part 3: Rilotumumab	Part 3: Ganitumab
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 46 (21.74%)	6 / 13 (46.15%)	2 / 11 (18.18%)
number of deaths (all causes)	4	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CANCER PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLORECTAL CANCER			
subjects affected / exposed	2 / 46 (4.35%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
COLORECTAL CANCER METASTATIC			

subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
CAPILLARY LEAK SYNDROME			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PYREXIA			

subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENED			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
HIP FRACTURE			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ARRHYTHMIA SUPRAVENTRICULAR			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASCITES			
subjects affected / exposed	2 / 46 (4.35%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			

subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
HYPERBILIRUBINAEMIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
HYDRONEPHROSIS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
URINARY RETENTION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
CATHETER SITE INFECTION			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOCCAL INFECTION			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPERCREATININAEMIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA			

subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1: Panitumumab + Rilotumumab	Part 2: Panitumumab Alone	Part 2: Panitumumab + Rilotumumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	43 / 48 (89.58%)	48 / 48 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANOGENITAL WARTS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
PYOGENIC GRANULOMA			
subjects affected / exposed	2 / 11 (18.18%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	6	0	0
Vascular disorders			
CAPILLARY LEAK SYNDROME			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	5	0	0
FLUSHING			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
HYPERTENSION			
subjects affected / exposed	3 / 11 (27.27%)	1 / 48 (2.08%)	2 / 48 (4.17%)
occurrences (all)	3	1	3
HYPERTENSIVE CRISIS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

ASTHENIA			
subjects affected / exposed	3 / 11 (27.27%)	7 / 48 (14.58%)	4 / 48 (8.33%)
occurrences (all)	3	11	5
CHILLS			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
FACE OEDEMA			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	1	5	1
FACIAL PAIN			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
FATIGUE			
subjects affected / exposed	4 / 11 (36.36%)	10 / 48 (20.83%)	4 / 48 (8.33%)
occurrences (all)	14	21	12
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	1	1	0
INFLAMMATION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
INFUSION SITE INFLAMMATION			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
MUCOSAL INFLAMMATION			
subjects affected / exposed	3 / 11 (27.27%)	3 / 48 (6.25%)	6 / 48 (12.50%)
occurrences (all)	3	3	10
LOCALISED OEDEMA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 11 (18.18%)	6 / 48 (12.50%)	9 / 48 (18.75%)
occurrences (all)	2	6	11
OEDEMA			

subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	2
PYREXIA			
subjects affected / exposed	1 / 11 (9.09%)	4 / 48 (8.33%)	2 / 48 (4.17%)
occurrences (all)	1	8	4
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
HYPERSENSITIVITY			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			
GENITAL TRACT INFLAMMATION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	2 / 48 (4.17%)
occurrences (all)	1	2	2
DYSPNOEA			
subjects affected / exposed	2 / 11 (18.18%)	1 / 48 (2.08%)	3 / 48 (6.25%)
occurrences (all)	5	1	3
EPISTAXIS			
subjects affected / exposed	2 / 11 (18.18%)	1 / 48 (2.08%)	7 / 48 (14.58%)
occurrences (all)	2	1	7
HICCUPS			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	1	1	0
NASAL CONGESTION			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	1	1	0
NASAL OEDEMA			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
OROPHARYNGEAL PAIN			

subjects affected / exposed	2 / 11 (18.18%)	1 / 48 (2.08%)	2 / 48 (4.17%)
occurrences (all)	2	2	2
PHARYNGEAL INFLAMMATION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 11 (0.00%)	4 / 48 (8.33%)	0 / 48 (0.00%)
occurrences (all)	0	4	0
CONFUSIONAL STATE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
DEPRESSION			
subjects affected / exposed	0 / 11 (0.00%)	4 / 48 (8.33%)	0 / 48 (0.00%)
occurrences (all)	0	4	0
INSOMNIA			
subjects affected / exposed	3 / 11 (27.27%)	6 / 48 (12.50%)	5 / 48 (10.42%)
occurrences (all)	4	6	5
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	0	3	2
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 11 (0.00%)	3 / 48 (6.25%)	1 / 48 (2.08%)
occurrences (all)	0	3	2
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	0	4	1
BREATH SOUNDS ABNORMAL			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
GLYCOSYLATED HAEMOGLOBIN INCREASED			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0

WEIGHT DECREASED			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences (all)	0	1	1
WEIGHT INCREASED			
subjects affected / exposed	0 / 11 (0.00%)	3 / 48 (6.25%)	1 / 48 (2.08%)
occurrences (all)	0	4	1
Injury, poisoning and procedural complications			
CONTRAST MEDIA REACTION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
EYE INJURY			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
INFUSION RELATED REACTION			
subjects affected / exposed	2 / 11 (18.18%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
PROCEDURAL PAIN			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
LACERATION			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
PROCEDURAL VOMITING			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	2 / 11 (18.18%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	1	2	2
DYSARTHRIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0

HEADACHE			
subjects affected / exposed	1 / 11 (9.09%)	6 / 48 (12.50%)	0 / 48 (0.00%)
occurrences (all)	1	6	0
LETHARGY			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	3 / 48 (6.25%)
occurrences (all)	0	4	6
NEUROPATHY PERIPHERAL			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	1	2	1
POLYNEUROPATHY			
subjects affected / exposed	2 / 11 (18.18%)	2 / 48 (4.17%)	0 / 48 (0.00%)
occurrences (all)	3	2	0
PARAESTHESIA			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	1	1	0
SOMNOLENCE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
TREMOR			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 11 (9.09%)	7 / 48 (14.58%)	2 / 48 (4.17%)
occurrences (all)	1	10	2
LEUKOPENIA			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	0	2	2
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	3 / 48 (6.25%)
occurrences (all)	1	0	3
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
HYPOACUSIS			

subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
OTORRHOEA			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
TINNITUS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
CONJUNCTIVITIS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	7 / 48 (14.58%)
occurrences (all)	1	0	8
DRY EYE			
subjects affected / exposed	2 / 11 (18.18%)	1 / 48 (2.08%)	2 / 48 (4.17%)
occurrences (all)	2	1	2
EYE IRRITATION			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences (all)	1	1	1
KERATITIS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
ABDOMINAL PAIN			
subjects affected / exposed	2 / 11 (18.18%)	7 / 48 (14.58%)	5 / 48 (10.42%)
occurrences (all)	6	10	10
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	5 / 48 (10.42%)
occurrences (all)	2	3	5
ANAL INFLAMMATION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
CHEILITIS			

subjects affected / exposed	2 / 11 (18.18%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	2	1	0
CONSTIPATION			
subjects affected / exposed	6 / 11 (54.55%)	12 / 48 (25.00%)	5 / 48 (10.42%)
occurrences (all)	8	15	7
DIARRHOEA			
subjects affected / exposed	4 / 11 (36.36%)	5 / 48 (10.42%)	8 / 48 (16.67%)
occurrences (all)	7	5	10
DRY MOUTH			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
DYSPHAGIA			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
DYSPEPSIA			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	1	2	1
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
GINGIVAL PAIN			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	1
GINGIVAL BLEEDING			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	3 / 48 (6.25%)
occurrences (all)	0	0	3
NAUSEA			
subjects affected / exposed	4 / 11 (36.36%)	8 / 48 (16.67%)	6 / 48 (12.50%)
occurrences (all)	5	16	7
STOMATITIS			
subjects affected / exposed	2 / 11 (18.18%)	1 / 48 (2.08%)	4 / 48 (8.33%)
occurrences (all)	5	1	7
PERITONEAL HAEMORRHAGE			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0

VOMITING			
subjects affected / exposed	2 / 11 (18.18%)	8 / 48 (16.67%)	3 / 48 (6.25%)
occurrences (all)	2	13	3
Hepatobiliary disorders			
HEPATIC PAIN			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
JAUNDICE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	3 / 48 (6.25%)
occurrences (all)	0	0	6
DERMATITIS			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	2 / 48 (4.17%)
occurrences (all)	1	1	7
DERMATITIS ACNEIFORM			
subjects affected / exposed	6 / 11 (54.55%)	16 / 48 (33.33%)	17 / 48 (35.42%)
occurrences (all)	34	47	47
DRY SKIN			
subjects affected / exposed	4 / 11 (36.36%)	7 / 48 (14.58%)	11 / 48 (22.92%)
occurrences (all)	16	11	16
ECZEMA			
subjects affected / exposed	2 / 11 (18.18%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
ERYTHEMA			
subjects affected / exposed	3 / 11 (27.27%)	2 / 48 (4.17%)	4 / 48 (8.33%)
occurrences (all)	8	2	4
HIRSUTISM			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	1	2	1
HYPERHIDROSIS			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
INGROWING NAIL			

subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	1
HYPERTRICHOSIS			
subjects affected / exposed	3 / 11 (27.27%)	2 / 48 (4.17%)	0 / 48 (0.00%)
occurrences (all)	6	4	0
KOILONYCHIA			
subjects affected / exposed	2 / 11 (18.18%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	4	0	0
NAIL DISORDER			
subjects affected / exposed	2 / 11 (18.18%)	0 / 48 (0.00%)	3 / 48 (6.25%)
occurrences (all)	6	0	3
PAIN OF SKIN			
subjects affected / exposed	3 / 11 (27.27%)	2 / 48 (4.17%)	0 / 48 (0.00%)
occurrences (all)	6	2	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences (all)	1	5	3
PRURITUS			
subjects affected / exposed	5 / 11 (45.45%)	12 / 48 (25.00%)	10 / 48 (20.83%)
occurrences (all)	20	18	15
RASH			
subjects affected / exposed	4 / 11 (36.36%)	24 / 48 (50.00%)	28 / 48 (58.33%)
occurrences (all)	9	47	106
SKIN FISSURES			
subjects affected / exposed	3 / 11 (27.27%)	8 / 48 (16.67%)	7 / 48 (14.58%)
occurrences (all)	9	9	12
SKIN OEDEMA			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
SKIN HYPERPIGMENTATION			
subjects affected / exposed	1 / 11 (9.09%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences (all)	2	4	1
Renal and urinary disorders			
OLIGURIA			

subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
RENAL FAILURE CHRONIC			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
RENAL IMPAIRMENT			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 11 (0.00%)	3 / 48 (6.25%)	4 / 48 (8.33%)
occurrences (all)	0	4	6
BACK PAIN			
subjects affected / exposed	2 / 11 (18.18%)	3 / 48 (6.25%)	4 / 48 (8.33%)
occurrences (all)	2	4	4
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
MUSCLE SPASMS			
subjects affected / exposed	2 / 11 (18.18%)	2 / 48 (4.17%)	3 / 48 (6.25%)
occurrences (all)	4	2	3
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 11 (0.00%)	3 / 48 (6.25%)	0 / 48 (0.00%)
occurrences (all)	0	3	0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	3 / 48 (6.25%)
occurrences (all)	0	2	4
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	1
MYOPATHY			

subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	3 / 48 (6.25%)
occurrences (all)	2	2	4
Infections and infestations			
CANDIDIASIS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	2
INFECTION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	3
PARONYCHIA			
subjects affected / exposed	4 / 11 (36.36%)	7 / 48 (14.58%)	16 / 48 (33.33%)
occurrences (all)	16	12	56
NASOPHARYNGITIS			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences (all)	0	1	1
PNEUMONIA			
subjects affected / exposed	2 / 11 (18.18%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
SKIN BACTERIAL INFECTION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
RASH PUSTULAR			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	2 / 48 (4.17%)
occurrences (all)	0	2	3
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	2 / 11 (18.18%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
VULVOVAGINAL CANDIDIASIS			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 11 (9.09%)	2 / 48 (4.17%)	2 / 48 (4.17%)
occurrences (all)	1	2	2

VULVOVAGINAL MYCOTIC INFECTION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 11 (18.18%)	8 / 48 (16.67%)	11 / 48 (22.92%)
occurrences (all)	2	11	12
DEHYDRATION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
HYPERCALCAEMIA			
subjects affected / exposed	1 / 11 (9.09%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
GLUCOSE TOLERANCE IMPAIRED			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
HYPERCREATININAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	3 / 48 (6.25%)	1 / 48 (2.08%)
occurrences (all)	0	4	2
HYPERKALAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	2 / 48 (4.17%)	0 / 48 (0.00%)
occurrences (all)	0	3	0
HYPERURICAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
HYPOCALCAEMIA			
subjects affected / exposed	3 / 11 (27.27%)	0 / 48 (0.00%)	3 / 48 (6.25%)
occurrences (all)	7	0	4
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	4 / 48 (8.33%)
occurrences (all)	0	1	5
HYPOKALAEMIA			

subjects affected / exposed	2 / 11 (18.18%)	5 / 48 (10.42%)	7 / 48 (14.58%)
occurrences (all)	2	12	8
HYPOMAGNESAEMIA			
subjects affected / exposed	2 / 11 (18.18%)	10 / 48 (20.83%)	14 / 48 (29.17%)
occurrences (all)	3	17	34
HYPONATRAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	1 / 48 (2.08%)	1 / 48 (2.08%)
occurrences (all)	0	1	1

Non-serious adverse events	Part 2: Panitumumab + Ganitumab	Part 3: Rilotumumab	Part 3: Ganitumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 46 (95.65%)	9 / 13 (69.23%)	9 / 11 (81.82%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ANOGENITAL WARTS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PYOGENIC GRANULOMA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
CAPILLARY LEAK SYNDROME			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
FLUSHING			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HYPERTENSION			
subjects affected / exposed	2 / 46 (4.35%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	3	1	1
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
ASTHENIA			

subjects affected / exposed	6 / 46 (13.04%)	0 / 13 (0.00%)	5 / 11 (45.45%)
occurrences (all)	14	0	9
CHILLS			
subjects affected / exposed	4 / 46 (8.70%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
FACE OEDEMA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
FACIAL PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
FATIGUE			
subjects affected / exposed	9 / 46 (19.57%)	1 / 13 (7.69%)	3 / 11 (27.27%)
occurrences (all)	13	1	4
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
INFLAMMATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
INFUSION SITE INFLAMMATION			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
MUCOSAL INFLAMMATION			
subjects affected / exposed	5 / 46 (10.87%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	7	0	0
LOCALISED OEDEMA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 46 (4.35%)	2 / 13 (15.38%)	0 / 11 (0.00%)
occurrences (all)	2	2	0
OEDEMA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

PYREXIA			
subjects affected / exposed	2 / 46 (4.35%)	1 / 13 (7.69%)	2 / 11 (18.18%)
occurrences (all)	2	1	2
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
HYPERSENSITIVITY			
subjects affected / exposed	1 / 46 (2.17%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Reproductive system and breast disorders			
GENITAL TRACT INFLAMMATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
DYSPNOEA			
subjects affected / exposed	3 / 46 (6.52%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	4	1	1
EPISTAXIS			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
HICCUPS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
NASAL CONGESTION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
NASAL OEDEMA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

PHARYNGEAL INFLAMMATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	2 / 46 (4.35%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	3	4	0
CONFUSIONAL STATE			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
DEPRESSION			
subjects affected / exposed	0 / 46 (0.00%)	2 / 13 (15.38%)	0 / 11 (0.00%)
occurrences (all)	0	4	0
INSOMNIA			
subjects affected / exposed	4 / 46 (8.70%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	4	1	0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
BREATH SOUNDS ABNORMAL			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
GLYCOSYLATED HAEMOGLOBIN INCREASED			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
WEIGHT DECREASED			

subjects affected / exposed	5 / 46 (10.87%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	6	1	0
WEIGHT INCREASED			
subjects affected / exposed	2 / 46 (4.35%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	3	1	0
Injury, poisoning and procedural complications			
CONTRAST MEDIA REACTION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
EYE INJURY			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
INFUSION RELATED REACTION			
subjects affected / exposed	4 / 46 (8.70%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	5	0	0
PROCEDURAL PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
LACERATION			
subjects affected / exposed	3 / 46 (6.52%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
PROCEDURAL VOMITING			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 46 (2.17%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
DYSARTHRIA			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
HEADACHE			

subjects affected / exposed	1 / 46 (2.17%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
LETHARGY			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
POLYNEUROPATHY			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
PARAESTHESIA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
SOMNOLENCE			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
TREMOR			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 46 (4.35%)	3 / 13 (23.08%)	3 / 11 (27.27%)
occurrences (all)	8	5	9
LEUKOPENIA			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 46 (6.52%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	14	0	0
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
HYPOACUSIS			

subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
OTORRHOEA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
TINNITUS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
CONJUNCTIVITIS			
subjects affected / exposed	4 / 46 (8.70%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
DRY EYE			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
EYE IRRITATION			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
KERATITIS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ABDOMINAL PAIN			
subjects affected / exposed	5 / 46 (10.87%)	1 / 13 (7.69%)	2 / 11 (18.18%)
occurrences (all)	13	4	5
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	4	0	1
ANAL INFLAMMATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
CHEILITIS			

subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
CONSTIPATION			
subjects affected / exposed	7 / 46 (15.22%)	3 / 13 (23.08%)	1 / 11 (9.09%)
occurrences (all)	13	6	1
DIARRHOEA			
subjects affected / exposed	12 / 46 (26.09%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	19	1	0
DRY MOUTH			
subjects affected / exposed	3 / 46 (6.52%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
DYSPHAGIA			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
DYSPEPSIA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 46 (2.17%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
GINGIVAL PAIN			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
GINGIVAL BLEEDING			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
NAUSEA			
subjects affected / exposed	4 / 46 (8.70%)	2 / 13 (15.38%)	2 / 11 (18.18%)
occurrences (all)	5	2	3
STOMATITIS			
subjects affected / exposed	6 / 46 (13.04%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	9	0	0
PERITONEAL HAEMORRHAGE			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

VOMITING			
subjects affected / exposed	5 / 46 (10.87%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	9	1	0
Hepatobiliary disorders			
HEPATIC PAIN			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
JAUNDICE			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	5 / 46 (10.87%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	8	0	0
DERMATITIS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
DERMATITIS ACNEIFORM			
subjects affected / exposed	13 / 46 (28.26%)	0 / 13 (0.00%)	2 / 11 (18.18%)
occurrences (all)	48	0	2
DRY SKIN			
subjects affected / exposed	10 / 46 (21.74%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	14	0	1
ECZEMA			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	5	0	0
ERYTHEMA			
subjects affected / exposed	7 / 46 (15.22%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	13	0	2
HIRSUTISM			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
INGROWING NAIL			

subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
HYPERTRICHOSIS			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
KOILONYCHIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
NAIL DISORDER			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PAIN OF SKIN			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
PRURITUS			
subjects affected / exposed	14 / 46 (30.43%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	27	0	0
RASH			
subjects affected / exposed	23 / 46 (50.00%)	3 / 13 (23.08%)	1 / 11 (9.09%)
occurrences (all)	57	3	1
SKIN FISSURES			
subjects affected / exposed	12 / 46 (26.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	31	0	0
SKIN OEDEMA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
SKIN HYPERPIGMENTATION			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
OLIGURIA			

subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
RENAL FAILURE CHRONIC			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
RENAL IMPAIRMENT			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
BACK PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	5
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
MUSCLE SPASMS			
subjects affected / exposed	4 / 46 (8.70%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	4	0	1
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
MYOPATHY			

subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 46 (2.17%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
CANDIDIASIS			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
INFECTION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PARONYCHIA			
subjects affected / exposed	10 / 46 (21.74%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	25	0	1
NASOPHARYNGITIS			
subjects affected / exposed	3 / 46 (6.52%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
PNEUMONIA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
SKIN BACTERIAL INFECTION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
RASH PUSTULAR			
subjects affected / exposed	3 / 46 (6.52%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	6	0	0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
VULVOVAGINAL CANDIDIASIS			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 46 (2.17%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	1	1	0

VULVOVAGINAL MYCOTIC INFECTION			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	9 / 46 (19.57%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	14	0	1
DEHYDRATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
HYPERCALCAEMIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
GLUCOSE TOLERANCE IMPAIRED			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
HYPERCREATININAEMIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HYPERGLYCAEMIA			
subjects affected / exposed	6 / 46 (13.04%)	1 / 13 (7.69%)	2 / 11 (18.18%)
occurrences (all)	8	3	3
HYPERKALAEMIA			
subjects affected / exposed	1 / 46 (2.17%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
HYPERURICAEMIA			
subjects affected / exposed	0 / 46 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
HYPOCALCAEMIA			
subjects affected / exposed	2 / 46 (4.35%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 46 (2.17%)	2 / 13 (15.38%)	1 / 11 (9.09%)
occurrences (all)	1	4	1
HYPOKALAEMIA			

subjects affected / exposed	5 / 46 (10.87%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	5	0	0
HYPOMAGNESAEMIA			
subjects affected / exposed	19 / 46 (41.30%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	47	0	2
HYPONATRAEMIA			
subjects affected / exposed	2 / 46 (4.35%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	2	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2010	• Added the secondary endpoint of on-treatment progression-free survival. • Clarified the inclusion criteria for wild-type KRAS tumor status. • Changed inclusion criteria for measureable lesion to also include ≥ 10 mm for spiral CT. • Added results of Part 1, specifying the determined dose of rilotumumab to be used in Parts 2 and 3. • Defined end of study as when all subjects have completed or have had the opportunity to complete the 30-day safety follow-up and 60-day follow-up visits or 2 years after the last subject is enrolled in Part 2, whichever is later. • Revised inclusion criteria for Part 3 to include hemoglobin ≥ 8 g/dL, bilirubin < 1.5 x ULN, and hypomagnesemia ≤ grade 2. • Revised inclusion criteria for Part 3 to include no history or evidence of thrombosis or vascular ischemic events with 12 months of enrollment into Part 3. • Clarified dose withholding or discontinuation procedures related to changes in ALT, AST, or thrombocytopenia. • Further explained procedures related to proscribed therapy during the study and added information on pre-emptive management of panitumumab-related skin toxicities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported