

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

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

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 08 July 2016 |
| First version publication date | 01 August 2015 |
| Version creation reason | • Correction of full data set Updates to full data set for consistency with ClinicalTrials.gov posting |

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | 20070820 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00891930 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Amgen, Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 July 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 July 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Part 1:

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

Part 2:

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

Protection of trial subjects:

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

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

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 42 |
| From 65 to 84 years | 34 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible participants were enrolled into Part 1 of the study to receive panitumumab plus irinotecan. Upon radiographically confirmed disease progression, eligible participants proceeded to Part 2 of the study to receive panitumumab plus ganitumab. A total of 100 subjects were screened, 76 subjects were enrolled in part 1 of the study.

Period 1

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

Arms

| | |
|------------------|--------------------------|
| Arm title | Panitumumab + Irinotecan |
|------------------|--------------------------|

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

| Number of subjects in period 1 | Panitumumab + Irinotecan |
|--------------------------------|--------------------------|
| Started | 76 |
| Received Treatment | 74 |
| Completed | 36 |
| Not completed | 40 |
| Consent withdrawn by subject | 1 |
| Death | 38 |
| Lost to follow-up | 1 |

Period 2

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

Arms

| | |
|------------------|-------------------------|
| Arm title | Panitumumab + Ganitumab |
|------------------|-------------------------|

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Panitumumab + Irinotecan |
|-----------------------|--------------------------|

Reporting group description:

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

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

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | Panitumumab + Irinotecan |
| Reporting group description: | |
| Subjects received panitumumab (6 mg/kg starting dose) with irinotecan (starting dose of 180 mg/m ²) every 2 weeks (Q2W). | |
| Reporting group title | Panitumumab + Ganitumab |
| Reporting group description: | |
| Subjects who responded (complete or partial response) or had stable disease in Part 1 proceeded to Part 2 of the study and received treatment with panitumumab (6 mg/kg starting dose) and ganitumab (12 mg/kg starting dose) Q2W. | |
| Subject analysis set title | Panitumumab |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Participants received panitumumab (6 mg/kg starting dose) with irinotecan (starting dose of 180 mg/m ²) every 2 weeks (Q2W) during Part 1. Upon radiographically confirmed disease progression, participants proceeded to Part 2 of the study and received treatment with panitumumab (6 mg/kg starting dose) and ganitumab (12 mg/kg starting dose) Q2W. | |

Primary: Part 1: Emergence of Mutant KRAS

| | |
|--|---|
| End point title | Part 1: Emergence of Mutant KRAS ^[1] |
| End point description: | |
| Mutation in Kirsten rat sarcoma-2 virus oncogene (KRAS) status was determined by examining KRAS exons 2, 3, and 4. The emergence of mutant KRAS was defined as a change in KRAS mutation status from wild-type at Baseline in KRAS exons 2, 3, and 4 to mutant in any of KRAS exons 2, 3, and 4 at the time of the second biopsy following the radiographic evidence of acquired resistance to panitumumab when given in combination with irinotecan. This analysis was performed in the KRAS analysis set which includes treated subjects with known KRAS status at both Baseline and at the 2nd biopsy. | |
| End point type | Primary |
| End point timeframe: | |
| From first dose of study drug until the 2nd biopsy at the time of disease progression/entry into Part 2; median duration of treatment in Part 1 was 16 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: This is a single-arm study; the EudraCT system does not accept statistics for single arm analyses. | |

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Objective Response Rate

| | |
|-----------------|--|
| End point title | Part 2: Objective Response Rate ^[3] |
|-----------------|--|

End point description:

Objective response rate (ORR) is defined as the incidence of either a confirmed complete response (CR) or partial response (PR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria during the treatment period.

This analysis was performed in the Tumor Response Evaluable Analysis Set, defined as all subjects who had radiographically confirmed disease progression on panitumumab and irinotecan in Part 1, who received at least 1 dose of panitumumab and/or ganitumab in Part 2, with at least one Baseline uni-dimensionally measurable lesion per the RECIST version 1.0 based on investigators' review.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Objective Response Rate

| | |
|-----------------|---------------------------------|
| End point title | Part 1: Objective Response Rate |
|-----------------|---------------------------------|

End point description:

Objective response rate is defined as the percentage of participants with either a confirmed complete response (CR) or partial response (PR) measured by the investigator per modified RECIST version 1.0 criteria during the treatment period.

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

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

End point timeframe:

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

| | | | | |
|----------------------------------|--------------------------|--|--|--|
| End point values | Panitumumab + Irinotecan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 74 | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 21.62 (12.89 to 32.72) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression-free Survival |
|-----------------|---------------------------|

End point description:

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

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

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

This endpoint was analyzed in the Primary Analysis Set.

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response

| | |
|---|----------------------------|
| End point title | Time to Objective Response |
| End point description: | |
| Time to objective response was defined as time from first dose of study drug to the first confirmed objective response. An objective response is defined as a confirmed complete response or partial response per modified RECIST v1.0 criteria during the treatment period. This endpoint was analyzed in the Tumor Response Evaluable Analysis Set - Part 1 and Part 2 participants with an objective response. | |
| End point type | Secondary |
| End point timeframe: | |
| From the first dose of study drug until the end of treatment in each part; median duration of treatment was 16 weeks in Part 1 and 8 weeks in Part 2. | |

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

| | |
|-----------------|----------------------|
| End point title | Duration of response |
|-----------------|----------------------|

End point description:

Duration of response is defined as the time from the first confirmed objective response to the earlier date of disease progression or death. An objective response is defined as a confirmed complete response or partial response per modified RECIST v1.0 criteria during the treatment period.

This endpoint was analyzed in the Tumor Response Evaluable Analysis Set - Part 1 and Part 2 participants with an objective response

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

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Developed Antibodies to Panitumumab

| | |
|-----------------|--|
| End point title | Number of Subjects Who Developed Antibodies to Panitumumab |
|-----------------|--|

End point description:

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

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

End point timeframe:

From first dose date to 30 days since the last dose date. The median time frame is 4.2 months for Part 1 and 2.4 months for Part 2.

| End point values | Panitumumab | | | |
|--------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 25 ^[8] | | | |
| Units: subjects | | | | |
| Binding antibody positive | 0 | | | |
| Neutralizing antibody positive | 0 | | | |

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Developed Antibodies to Ganitumab

| | |
|-----------------|--|
| End point title | Number of Subjects Who Developed Antibodies to Ganitumab |
|-----------------|--|

End point description:

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

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

End point timeframe:

From first dose of ganitumab until 30 days after last dose; median time frame was 2.4 months.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

| | |
|-----------------|--|
| End point title | Number of Subjects With Adverse Events |
|-----------------|--|

End point description:

The severity of each adverse event (AE) was graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (where 1 = Mild [aware of sign or symptom, but easily tolerated]; 2 = Moderate [discomfort enough to cause interference with usual activity]; 3 = severe [incapacitating with inability to work or do usual activity]; 4 = life-threatening; 5 = fatal), with the exception of selected skin toxicities that were graded using a modified version of CTC. Treatment-related adverse events were those events for which the investigator considered there to be a reasonable possibility that the event may have been caused by panitumumab (Part 1) and by panitumumab and/or ganitumab (Part 2). Discontinuation includes AEs leading to discontinuation of panitumumab (Part 1) and panitumumab, ganitumab (Part 2) or removal from the study.

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

End point timeframe:

From first dose date to 30 days since the last dose date in each part of the study. The median time frame is 4.2 months for Part 1 and 2.4 months for Part 2.

| End point values | Panitumumab + Irinotecan | Panitumumab + Ganitumab | | |
|--|--------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 36 | | |
| Units: subjects | | | | |
| Any adverse event (AE) | 74 | 35 | | |
| Worst grade of 3 | 43 | 17 | | |
| Worst grade of 4 | 6 | 1 | | |
| Worst grade of 5 | 6 | 2 | | |
| Worst grade of 5 excluding progressive disease | 1 | 0 | | |
| Serious adverse event (SAE) | 26 | 8 | | |
| AE leading to discontinuation | 3 | 1 | | |
| SAE leading to discontinuation | 8 | 1 | | |
| Any treatment-related adverse event (TRAE) | 70 | 33 | | |
| TRAE worst grade of 3 | 34 | 7 | | |
| TRAE worst grade of 4 | 3 | 1 | | |
| TRAE worst grade of 5 | 0 | 0 | | |
| TRAE worst grade 5 excluding progressive disease | 0 | 0 | | |
| Treatment-related SAE | 7 | 1 | | |
| TRAE leading to discontinuation | 0 | 1 | | |
| Serious TRAE leading to discontinuation | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Number of Subjects With Worst Post-baseline Grade 3 or Higher Laboratory Toxicities |
|-----------------|---|

End point description:

The severity of laboratory toxicities was graded using CTCAE v3.0.

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

End point timeframe:

From first dose date to 30 days since the last dose date in each part of the study. The median time frame is 4.2 months for Part 1 and 2.4 months for Part 2.

| End point values | Panitumumab + Irinotecan | Panitumumab + Ganitumab | | |
|-------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 36 | | |
| Units: subjects | | | | |
| Decreased absolute neutrophil count | 3 | 0 | | |
| Decreased hemoglobin | 3 | 0 | | |
| Decreased lymphocytes | 3 | 0 | | |
| Decreased total neutrophils | 2 | 0 | | |

| | | | | |
|--------------------------------------|---|---|--|--|
| Decreased white blood cells | 2 | 0 | | |
| Decreased albumin | 1 | 0 | | |
| Increased alkaline phosphatase | 5 | 2 | | |
| Increased aspartate aminotransferase | 1 | 1 | | |
| Decreased calcium | 4 | 1 | | |
| Increased creatinine | 1 | 0 | | |
| Decreased glucose | 2 | 0 | | |
| Increased glucose | 1 | 2 | | |
| Decreased magnesium | 9 | 2 | | |
| Increased magnesium | 2 | 2 | | |
| Decreased phosphorus | 2 | 1 | | |
| Decreased potassium | 7 | 0 | | |
| Increased potassium | 3 | 0 | | |
| Decreased sodium | 7 | 0 | | |
| Increased total bilirubin | 3 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose date to 30 days since the last dose date in each part of the study. The median time frame is 4.2 months for Part 1 and 2.4 months for Part 2.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Part2: Panitumumab + Ganitumab |
|-----------------------|--------------------------------|

Reporting group description:

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

| | |
|-----------------------|---------------------------------|
| Reporting group title | Part1: Panitumumab + Irinotecan |
|-----------------------|---------------------------------|

Reporting group description:

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

| Serious adverse events | Part2: Panitumumab + Ganitumab | Part1: Panitumumab + Irinotecan | |
|---|--------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 36 (22.22%) | 26 / 74 (35.14%) | |
| number of deaths (all causes) | 2 | 6 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colorectal cancer | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 74 (1.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 74 (1.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |

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

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

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

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

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

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 74 (1.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 74 (1.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 74 (1.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 74 (1.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

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

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

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

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

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 2 / 36 (5.56%) | 6 / 74 (8.11%) | |
| occurrences (all) | 2 | 6 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 4 / 74 (5.41%) | |
| occurrences (all) | 0 | 6 | |
| Nausea | | | |
| subjects affected / exposed | 10 / 36 (27.78%) | 38 / 74 (51.35%) | |
| occurrences (all) | 14 | 91 | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 5 / 74 (6.76%) | |
| occurrences (all) | 2 | 11 | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 28 / 74 (37.84%) | |
| occurrences (all) | 7 | 49 | |
| Hepatobiliary disorders | | | |
| Hepatic pain | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 74 (2.70%) | |
| occurrences (all) | 2 | 3 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 10 / 74 (13.51%) | |
| occurrences (all) | 4 | 25 | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 23 / 74 (31.08%) | |
| occurrences (all) | 1 | 38 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 8 / 74 (10.81%) | |
| occurrences (all) | 3 | 21 | |
| Dry skin | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 24 / 74 (32.43%) | |
| occurrences (all) | 6 | 42 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 5 / 74 (6.76%) | |
| occurrences (all) | 1 | 9 | |
| Eczema | | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 01 October 2009 | <ul style="list-style-type: none">- Inclusion criteria were updated to allow the use of other experienced laboratories to confirm wild-type KRAS tumor status of archival tumor tissue using a validated test method per local regulatory guidelines, in addition to Amgen approved central laboratory.- Screening procedures were updated to include various methods of obtaining KRAS tumor status determination by an Amgen approved central laboratory or an experienced laboratory (local laboratory) per local regulatory guidelines using a validated test method.- Inclusion/exclusion criteria, dose adjustment, and discontinuation criteria were updated based on new requirements for ganitumab.- The section on long-term follow-up was updated to include the procedure for assessment of anti-panitumumab and antiganitumab antibodies.- Reporting procedures for all adverse events were updated with specific timelines to report any adverse event.- The version of Response Evaluation Criteria in Solid Tumors (RECIST) utilized in this study was updated to 1.0.- The drug storage and handling information for panitumumab and ganitumab was updated in the pharmacy guide. |
| 27 May 2011 | <ul style="list-style-type: none">- To address a potential risk of formation of particles in vials of ganitumab that has been exposed to temperatures < - 30°C, a requirement was added to use an in-line, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron filter when administering ganitumab.- Reporting procedures for all adverse events were updated to clarify the reporting procedures for non-serious adverse events. Additionally, serious adverse event reporting procedures were updated to include reporting methods other than fax, eg, electronic reporting.- Secondary endpoints were updated in line with the statistical analysis plan. |
| 14 November 2012 | <ul style="list-style-type: none">- The duration of the long term follow-up for survival was shortened and the primary analysis and final analysis were combined into a single analysis because the majority of enrolled subjects (75 out of the 76 [99%]) had already ended the study treatment and safety follow-up, and it was expected that at least 66 out of the 76 enrolled subjects [87%] would end the long term follow-up and the study due to death by the time of the analysis data cut-off date.- The period of long term follow-up for survival was modified to end approximately 2 years (\pm 2 months) after the last subject is enrolled in part 1.- The definition of the end of study for a subject was updated to include the date the subject completes the 30-day safety follow-up visit.- The criterion for end of study was revised to include flexibility of \pm 2 months at 2 years after the last subject is enrolled in part 1.- A new section was added to limit data collection from subjects who remained on treatment after all planned study analyses were completed to investigational product administration and serious adverse event reporting through 30 days after the last dose of study treatment.- The serious adverse event reporting timeline was changed from 1 working day to 24 hours.- A new section was added on pregnancy and lactation reporting procedures.- The timing of the final analysis was updated to occur after a minimum potential follow-up of 2 years (\pm 2 months) after the last subject is enrolled in part 1.- Pregnancy Notification Worksheet was updated and the Lactation Notification Worksheet was included. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported