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. 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 Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	58.2	58.9	
standard deviation	± 8.6	± 7.4	-
Gender, Male/Female 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; 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; 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; Grade 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Grade 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; Grade 5: Dead.			
Units: Subjects			
ECOG Performance Status: 0	21	20	41
ECOG Performance Status: 1	35	37	72
Disease Status 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 - 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. - Added a requirement for first-cycle G-CSF prophylaxis. - 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). - A mid cycle (day 11 visit) was added to check subjects' vital signs, key laboratory values, and to document adverse events - The entry criterion for creatinine clearance was increased to ≥ 60 mL/min - 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. - 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. - 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