# Clinical trial results:
# A Randomized, Open-Label, Controlled, Phase II Trial of Combination Chemotherapy with or without Panitumumab as First-line Treatment of Subjects with Metastatic or Recurrent Head and Neck Cancer, and Cross-over Second-line Panitumumab Monotherapy of Subjects who Fail the Combination Chemotherapy Only Arm

## Summary

| | |
|---|---|
| EudraCT number | 2007-005722-79 |
| Trial protocol | CZ FR SK ES AT LT BE |
| Global end of trial date | 06 March 2014 |

**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 | 20050236 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00454779 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 11 June 2012 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 06 March 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To estimate the effect of panitumumab on progression-free survival based on investigators' tumor response assessments when added to combination chemotherapy in the first-line treatment of metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN).

Protection of trial subjects:

This study was conducted in accordance with applicable FDA and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 29 January 2007 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 24 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 10 |
| Country: Number of subjects enrolled | Belgium: 16 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Lithuania: 1 |
| Country: Number of subjects enrolled | Slovakia: 2 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | United States: 68 |
| Worldwide total number of subjects | 113 |
| EEA total number of subjects | 45 |

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) | 88 |
| From 65 to 84 years | 25 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled from 29 January 2007 to 1 September 2010.

### Pre-assignment

Screening details:

A total of 148 subjects were screened; 113 subjects were randomized to first-line treatment (56 in the panitumumab plus chemotherapy arm and 57 in the chemotherapy alone arm) and 35 were considered screen failures.

### Period 1

| | |
|---|---|
| Period 1 title | First-line Treatment Phase |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Panitumumab + Chemotherapy |

Arm description:

During the first-line treatment phase, subjects received panitumumab 9 mg/kg as an intravenous infusion before docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles.
Subjects who had complete response, partial response, or stable disease and completed 6 cycles of first-line treatment and those subjects who discontinued chemotherapy for intolerability prior to progression remained on first-line panitumumab monotherapy until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first.

| | |
|---|---|
| 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:

Panitumumab 9 mg/kg was administered intravenously over 1 hour every 21 ± 3 days.

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

Dosage and administration details:

Docetaxel 75 mg/m² was administered by continuous intravenous infusion over 1 hour on day 1 of each cycle.

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

Dosage and administration details:

Cisplatin 75 mg/m² was infused after docetaxel infusion over 1 hour ± 15 minutes on day 1 of each cycle.

| | |
|---|---|
| **Arm title** | Chemotherapy Alone |

Arm description:

During the first-line treatment phase, subjects received docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel 75 mg/m² was administered by continuous intravenous infusion over 1 hour on day 1 of each cycle.

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

Dosage and administration details:

Cisplatin 75 mg/m² was infused after docetaxel infusion over 1 hour ± 15 minutes on day 1 of each cycle.

| **Number of subjects in period 1** | Panitumumab + Chemotherapy | Chemotherapy Alone |
|---|---|---|
| Started | 56 | 57 |
| Received Study Medication | 56 | 55 |
| Completed | 51 | 49 |
| Not completed | 5 | 8 |
| Consent withdrawn by subject | 2 | 4 |
| Ongoing | 1 | - |
| Ended follow-up prior to analysis | 1 | 1 |
| Lost to follow-up | 1 | - |
| Lack of efficacy | - | 2 |
| Protocol deviation | - | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | Second-line Treatment Phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| **Arm title** | Panitumumab Monotherapy |
|---|---|

Arm description:

Eligible subjects in the chemotherapy alone arm who were determined to have disease progression before or after completing 6 cycles of chemotherapy in first-line treatment received second-line panitumumab monotherapy in cycles repeated every 21 days until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first.

| Arm type | Crossover |
|---|---|
| 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:

Panitumumab 9 mg/kg was administered intravenously over 1 hour every 21 ± 3 days.

| **Number of subjects in period 2[1]** | Panitumumab Monotherapy |
|---|---|
| Started | 30 |
| Completed | 27 |
| Not completed | 3 |
| Consent withdrawn by subject | 1 |
| Ongoing | 1 |
| Ended follow-up prior to analysis | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only eligible subjects in the chemotherapy alone arm who were determined to have disease progression before or after completing 6 cycles of chemotherapy in first-line treatment received second-line panitumumab monotherapy.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Panitumumab + Chemotherapy |
| Reporting group description: | |
| During the first-line treatment phase, subjects received panitumumab 9 mg/kg as an intravenous infusion before docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles.<br>Subjects who had complete response, partial response, or stable disease and completed 6 cycles of first-line treatment and those subjects who discontinued chemotherapy for intolerability prior to progression remained on first-line panitumumab monotherapy until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first. | |
| Reporting group title | Chemotherapy Alone |
| Reporting group description: | |
| During the first-line treatment phase, subjects received docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles. | |

| Reporting group values | Panitumumab + Chemotherapy | Chemotherapy Alone | Total |
|---|---|---|---|
| Number of subjects | 56 | 57 | 113 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 58.2 | 58.9 | |
| standard deviation | ± 8.6 | ± 7.4 | - |
| Gender, Male/Female<br>Units: Participants | | | |
| Female | 9 | 5 | 14 |
| Male | 47 | 52 | 99 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status | | | |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction;<br>Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house or office work;<br>Grade 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours;<br>Grade 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours;<br>Grade 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair;<br>Grade 5: Dead. | | | |
| Units: Subjects | | | |
| ECOG Performance Status: 0 | 21 | 20 | 41 |
| ECOG Performance Status: 1 | 35 | 37 | 72 |
| Disease Status<br>Units: Subjects | | | |
| newly diagnosed/previously untreated | 8 | 7 | 15 |
| Recurrent | 48 | 50 | 98 |

## End points

### End points reporting groups

| Reporting group title | Panitumumab + Chemotherapy |
|---|---|

Reporting group description:

During the first-line treatment phase, subjects received panitumumab 9 mg/kg as an intravenous infusion before docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles.
Subjects who had complete response, partial response, or stable disease and completed 6 cycles of first-line treatment and those subjects who discontinued chemotherapy for intolerability prior to progression remained on first-line panitumumab monotherapy until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first.

| Reporting group title | Chemotherapy Alone |
|---|---|

Reporting group description:

During the first-line treatment phase, subjects received docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles.

| Reporting group title | Panitumumab Monotherapy |
|---|---|

Reporting group description:

Eligible subjects in the chemotherapy alone arm who were determined to have disease progression before or after completing 6 cycles of chemotherapy in first-line treatment received second-line panitumumab monotherapy in cycles repeated every 21 days until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first.

### Primary: Progression Free Survival (PFS) During the First-line Treatment Phase

| End point title | Progression Free Survival (PFS) During the First-line Treatment Phase |
|---|---|

End point description:

The time from the date of randomization to the date of first disease progression determined by the investigators per a modified version of the Response Evaluation Criteria in Solid Tumors (RECIST v1.0) guidelines, or death within 60 days after the last evaluable tumor assessment or randomization date (whichever is later) during the first-line treatment phase. Subjects not meeting the criteria by the cutoff date were censored at the last evaluable tumor assessment during the first-line treatment phase.
This analysis was performed in the Primary Analysis Set: all randomized subjects < 70 years of age who provided informed consent and received at least 1 dose of first-line treatment.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 67 months

| End point values | Panitumumab + Chemotherapy | Chemotherapy Alone | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 51 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.9 (4.7 to 8.3) | 5.5 (4.1 to 6.8) | | |

### Statistical analyses

| Statistical analysis title | Primary Analysis |
|---|---|

Statistical analysis description:

The primary analysis reflects the Cox proportional hazards model stratified by the interactive voice response system (IVRS) randomization factors: ECOG performance score (0 vs. 1) and disease status (newly diagnosed/previously untreated vs. recurrent).
The hazard ratio is presented as panitumumab plus chemotherapy:chemotherapy alone. A value < 1.0 indicates a lower average event rate and longer time to event for panitumumab plus chemotherapy relative to chemotherapy alone.

| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
|---|---|
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | = 0.051 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.629 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.395 |
| upper limit | 1.002 |

Notes:

[1] - A formal hypothesis was not tested in this trial. This study provided an estimate and corresponding 2-sided 95% confidence interval (CI) of the relative efficacy of panitumumab plus combination chemotherapy vs combination chemotherapy only as measured by the PFS hazard ratio for combination chemotherapy with panitumumab relative to combination chemotherapy only in the first-line treatment of metastatic or recurrent SCCHN.

| Statistical analysis title | Secondary Analysis |
|---|---|

Statistical analysis description:

The secondary analysis reflects a log-rank test stratified by IVRS randomization factors: ECOG performance score (0 vs. 1) and disease status (newly diagnosed/previously untreated vs. recurrent).

| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
|---|---|
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.048 |
| Method | Logrank |

## Secondary: Overall Objective Response Rate (ORR) During the First-line Treatment Phase

| End point title | Overall Objective Response Rate (ORR) During the First-line Treatment Phase |
|---|---|

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by the investigator using magnetic resonance imaging (MRI): Complete Response (CR), the disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter (SLD) of target lesions from Baseline; An objective response is defined as a best tumor response of CR or PR. An overall objective response of CR or PR must be confirmed at least 4 weeks after the criteria for response are first met. ORR is the percentage of subjects with an overall objective response among the analysis population.
This analysis was performed in the Evaluable for Local Tumor Response Analysis Set: subset of subjects in the Primary Analysis Set with at least one unidimensionally measurable lesion at Baseline using a modified RECIST v1.0 per investigators' review.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 67 months

| **End point values** | Panitumumab + Chemotherapy | Chemotherapy Alone | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 51 | | |
| Units: Percentage of Participants | | | | |
| arithmetic mean (confidence interval 95%) | 44.23 (30.73 to 57.73) | 37.25 (23.99 to 50.52) | | |

## Statistical analyses

| **Statistical analysis title** | Weighted Difference in Rates |
|---|---|

Statistical analysis description:

The difference in rates and confidence intervals are calculated using the Mantel-Haenszel weights within strata defined by IVRS randomization factors: ECOG performance score (0 vs. 1) and disease status (newly diagnosed/previously untreated vs recurrent).

| | |
|---|---|
| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 6.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.67 |
| upper limit | 24.12 |

| **Statistical analysis title** | Treatment Odds Ratio |
|---|---|

Statistical analysis description:

The odds ratio is defined as the odds of having an objective response in the panitumumab plus chemotherapy arm relative to the odds in the chemotherapy alone arm. It is calculated from a logistic regression model with treatment indicator and randomization factors (recorded on the case report form [CRF]) as covariates: ECOG performance status (0 vs. 1/2) and disease status (newly diagnosed/previously untreated vs previously treated).

| | |
|---|---|
| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.37 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 3.33 |

## Secondary: Rate of Disease Control (RDC) During the First-line Treatment Phase

| End point title | Rate of Disease Control (RDC) During the First-line Treatment Phase |
|---|---|

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI: Complete Response (CR), the disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter (SLD) of target lesions from baseline; Disease Progression (PD), >=20% increase in the SLD of target lesions from nadir; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. An overall response of CR or PR must be confirmed at least 4 weeks after the criteria for response are first met. A best overall response of SD requires a visit response of SD or better no earlier than 35 days after randomization. RDC is the percentage of subjects with a best overall response of CR, PR or SD among the analysis population (Evaluable for Local Tumor Response Analysis Set).

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 67 months

| End point values | Panitumumab + Chemotherapy | Chemotherapy Alone | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 51 | | |
| Units: Percentage of Participants | | | | |
| arithmetic mean (confidence interval 95%) | 80.77 (70.06 to 91.48) | 72.55 (60.3 to 84.8) | | |

### Statistical analyses

| Statistical analysis title | Treatment Odds Ratio |
|---|---|

Statistical analysis description:

The odds ratio is defined as the odds of having an objective response in the panitumumab plus chemotherapy arm relative to the odds in the chemotherapy alone arm. It is calculated from a logistic regression model with treatment indicator and randomization factors (recorded on the case report form) as covariates: ECOG performance status (0 vs. 1/2) and disease status (newly diagnosed/previously untreated vs. previously treated).

| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 5.26 |

| **Statistical analysis title** | Weighted Difference in Rates |
|---|---|

Statistical analysis description:

The difference in rates and confidence intervals are calculated using the Mantel-Haenszel weights within strata defined by randomization factors recorded in the IVRS: ECOG performance score (0 vs. 1) and disease status (newly diagnosed/previously untreated vs. recurrent).

| | |
|---|---|
| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 7.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.29 |
| upper limit | 23.85 |

## Secondary: Duration of Response (DOR) During the First-line Treatment Phase

| | |
|---|---|
| End point title | Duration of Response (DOR) During the First-line Treatment Phase |

End point description:

Calculated only for the subset of subjects with an overall response of CR or PR while on first-line treatment (subsequently confirmed at least 4 weeks thereafter) assessed by the investigator, and defined as the time from the first CR or PR to the first observed disease progression according to a modified RECIST v1.0. Subjects not meeting the criteria for progression by the analysis data cutoff date were censored at their last evaluable disease assessment date. Analyzed in the Evaluable for Local Tumor Response Analysis Set; Subjects With Objective Responses.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 67 months

| End point values | Panitumumab + Chemotherapy | Chemotherapy Alone | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 19 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8 (5.7 to 11.1) | 5.1 (4.4 to 7.2) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response (TTR) During the First-line Treatment Phase

| End point title | Time to Response (TTR) During the First-line Treatment Phase |
|---|---|

End point description:

Time from the date of randomization to the first CR or PR during first line treatment phase (subsequently confirmed at least 4 weeks thereafter), analyzed in the Evaluable for Local Tumor Response Analysis Set; Subjects With Objective Responses.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 67 months

| End point values | Panitumumab + Chemotherapy | Chemotherapy Alone | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 19 | | |
| Units: Weeks | | | | |
| arithmetic mean (standard deviation) | 8.8 (± 3.9) | 10.6 (± 6.1) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS) For the First-line Treatment

| End point title | Overall Survival (OS) For the First-line Treatment |
|---|---|

End point description:

Time from the date of randomization to the date of death during the entire study, analyzed in the Primary Analysis Set.

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

End point timeframe:

Until death, up to 67 months

| End point values | Panitumumab + Chemotherapy | Chemotherapy Alone | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 51 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 12.9 (9.4 to 18.5) | 13.8 (11.8 to 22.9) | | |

**Statistical analyses**

| Statistical analysis title | Primary Analysis |
|---|---|

Statistical analysis description:

The primary analysis reflects the Cox proportional hazards model stratified by IVRS randomization factors: ECOG performance score (0 vs. 1) and disease status (newly diagnosed/previously untreated vs. recurrent).
Hazard ratio is presented as panitumumab plus chemotherapy:chemotherapy alone. A value < 1.0 indicates a lower average event rate and longer time to event for panitumumab plus chemotherapy relative to chemotherapy alone.

| | |
|---|---|
| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.663 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.103 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.709 |
| upper limit | 1.717 |

| Statistical analysis title | Secondary Analysis |
|---|---|

Statistical analysis description:

The secondary analysis reflects a log-rank test stratified by IVRS randomization factors: ECOG performance score (0 vs. 1) and disease status (newly diagnosed/previously untreated vs. recurrent).

| | |
|---|---|
| Comparison groups | Panitumumab + Chemotherapy v Chemotherapy Alone |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.666 |
| Method | Logrank |

**Secondary: Progression Free Survival (PFS) During the Second-line Treatment Phase**

| End point title | Progression Free Survival (PFS) During the Second-line |
|---|---|

| | |
|---|---|
| | Treatment Phase |

End point description:

The time from the first dose of panitumumab monotherapy to the date of first disease progression determined by the investigator per modified RECIST v1.0, or death within 60 days after the last evaluable tumor assessment or the second-line first dose date (whichever is later) during the second-line treatment phase. Subjects not meeting the criteria by the cutoff date were censored at the last evaluable tumor assessment during the second-line treatment phase.
This endpoint was analyzed in the Evaluable Subset for Second-line Panitumumab Monotherapy: subjects who were randomized to docetaxel and cisplatin chemotherapy alone treatment for their first-line treatments and treated subsequently with at least 1 dose of panitumumab monotherapy.

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

End point timeframe:

From the first dose of panitumumab monotherapy, every 6 weeks until disease progression or death, up to 57 months

| **End point values** | Panitumumab Monotherapy | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.2 (1.5 to 7.6) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Objective Response Rate (ORR) During the Second-line Treatment Phase

| End point title | Overall Objective Response Rate (ORR) During the Second-line Treatment Phase |
|---|---|

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by the investigator using MRI: Complete Response (CR), the disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter (SLD) of target lesions from baseline; Overall Response (OR) = CR + PR. An overall response of CR or PR must be confirmed at least 4 weeks after the criteria for response are first met. ORR is the percentage of subjects with an overall objective response among the Evaluable for Local Tumor Response Analysis Set for Second-line Panitumumab Monotherapy population.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 57 months

| End point values | Panitumumab Monotherapy | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: Percentage of Participants | | | | |
| arithmetic mean (confidence interval 95%) | 13.33 (1.17 to 25.5) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR) During the Second-line Treatment Phase

| End point title | Duration of Response (DOR) During the Second-line Treatment Phase |
|---|---|

End point description:

Time from the first CR or PR in the second-line treatment phase to the first observed disease progression by a modified RECIST v1.0 per Investigator assessment. Subjects not meeting the criteria for progression by the analysis data cutoff date were censored at their last evaluable disease assessment date. Analyzed in the Evaluable for Local Tumor Response Analysis Set for Second-line Panitumumab Monotherapy: Subjects With Objective Responses. "99999" indicates values not estimable due to the low number of events.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 57 months

| End point values | Panitumumab Monotherapy | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (5.1 to 99999) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of Disease Control (RDC) During the Second-line Treatment Phase

| End point title | Rate of Disease Control (RDC) During the Second-line Treatment Phase |
|---|---|

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI: Complete Response (CR), the disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter (SLD) of target lesions from Baseline; Disease Progression (PD), >=20% increase in the SLD of target lesions from nadir; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. An overall response of CR or PR must be confirmed at least 4 weeks after the criteria for response are first met. A best overall response of SD requires a visit response of SD or better no earlier than 35 days after the first dose date

in second-line treatment. RDC is the percentage of subjects with a best overall response of CR, PR or SD among the Evaluable for Local Tumor Response Analysis Set for Second-line Panitumumab Monotherapy population.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 57 months

| **End point values** | Panitumumab Monotherapy | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: Percentage of Participants | | | | |
| arithmetic mean (confidence interval 95%) | 53.33 (35.48 to 71.19) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response (TTR) During the Second-line Treatment Phase

| End point title | Time to Response (TTR) During the Second-line Treatment Phase |
|---|---|

End point description:

Time from the first dose of panitumumab monotherapy to the first CR or PR during second-line treatment phase (subsequently confirmed at least 4 weeks thereafter) analyzed in the Evaluable for Local Tumor Response Analysis Set for Second-line Panitumumab Monotherapy: Subjects With Objective Responses.

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

End point timeframe:

Every 6 weeks until disease progression or death, up to 57 months

| **End point values** | Panitumumab Monotherapy | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: Weeks | | | | |
| arithmetic mean (standard deviation) | 10.6 (± 5.6) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS) for Second-line Treatment

| End point title | Overall Survival (OS) for Second-line Treatment |
|---|---|

End point description:

Time from the first dose of panitumumab monotherapy to the date of death during the second-line treatment phase, analyzed in the Evaluable Subset for Second-line Panitumumab Monotherapy population.

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

End point timeframe:

Until death, up to 57 months

| **End point values** | Panitumumab Monotherapy | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.5 (6.5 to 13.2) | | | |

## 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 4.5, 4.4 and 3.7 months by treatment group respectively.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | First-line: Panitumumab Plus Chemotherapy |

Reporting group description:

During the first-line treatment phase, subjects received panitumumab 9 mg/kg as an intravenous infusion before docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles.

| | |
|---|---|
| Reporting group title | First-line: Chemotherapy Alone |

Reporting group description:

During the first-line treatment phase, subjects received docetaxel 75 mg/m² and cisplatin 75 mg/m² combination chemotherapy in cycles repeated every 21 days for a maximum of 6 cycles.

| | |
|---|---|
| Reporting group title | Second-line: Panitumumab Monotherapy |

Reporting group description:

Eligible subjects in the chemotherapy alone arm who were determined to have disease progression before or after completing 6 cycles of chemotherapy in first-line treatment received second-line panitumumab monotherapy in cycles repeated every 21 days until disease progression, unacceptable toxicities, withdrawal of consent, or death, whichever occurred first.

| **Serious adverse events** | First-line: Panitumumab Plus Chemotherapy | First-line: Chemotherapy Alone | Second-line: Panitumumab Monotherapy |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 34 / 56 (60.71%) | 27 / 55 (49.09%) | 10 / 30 (33.33%) |
| number of deaths (all causes) | 9 | 3 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| HEAD AND NECK CANCER | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MALIGNANT ASCITES | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |

| | | | |
|---|---|---|---|
| NEOPLASM MALIGNANT | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| NEOPLASM PROGRESSION | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| TUMOUR HAEMORRHAGE | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| TUMOUR ULCERATION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 | | | |
| ARTERIAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| HYPOTENSION | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |

| | | | |
|---|---|---|---|
| CHILLS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| DEVICE DISLOCATION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| LOCALISED OEDEMA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| MALAISE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| PYREXIA | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 4 / 55 (7.27%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| ASPIRATION | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| DYSPNOEA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| HYPOXIA | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| PNEUMONIA ASPIRATION | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| Investigations | | | |
| BLOOD CREATINE INCREASED | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| HEPATIC ENZYME INCREASED | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| INTERNATIONAL NORMALISED RATIO INCREASED | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| TRANSAMINASES INCREASED | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| Injury, poisoning and procedural complications | | | |
| ARTERIAL INJURY | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| FEEDING TUBE COMPLICATION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| POST PROCEDURAL DISCHARGE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| POST PROCEDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| STERNAL FRACTURE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| Cardiac disorders | | | |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| ARTERIOSCLEROSIS CORONARY ARTERY | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| CARDIAC FAILURE CONGESTIVE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| Nervous system disorders | | | |
| ATAXIA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| CONVULSION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIZZINESS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PRESYNCOPE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEBRILE NEUTROPENIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 56 (5.36%) | 4 / 55 (7.27%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABDOMINAL WALL DISORDER | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| APHAGIA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| APHTHOUS STOMATITIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| CONSTIPATION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| DIARRHOEA | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 2 / 55 (3.64%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 8 / 9 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DUODENAL ULCER PERFORATION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| DYSPHAGIA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMATEMESIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| ILEUS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| NAUSEA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 56 (3.57%) | 4 / 55 (7.27%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OESOPHAGEAL STENOSIS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ORAL CAVITY FISTULA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| TONGUE HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOMITING | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 4 / 55 (7.27%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| HEPATIC FAILURE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| ACNE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| ACUTE PRERENAL FAILURE | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| RENAL FAILURE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RENAL FAILURE ACUTE | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| RHABDOMYOLYSIS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 | | | |
| ABDOMINAL ABSCESS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| BETA HAEMOLYTIC STREPTOCOCCAL INFECTION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CELLULITIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| CLOSTRIDIUM DIFFICILE COLITIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| FUNGAEMIA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| ORAL INFECTION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| OSTEOMYELITIS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 | 4 / 56 (7.14%) | 6 / 55 (10.91%) | 3 / 30 (10.00%) |
| occurrences causally related to treatment / all | 3 / 5 | 4 / 6 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA STAPHYLOCOCCAL | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| PSEUDOMONAL SEPSIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| PSEUDOMONAS INFECTION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| SEPSIS | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| STAPHYLOCOCCAL INFECTION | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 55 (3.64%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| STAPHYLOCOCCAL SEPSIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| STENOTROPHOMONAS INFECTION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| UROSEPSIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| WOUND INFECTION | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| DEHYDRATION | | | |
| subjects affected / exposed | 8 / 56 (14.29%) | 2 / 55 (3.64%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 6 / 10 | 2 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ELECTROLYTE IMBALANCE | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FAILURE TO THRIVE | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERNATRAEMIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 0 / 30 (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 |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 0 / 30 (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 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 55 (3.64%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MALNUTRITION | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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** | First-line: Panitumumab Plus Chemotherapy | First-line: Chemotherapy Alone | Second-line: Panitumumab Monotherapy |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 54 / 56 (96.43%) | 53 / 55 (96.36%) | 26 / 30 (86.67%) |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 2 / 55 (3.64%) | 0 / 30 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |

| | | | |
|---|---|---|---|
| HYPOTENSION | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 2 / 55 (3.64%) | 2 / 30 (6.67%) |
| occurrences (all) | 6 | 3 | 2 |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 13 / 56 (23.21%) | 5 / 55 (9.09%) | 3 / 30 (10.00%) |
| occurrences (all) | 25 | 6 | 4 |
| CHILLS | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 3 / 55 (5.45%) | 2 / 30 (6.67%) |
| occurrences (all) | 6 | 3 | 2 |
| FACE OEDEMA | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 55 (1.82%) | 1 / 30 (3.33%) |
| occurrences (all) | 5 | 1 | 1 |
| LOCALISED OEDEMA | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 1 | 2 |
| FATIGUE | | | |
| subjects affected / exposed | 28 / 56 (50.00%) | 28 / 55 (50.91%) | 5 / 30 (16.67%) |
| occurrences (all) | 50 | 43 | 5 |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 15 / 56 (26.79%) | 7 / 55 (12.73%) | 1 / 30 (3.33%) |
| occurrences (all) | 24 | 7 | 2 |
| OEDEMA | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 10 / 55 (18.18%) | 2 / 30 (6.67%) |
| occurrences (all) | 4 | 12 | 2 |
| PAIN | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 55 (1.82%) | 1 / 30 (3.33%) |
| occurrences (all) | 4 | 1 | 1 |
| PYREXIA | | | |
| subjects affected / exposed | 8 / 56 (14.29%) | 8 / 55 (14.55%) | 3 / 30 (10.00%) |
| occurrences (all) | 12 | 8 | 3 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| COUGH | | | |
| subjects affected / exposed | 8 / 56 (14.29%) | 5 / 55 (9.09%) | 3 / 30 (10.00%) |
| occurrences (all) | 10 | 8 | 3 |
| DYSPNOEA | | | |
| subjects affected / exposed | 11 / 56 (19.64%) | 9 / 55 (16.36%) | 2 / 30 (6.67%) |
| occurrences (all) | 14 | 10 | 2 |
| EPISTAXIS | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 2 / 55 (3.64%) | 1 / 30 (3.33%) |
| occurrences (all) | 7 | 2 | 1 |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| HICCUPS | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 6 / 55 (10.91%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 6 | 0 |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 4 / 55 (7.27%) | 2 / 30 (6.67%) |
| occurrences (all) | 7 | 4 | 4 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| PRODUCTIVE COUGH | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 55 (3.64%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 2 | 2 |
| RHINORRHOEA | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Psychiatric disorders | | | |
| ANXIETY | | | |
| subjects affected / exposed | 8 / 56 (14.29%) | 6 / 55 (10.91%) | 3 / 30 (10.00%) |
| occurrences (all) | 10 | 7 | 4 |
| DEPRESSION | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 4 / 55 (7.27%) | 0 / 30 (0.00%) |
| occurrences (all) | 7 | 4 | 0 |
| INSOMNIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 56 (8.93%) | 4 / 55 (7.27%) | 1 / 30 (3.33%) |
| occurrences (all) | 7 | 4 | 1 |
| Investigations | | | |
| HAEMOGLOBIN DECREASED | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 13 / 56 (23.21%) | 11 / 55 (20.00%) | 6 / 30 (20.00%) |
| occurrences (all) | 21 | 12 | 7 |
| Injury, poisoning and procedural complications | | | |
| LACERATION | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 13 / 56 (23.21%) | 7 / 55 (12.73%) | 4 / 30 (13.33%) |
| occurrences (all) | 17 | 8 | 5 |
| DYSGEUSIA | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 6 / 55 (10.91%) | 1 / 30 (3.33%) |
| occurrences (all) | 11 | 6 | 1 |
| HEADACHE | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 8 / 55 (14.55%) | 2 / 30 (6.67%) |
| occurrences (all) | 5 | 9 | 2 |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 9 / 56 (16.07%) | 11 / 55 (20.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 15 | 15 | 1 |
| PARAESTHESIA | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 5 / 55 (9.09%) | 2 / 30 (6.67%) |
| occurrences (all) | 2 | 6 | 3 |
| POLYNEUROPATHY | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 55 (1.82%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 1 | 2 |
| SOMNOLENCE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| SYNCOPE | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| TREMOR | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 22 / 56 (39.29%) | 27 / 55 (49.09%) | 7 / 30 (23.33%) |
| occurrences (all) | 58 | 87 | 7 |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| LEUKOPENIA | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 5 / 55 (9.09%) | 0 / 30 (0.00%) |
| occurrences (all) | 8 | 9 | 0 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 9 / 56 (16.07%) | 9 / 55 (16.36%) | 1 / 30 (3.33%) |
| occurrences (all) | 13 | 16 | 1 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 5 / 55 (9.09%) | 1 / 30 (3.33%) |
| occurrences (all) | 8 | 14 | 1 |
| Ear and labyrinth disorders | | | |
| TINNITUS | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 4 / 55 (7.27%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 5 | 2 |
| VERTIGO | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 4 / 55 (7.27%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 4 | 1 |
| Eye disorders | | | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 8 / 56 (14.29%) | 0 / 55 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 13 | 0 | 2 |
| DRY EYE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 0 | 2 |
| LACRIMATION INCREASED | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 4 / 55 (7.27%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 7 | 6 | 0 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 3 / 55 (5.45%) | 1 / 30 (3.33%) |
| occurrences (all) | 2 | 3 | 1 |
| CONSTIPATION | | | |
| subjects affected / exposed | 15 / 56 (26.79%) | 9 / 55 (16.36%) | 3 / 30 (10.00%) |
| occurrences (all) | 19 | 11 | 3 |
| DIARRHOEA | | | |
| subjects affected / exposed | 25 / 56 (44.64%) | 16 / 55 (29.09%) | 5 / 30 (16.67%) |
| occurrences (all) | 51 | 20 | 5 |
| DRY MOUTH | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 3 / 55 (5.45%) | 2 / 30 (6.67%) |
| occurrences (all) | 2 | 3 | 2 |
| DYSPEPSIA | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 6 / 55 (10.91%) | 1 / 30 (3.33%) |
| occurrences (all) | 4 | 6 | 1 |
| DYSPHAGIA | | | |
| subjects affected / exposed | 9 / 56 (16.07%) | 4 / 55 (7.27%) | 5 / 30 (16.67%) |
| occurrences (all) | 11 | 4 | 6 |
| MOUTH ULCERATION | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| NAUSEA | | | |
| subjects affected / exposed | 34 / 56 (60.71%) | 33 / 55 (60.00%) | 4 / 30 (13.33%) |
| occurrences (all) | 60 | 45 | 4 |
| RECTAL HAEMORRHAGE | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

| | | | |
|---|---|---|---|
| STOMATITIS | | | |
| subjects affected / exposed | 9 / 56 (16.07%) | 3 / 55 (5.45%) | 1 / 30 (3.33%) |
| occurrences (all) | 12 | 4 | 1 |
| VOMITING | | | |
| subjects affected / exposed | 15 / 56 (26.79%) | 18 / 55 (32.73%) | 2 / 30 (6.67%) |
| occurrences (all) | 28 | 26 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| ACNE | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 0 / 55 (0.00%) | 3 / 30 (10.00%) |
| occurrences (all) | 23 | 0 | 4 |
| ALOPECIA | | | |
| subjects affected / exposed | 18 / 56 (32.14%) | 14 / 55 (25.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 22 | 18 | 0 |
| DECUBITUS ULCER | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 3 | 0 | 1 |
| DERMATITIS | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 0 / 55 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 4 | 0 | 1 |
| DERMATITIS ACNEIFORM | | | |
| subjects affected / exposed | 13 / 56 (23.21%) | 0 / 55 (0.00%) | 3 / 30 (10.00%) |
| occurrences (all) | 33 | 0 | 4 |
| DRY SKIN | | | |
| subjects affected / exposed | 13 / 56 (23.21%) | 3 / 55 (5.45%) | 10 / 30 (33.33%) |
| occurrences (all) | 16 | 3 | 10 |
| ERYTHEMA | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 11 | 0 | 0 |
| NAIL DISORDER | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 2 / 55 (3.64%) | 1 / 30 (3.33%) |
| occurrences (all) | 21 | 3 | 1 |
| PRURITUS | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 3 / 55 (5.45%) | 4 / 30 (13.33%) |
| occurrences (all) | 6 | 3 | 4 |
| RASH | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 21 / 56 (37.50%) | 2 / 55 (3.64%) | 13 / 30 (43.33%) |
| occurrences (all) | 42 | 2 | 24 |
| SKIN EXFOLIATION | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| SKIN FISSURES | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 55 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Renal and urinary disorders | | | |
| NOCTURIA | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 5 | 0 | 2 |
| BACK PAIN | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 2 / 55 (3.64%) | 1 / 30 (3.33%) |
| occurrences (all) | 5 | 2 | 1 |
| BONE PAIN | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 2 | 0 | 2 |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| NECK PAIN | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 0 / 55 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 4 | 0 | 3 |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 55 (1.82%) | 1 / 30 (3.33%) |
| occurrences (all) | 6 | 1 | 1 |
| PAIN IN JAW | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 56 (5.36%) | 4 / 55 (7.27%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 1 / 55 (1.82%) | 1 / 30 (3.33%) |
| occurrences (all) | 3 | 1 | 1 |
| CANDIDIASIS | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 2 / 55 (3.64%) | 1 / 30 (3.33%) |
| occurrences (all) | 3 | 3 | 1 |
| CELLULITIS | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 55 (1.82%) | 2 / 30 (6.67%) |
| occurrences (all) | 2 | 1 | 2 |
| PARONYCHIA | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 55 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 3 | 0 | 2 |
| PNEUMONIA | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| CACHEXIA | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 55 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 20 / 56 (35.71%) | 10 / 55 (18.18%) | 4 / 30 (13.33%) |
| occurrences (all) | 26 | 12 | 4 |
| DEHYDRATION | | | |
| subjects affected / exposed | 11 / 56 (19.64%) | 3 / 55 (5.45%) | 3 / 30 (10.00%) |
| occurrences (all) | 12 | 3 | 3 |
| HYPOALBUMINAEMIA | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 55 (1.82%) | 0 / 30 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| HYPOCALCAEMIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 56 (12.50%) | 4 / 55 (7.27%) | 1 / 30 (3.33%) |
| occurrences (all) | 13 | 17 | 1 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 17 / 56 (30.36%) | 6 / 55 (10.91%) | 0 / 30 (0.00%) |
| occurrences (all) | 29 | 12 | 0 |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 23 / 56 (41.07%) | 13 / 55 (23.64%) | 5 / 30 (16.67%) |
| occurrences (all) | 84 | 21 | 17 |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 3 / 55 (5.45%) | 0 / 30 (0.00%) |
| occurrences (all) | 8 | 5 | 0 |
| HYPOPHOSPHATAEMIA | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 3 / 55 (5.45%) | 2 / 30 (6.67%) |
| occurrences (all) | 4 | 3 | 2 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 December 2007 | - Added global language from protocol template and increased enrollment period to allow for EU expansion<br>- Incorporated information from the EXTREME trial into the background and sample size calculation section. This change resulted in a reduction of the sample size from 150 to 110.<br>- Added a requirement for first-cycle G-CSF prophylaxis.<br>- Inclusion and exclusion criteria were modified to minimize identified burdens to enrollment and to be consistent with other internal/external head and neck trials. |
| 10 August 2009 | - Subjects ≥ 70 years of age were excluded. This is based on an observation that prior to Amendment 2, more deaths that occurred within 60 days of last protocol treatment arm occurred among older subjects (50% of deaths within 60 days of the last protocol-defined treatment among 13% of randomized subjects across arms).<br>- A mid cycle (day 11 visit) was added to check subjects' vital signs, key laboratory values, and to document adverse events<br>- The entry criterion for creatinine clearance was increased to ≥ 60 mL/min<br>- Added an additional safety data review once each additional group of 10 randomized subjects all had the opportunity to complete 2 cycles of treatment. |
| 11 January 2012 | - Revised the definition of PFS to "the time from the date of randomization to the date of first disease progression determined by the investigators per modified RECIST v1.0, or death within 60 days after the last evaluable tumor assessment or randomization date (whichever was later) during the first-line treatment phase." Subjects not meeting the criteria by the cutoff date are censored at the last evaluable tumor assessment date during the first-line treatment.<br>- Used the investigators' assessment of response to determine the primary endpoint of PFS because the target 80 PFS events based on response assessment by the independent central review group may not be attained at the time of data cut-off of the PFS analysis.<br>- Consolidated the timing the primary and final analyses into a single analysis approximately 24 months after the last subject was randomized. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported