Clinical trial results:
A Randomized, Multicenter, Open-label, Phase 3 Study to Compare the Efficacy and Safety of Panitumumab and Cetuximab in Subjects with Previously Treated, Wild-type KRAS, Metastatic Colorectal Cancer

Summary

EudraCT number	2009-010715-32
Trial protocol	LV FR LT CZ SE BE SK IT NL GB BG
Global end of trial date	03 March 2017

Results information

Result version number	v1 (current)
This version publication date	03 March 2018
First version publication date	03 March 2018

Trial information

Trial identification

Sponsor protocol code	20080763

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01001377
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	18 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the effect of panitumumab versus cetuximab on overall survival (OS) for chemorefractory metastatic colorectal cancer (mCRC) among patients with wild-type Kirsten rat Sarcoma-2 virus (KRAS) tumors.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The protocol and amendment were reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB)at each center.
The investigator or a designee was to obtain written informed consent from all subjects or legally acceptable representatives after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures were conducted or investigational products were administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2010
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	Australia: 105
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Sweden: 29
Country: Number of subjects enrolled	United Kingdom: 82
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	China: 100
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Hong Kong: 23
Country: Number of subjects enrolled	India: 50
Country: Number of subjects enrolled	Israel: 3

Country: Number of subjects enrolled	Korea, Republic of: 210
Country: Number of subjects enrolled	Latvia: 13
Country: Number of subjects enrolled	Lithuania: 24
Country: Number of subjects enrolled	Malaysia: 21
Country: Number of subjects enrolled	Peru: 11
Country: Number of subjects enrolled	Philippines: 8
Country: Number of subjects enrolled	Poland: 64
Country: Number of subjects enrolled	Russian Federation: 80
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	South Africa: 23
Country: Number of subjects enrolled	Taiwan: 25
Worldwide total number of subjects	1010
EEA total number of subjects	312

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)	657
From 65 to 84 years	350
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A total of 1010 subjects with wild-type KRAS exon 2 mCRC were randomized into the global protocol from 133 study centers in 27 countries between 02 February 2010 and 19 July 2012.

Pre-assignment

Screening details:

Enrollment was stratified by geographic region (North America, Western Europe, and Australia versus the rest of the world) and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) and randomized in a 1:1 ratio to receive either intravenous (IV) panitumumab or IV cetuximab.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cetuximab

Arm description:

Cetuximab 400 mg/m² as an initial dose, followed by 250 mg/m² intravenously (IV) every 7 days until disease progression, intolerability, withdrawal of consent, or death.

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

Dosage and administration details:

Cetuximab was administered by IV infusion on day 1 of each 7-day cycle. The initial loading dose of cetuximab was 400 mg/m². All subsequent doses were 250 mg/m².

Arm title	Panitumumab

Arm description:

Panitumumab 6 mg/kg IV every 14 days until disease progression, intolerability, withdrawal of consent, or death.

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

Dosage and administration details:

Panitumumab was administered by IV infusion at a dose of 6 mg/kg on day 1 of every 14-day cycle.

Number of subjects in period 1	Cetuximab	Panitumumab
Started	504	506
Received Treatment	500	499
Completed	0	2
Not completed	504	504
Consent withdrawn by subject	19	20
Administrative decision	14	15
Death	454	448
Lost to follow-up	15	21
Ineligibility determined	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Cetuximab
Reporting group description:	
Cetuximab 400 mg/m² as an initial dose, followed by 250 mg/m² intravenously (IV) every 7 days until disease progression, intolerability, withdrawal of consent, or death.	
Reporting group title	Panitumumab
Reporting group description:	
Panitumumab 6 mg/kg IV every 14 days until disease progression, intolerability, withdrawal of consent, or death.	

Reporting group values	Cetuximab	Panitumumab	Total
Number of subjects	504	506	1010
Age Categorical Units: Subjects			
< 65 years	319	338	657
≥ 65 years	185	168	353
Age Continuous Units: years			
arithmetic mean	60.2	59.6	
standard deviation	± 11.2	± 10.9	-
Gender Categorical Units: Subjects			
Female	183	187	370
Male	321	319	640
Race Units: Subjects			
Asian	230	225	455
Black or African American	4	2	6
Hispanic or Latino	7	6	13
Japanese	0	1	1
Other	3	2	5
White or Caucasian	260	270	530
Geographic Region Units: Subjects			
North America, Western Europe and Australia	158	158	316
Rest of the world	346	348	694
Eastern Cooperative Oncology Group (ECOG) performance status			
0 = Fully active, able to carry on all pre-disease performance without restriction. 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework or office work. 2 = Ambulatory and capable of all self-care but unable to carry out any work. activities. Up and about > 50% of waking hours. 3 = Capable of only limited self-care, confined to a bed or chair > 50% of waking hours. 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. 5 = Dead.			
Units: Subjects			
Grade 0	165	155	320
Grade 1	299	309	608

Grade 2	40	42	82

End points

End points reporting groups

Reporting group title	Cetuximab
Reporting group description:	
Cetuximab 400 mg/m² as an initial dose, followed by 250 mg/m² intravenously (IV) every 7 days until disease progression, intolerability, withdrawal of consent, or death.	
Reporting group title	Panitumumab
Reporting group description:	
Panitumumab 6 mg/kg IV every 14 days until disease progression, intolerability, withdrawal of consent, or death.	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival (OS) is the time from the date of randomization until the date of death. Participants who had not died by the analysis data cut-off date were censored at their last contact date. The analysis was conducted using the primary analysis set, which included all participants who were randomized and who received at least 1 dose of panitumumab or cetuximab; analyzed according to randomized treatment arm.	
End point type	Primary
End point timeframe:	
From randomization until the final analysis data cut-off date of 18 July 2014. Median time on study was 41 weeks, maximum time on study was 214 weeks.	

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	500	499		
Units: months				
median (confidence interval 95%)	9.9 (9.0 to 10.8)	10.2 (9.4 to 11.4)		

Statistical analyses

Statistical analysis title	Primary Analysis of Overall Survival
Statistical analysis description:	
The hazard ratio and its corresponding 95% CI were estimated from a Cox proportional hazards model stratified by the randomization factors (geographic region [North America, western Europe and Australia vs rest of world] and ECOG performance status [0 or 1 vs 2]). The hazard ratio is presented as panitumumab : cetuximab. A value < 1.0 indicates a lower average event rate and longer time to event for panitumumab relative to cetuximab.	
Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0002
Method	Asymptotic standard normal test
Parameter estimate	Cox proportional hazard
Point estimate	0.938
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.823
upper limit	1.071

Notes:

[1] - A synthesis approach with an asymptotic standard normal test statistic based on the logarithm of the hazard ratio was used to test the hypothesis that panitumumab is noninferior to cetuximab for OS (ie, that panitumumab retains at least 50% of the OS benefit of cetuximab relative to BSC). The OS noninferiority hypothesis based on an asymptotic normal score was tested at a 1-sided 2.5% significance level. A value < -1.96 indicates non-inferiority at a significance level of 1-sided 0.025.

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression free survival (PFS) is the time from the date of randomization to the date of disease progression per the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 or death. Participants alive and not meeting criteria for progression by the analysis data cut-off date were censored at their last evaluable disease assessment date.
Progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study based on all target lesions recorded since the treatment started (the sum must also demonstrate an absolute increase of at least 5 mm), or unequivocal progression of existing non-target lesions, or any new lesions.
The analysis was conducted using the primary analysis set.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 18 July 2014. Median time on study was 41 weeks, maximum time on study was 214 weeks.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	500	499		
Units: months				
median (confidence interval 95%)	4.4 (3.2 to 4.8)	4.2 (3.2 to 4.8)		

Statistical analyses

Statistical analysis title	Analysis of Progression-Free Survival

Statistical analysis description:

The hazard ratio and its corresponding 95% CI were estimated from a Cox proportional hazards model stratified by the randomization factors (geographic region [North America, western Europe and Australia vs rest of world] and ECOG performance status [0 or 1 vs 2]).
The hazard ratio is presented as panitumumab : cetuximab. A value < 1.0 indicates a lower average event rate and longer time to event for panitumumab relative to cetuximab.

Comparison groups	Cetuximab v Panitumumab
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.867
upper limit	1.117

Secondary: Objective Response

End point title	Objective Response

End point description:

Assessments are based on the investigator's review of scans using modified RECIST v1.1. Objective response is defined as either a complete response (CR) or partial response (PR). Participants who did not meet the criteria for an objective response by the analysis cut-off date were considered non-responders.
CR: Disappearance of all target and non-target lesions, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm, and no new lesions.
PR: Disappearance of all target lesions, persistence of one or more non-target lesions not qualifying for either CR or progressive disease, or, at least a 30% decrease in the size of target lesions with no unequivocal progression of existing non-target lesions and no new lesions.
Objective response was analyzed using the tumor response analysis set, which includes participants in the primary analysis set with at least 1 baseline unidimensionally measurable lesion per RECIST version 1.1.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 18 July 2014. Median time on study was 41 weeks, maximum time on study was 214 weeks.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	486		
Units: percentage of participants				
number (confidence interval 95%)	19.79 (16.34 to 23.62)	22.02 (18.41 to 25.97)		

Statistical analyses

Statistical analysis title	Analysis of Objective Response

Statistical analysis description:

The common treatment odds ratio stratified by geographic region (North America, western Europe and Australia vs rest of world) and ECOG performance status (0 or 1 vs 2).
The odds ratio is defined as the odds of having an objective response (CR or PR) in the panitumumab arm relative to the odds in the cetuximab arm.

Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	971
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.58

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR), calculated only for those participants with an objective response, is the time from first objective response to disease progression per the RECIST v1.1 or death. Participants not meeting criteria for progression or who died by the analysis data cutoff date were censored at their last evaluable disease assessment date.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 18 July 2014. Median time on study was 41 weeks, maximum time on study was 214 weeks.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	107		
Units: months				
median (confidence interval 95%)	5.4 (3.9 to 5.5)	3.8 (3.7 to 4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response (TTR), calculated for those participants with an objective response, is defined as the time from the randomization date to the date of first objective response.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 18 July 2014. Median time on study was 41 weeks, maximum time on study was 214 weeks.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	107		
Units: months				
median (inter-quartile range (Q1-Q3))	2.56 (1.23 to 3.07)	1.48 (1.18 to 3.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure

End point description:

Time to treatment failure (TTF) is the time from the randomization date to the date that the decision was made to end the treatment period for any reason; participants who remained in the treatment period at the time of analysis were censored at the date of the last on-study assessment.
The analysis was conducted using the primary analysis set.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 18 July 2014. Median time on study was 41 weeks, maximum time on study was 214 weeks.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	500	499		
Units: months				
median (confidence interval 95%)	3.3 (3.2 to 3.9)	3.4 (3.2 to 4.6)		

Statistical analyses

Statistical analysis title	Analysis of Time to Treatment Failure

Statistical analysis description:

The hazard ratio and its corresponding 95% CI were estimated from a Cox proportional hazards model stratified by the randomization factors (geographic region [North America, western Europe and Australia vs rest of world] and ECOG performance status [0 or 1 vs 2]).
The hazard ratio is presented as panitumumab : cetuximab. A value < 1.0 indicates a lower average event rate and longer time to event for panitumumab relative to cetuximab.

Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	0.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.867
upper limit	1.113

Secondary: Change From Baseline in EuroQOL 5 Dimension (EQ-5D) Health State Index Score

End point title	Change From Baseline in EuroQOL 5 Dimension (EQ-5D) Health State Index Score

End point description:

The EQ-5D is a generic measure of health outcome. The health state index measures 5 health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, using 3 levels of response to reflect degree of problems: no problem (1), some problem (2) and extreme problems (3). The health states for each respondent are converted into a single index number using a specified set of weights. Resulting scores can range from 1.0 and –0.594. A higher score indicates a more preferred health status with 1.0 representing perfect health and 0 representing death. Negative scores are possible and represent health states regarded as less preferable than death (0).
The analysis was conducted using the patient reported outcomes (PRO) analysis set, which included all participants in the primary analysis set who had a baseline and at least one follow-up PRO assessment prior to clinical or objective disease progression per RECIST v1.1. Participants with available data are included.

End point type	Secondary

End point timeframe:

From Study Day 1 through the last day of treatment or disease progression, up to Week 85.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	143		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-0.0341 (-0.0806 to 0.0123)	-0.0216 (-0.0691 to 0.0260)		

Statistical analyses

Statistical analysis title	Analysis of EQ-5D Health State Index Score

Statistical analysis description:

Repeated measures mixed model includes treatment, geographic region, ECOG score, assessment week, and treatment by assessment week interaction as fixed effects, and subjects a random effect. An unstructured covariance matrix is used in the mixed model.
A positive difference between the treatment groups favors the panitumumab group.

Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	0.0126
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0353
upper limit	0.0605

Secondary: Change From Baseline in EuroQOL 5 Dimension (EQ-5D) Visual Analog Scale (VAS)

End point title	Change From Baseline in EuroQOL 5 Dimension (EQ-5D) Visual Analog Scale (VAS)

End point description:

The EQ-5D is a standardized instrument for use as a generic measure of health outcome. The VAS asks respondents to rate their present health status on a scale from 0 to 100, with 0 labeled as "Worst imaginable health state" and 100 labeled as "Best imaginable health state." The VAS score is determined by observing the point at which the participant's hand drawn line intersects the scale.
The analysis was conducted using the patient reported outcomes (PRO) analysis set with available data.

End point type	Secondary

End point timeframe:

From Study Day 1 through the last day of treatment or disease progression, up to Week 85.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	142		
Units: scores on a scale				
least squares mean (confidence interval 95%)	3.9782 (0.8842 to 7.0722)	2.3037 (-0.8532 to 5.4605)		

Statistical analyses

Statistical analysis title	Analysis of EQ-5D Visual Analog Scale

Statistical analysis description:

Repeated measures mixed model includes treatment, geographic region, ECOG score, assessment week, and treatment by assessment week interaction as fixed effects, and subjects a random effect. An unstructured covariance matrix is used in the mixed model. A positive difference between the treatment groups favors the panitumumab group.

Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-1.6745
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9331
upper limit	1.5841

Secondary: Change From Baseline in National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Colorectal Symptom Index (NCCN FCSI) Symptoms Score

End point title	Change From Baseline in National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Colorectal Symptom Index (NCCN FCSI) Symptoms Score

End point description:

The FCSI consists of 9 questions comprising the most important symptoms associated with colorectal cancer, including energy, pain, weight, diarrhea, nausea, swelling or cramps in the stomach area, appetite, ability to enjoy life, and overall quality of life. The 9 questions are combined in three algorithms to provide information for 3 domains: colorectal cancer symptoms, physical well-being, and functional well-being. Each of the 9 items are scored from "0" to "4" representing "Not at All" through to "Very Much True". The raw score for all items is transformed to a 0-100 scale, and the average for each of the 3 subscales is calculated; high scores illustrate an improved state (e.g. able to enjoy life more). The analysis was conducted using the patient reported outcomes (PRO) analysis set with available data.

End point type	Secondary

End point timeframe:

From Study Day 1 through the last day of treatment or disease progression, up to Week 85.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	142		
Units: scores on a scale				
least squares mean (confidence interval 95%)	2.0101 (-1.1477 to 5.1679)	3.0473 (-0.1782 to 6.2728)		

Statistical analyses

Statistical analysis title	Analysis of NCCN FCSI Symptoms Score

Statistical analysis description:

Repeated measures mixed model includes treatment, geographic region, ECOG score, assessment week, and treatment by assessment week interaction as fixed effects, and subjects a random effect. An unstructured covariance matrix is used in the mixed model. A positive difference between the treatment groups favors the panitumumab group.

Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	1.0372
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3267
upper limit	4.401

Secondary: Change From Baseline in NCCN FCSI Physical Well-being Scale Score

End point title	Change From Baseline in NCCN FCSI Physical Well-being Scale Score

End point description:

The FCSI consists of 9 questions comprising the most important symptoms associated with colorectal cancer, including energy, pain, weight, diarrhea, nausea, swelling or cramps in the stomach area, appetite, ability to enjoy life, and overall quality of life. The 9 questions are combined in three algorithms to provide information for 3 domains: colorectal cancer symptoms, physical well-being, and functional well-being. Each of the 9 items are scored from "0" to "4" representing "Not at All" through to "Very Much True". The raw score for all items is transformed to a 0-100 scale, and the average for each of the 3 subscales is calculated; high scores illustrate an improved state (e.g. able to enjoy life more). The analysis was conducted using the patient reported outcomes (PRO) analysis set with available data.

End point type	Secondary

End point timeframe:

From Study Day 1 through the last day of treatment or disease progression, up to Week 85.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	142		
Units: scores on a scale				
least squares mean (confidence interval 95%)	1.8778 (-1.5524 to 5.3080)	2.4614 (-1.0442 to 5.9670)		

Statistical analyses

Statistical analysis title	Analysis of NCCN FCSI Physical Well-being Scale

Statistical analysis description:

Repeated measures mixed model includes treatment, geographic region, ECOG score, assessment week, and treatment by assessment week interaction as fixed effects, and subjects a random effect. An unstructured covariance matrix is used in the mixed model.
A positive difference between the treatment groups favors the panitumumab group.

Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	0.5836
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.0269
upper limit	4.1941

Secondary: Change From Baseline in NCCN FCSI Functional Well-being Scale Score

End point title	Change From Baseline in NCCN FCSI Functional Well-being Scale Score

End point description:

The FCSI consists of 9 questions comprising the most important symptoms associated with colorectal cancer, including energy, pain, weight, diarrhea, nausea, swelling or cramps in the stomach area, appetite, ability to enjoy life, and overall quality of life. The 9 questions are combined in three algorithms to provide information for 3 domains: colorectal cancer symptoms, physical well-being, and functional well-being. Each of the 9 items are scored from "0" to "4" representing "Not at All" through to "Very Much True". The raw score for all items is transformed to a 0-100 scale, and the average for each of the 3 subscales is calculated; high scores illustrate an improved state (e.g. able to enjoy life more). The analysis was conducted using the patient reported outcomes (PRO) analysis set with available data.

End point type	Secondary

End point timeframe:

From Study Day 1 through the last day of treatment or disease progression, up to Week 85.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	143		
Units: scores on a scale				
least squares mean (confidence interval 95%)	1.3567 (-4.1564 to 6.8697)	1.1569 (-4.4887 to 6.8025)		

Statistical analyses

Statistical analysis title	Anlaysis of NCCN FCSI Functional Well-being Scale

Statistical analysis description:

Repeated measures mixed model includes treatment, geographic region, ECOG score, assessment week, and treatment by assessment week interaction as fixed effects, and subjects a random effect. An unstructured covariance matrix is used in the mixed model.
A positive difference between the treatment groups favors the panitumumab group.

Comparison groups	Cetuximab v Panitumumab

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-0.1998
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.0093
upper limit	5.6098

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

End point description:

Serious adverse events include any event that is fatal, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other significant medical hazard. Treatment-related AEs are those the investigator considered as a reasonable possibility to have been caused by study drug.
The safety analysis set included all randomized participants who received at least 1 dose of study medication. Five participants who received the incorrect study medication (4 assigned to panitumumab but received cetuximab and 1 assigned to cetuximab but received panitumumab) were included in different treatment arms for safety analyses.

End point type	Secondary

End point timeframe:

From the day of the first dose of study therapy through 30 days after the last dose. Median duration of treatment was 14 weeks.

End point values	Cetuximab	Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	503	496		
Units: participants				
Any adverse event (AE)	494	487		
Serious adverse events	171	151		
AEs leading to discontinuation of study drug	62	69		
Treatment-related adverse events (TRAE)	459	438		
Treatment-related serious adverse events	22	24		
TRAEs leading to discontinuation of study drug	15	14		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day of the first dose of study therapy through 30 days after the last dose. Median duration of treatment was 14 weeks.

Adverse event reporting additional description:

The safety analysis set included all randomized participants who received at least 1 dose of study medication. Five participants who received the incorrect study medication (4 assigned to panitumumab but received cetuximab and 1 assigned to cetuximab but received panitumumab) were included in different treatment arms for safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Cetuximab

Reporting group description:

Cetuximab 400 mg/m² as an initial dose, followed by 250 mg/m² intravenously (IV) every 7 days until disease progression, intolerability, withdrawal of consent, or death.

Reporting group title	Panitumumab

Reporting group description:

Panitumumab 6 mg/kg IV every 14 days until disease progression, intolerability, withdrawal of consent, or death.

Serious adverse events	Cetuximab	Panitumumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	171 / 503 (34.00%)	151 / 496 (30.44%)	
number of deaths (all causes)	50	29	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon cancer			
subjects affected / exposed	4 / 503 (0.80%)	5 / 496 (1.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 4	0 / 5	
Colon cancer metastatic			

subjects affected / exposed	6 / 503 (1.19%)	4 / 496 (0.81%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 6	0 / 4	
Colorectal cancer			
subjects affected / exposed	10 / 503 (1.99%)	6 / 496 (1.21%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 9	0 / 4	
Colorectal cancer metastatic			
subjects affected / exposed	14 / 503 (2.78%)	7 / 496 (1.41%)	
occurrences causally related to treatment / all	0 / 14	0 / 7	
deaths causally related to treatment / all	0 / 12	0 / 7	
Infected neoplasm			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	2 / 503 (0.40%)	4 / 496 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour thrombosis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Artery dissection			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophorectomy bilateral			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 503 (0.80%)	6 / 496 (1.21%)	
occurrences causally related to treatment / all	0 / 4	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest discomfort			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 503 (0.80%)	4 / 496 (0.81%)	
occurrences causally related to treatment / all	2 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 503 (0.40%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 503 (0.40%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 503 (1.59%)	3 / 496 (0.60%)	
occurrences causally related to treatment / all	1 / 10	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	3 / 503 (0.60%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 503 (0.40%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema genital			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	7 / 503 (1.39%)	3 / 496 (0.60%)	
occurrences causally related to treatment / all	1 / 8	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 503 (0.60%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Productive cough			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 503 (0.60%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	2 / 503 (0.40%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood uric acid increased			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell count decreased			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			

subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 503 (0.60%)	6 / 496 (1.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 503 (0.80%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal mass			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	13 / 503 (2.58%)	10 / 496 (2.02%)	
occurrences causally related to treatment / all	2 / 14	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 503 (0.40%)	3 / 496 (0.60%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	5 / 503 (0.99%)	5 / 496 (1.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 503 (0.60%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 503 (1.59%)	6 / 496 (1.21%)	
occurrences causally related to treatment / all	1 / 8	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			

subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	5 / 503 (0.99%)	5 / 496 (1.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal infarction			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	9 / 503 (1.79%)	13 / 496 (2.62%)	
occurrences causally related to treatment / all	0 / 9	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestinal obstruction			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 503 (0.99%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obturator hernia			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal adhesions			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal tenesmus			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	3 / 503 (0.60%)	4 / 496 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	5 / 503 (0.99%)	12 / 496 (2.42%)	
occurrences causally related to treatment / all	1 / 5	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	2 / 503 (0.40%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 503 (0.40%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	4 / 503 (0.80%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic lesion			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			

subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	4 / 503 (0.80%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 503 (0.00%)	3 / 496 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	3 / 503 (0.60%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice extrahepatic obstructive			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder dilatation			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			

subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 503 (0.40%)	4 / 496 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Renal failure chronic			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 503 (0.40%)	4 / 496 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			

subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			

subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 503 (0.20%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 503 (0.40%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Nail infection			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Paronychia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 503 (1.39%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	1 / 9	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			

subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 503 (0.20%)	5 / 496 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Septic shock			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder abscess			

subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 503 (1.39%)	9 / 496 (1.81%)	
occurrences causally related to treatment / all	2 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 503 (0.60%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	1 / 503 (0.20%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 503 (0.00%)	4 / 496 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 503 (0.20%)	0 / 496 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 503 (0.00%)	1 / 496 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 503 (0.20%)	3 / 496 (0.60%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 503 (0.00%)	2 / 496 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cetuximab	Panitumumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	475 / 503 (94.43%)	462 / 496 (93.15%)	
Investigations			
Weight decreased			
subjects affected / exposed	21 / 503 (4.17%)	26 / 496 (5.24%)	
occurrences (all)	25	31	
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 503 (7.16%)	17 / 496 (3.43%)	
occurrences (all)	48	18	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 503 (6.16%)	30 / 496 (6.05%)	
occurrences (all)	39	55	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 503 (9.15%)	32 / 496 (6.45%)	
occurrences (all)	55	44	
Fatigue			
subjects affected / exposed	86 / 503 (17.10%)	72 / 496 (14.52%)	
occurrences (all)	130	97	
Oedema peripheral			
subjects affected / exposed	35 / 503 (6.96%)	20 / 496 (4.03%)	
occurrences (all)	47	22	
Pyrexia			
subjects affected / exposed	53 / 503 (10.54%)	28 / 496 (5.65%)	
occurrences (all)	74	34	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	74 / 503 (14.71%)	54 / 496 (10.89%)	
occurrences (all)	103	79	
Constipation			

subjects affected / exposed	72 / 503 (14.31%)	39 / 496 (7.86%)	
occurrences (all)	88	45	
Diarrhoea			
subjects affected / exposed	87 / 503 (17.30%)	89 / 496 (17.94%)	
occurrences (all)	129	158	
Dyspepsia			
subjects affected / exposed	27 / 503 (5.37%)	19 / 496 (3.83%)	
occurrences (all)	31	19	
Nausea			
subjects affected / exposed	57 / 503 (11.33%)	66 / 496 (13.31%)	
occurrences (all)	77	91	
Stomatitis			
subjects affected / exposed	34 / 503 (6.76%)	26 / 496 (5.24%)	
occurrences (all)	42	41	
Vomiting			
subjects affected / exposed	50 / 503 (9.94%)	49 / 496 (9.88%)	
occurrences (all)	65	71	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	40 / 503 (7.95%)	40 / 496 (8.06%)	
occurrences (all)	46	49	
Dyspnoea			
subjects affected / exposed	33 / 503 (6.56%)	21 / 496 (4.23%)	
occurrences (all)	44	24	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	69 / 503 (13.72%)	52 / 496 (10.48%)	
occurrences (all)	137	98	
Dermatitis acneiform			
subjects affected / exposed	136 / 503 (27.04%)	140 / 496 (28.23%)	
occurrences (all)	274	250	
Dry skin			
subjects affected / exposed	79 / 503 (15.71%)	83 / 496 (16.73%)	
occurrences (all)	95	119	
Nail disorder			

subjects affected / exposed	31 / 503 (6.16%)	26 / 496 (5.24%)	
occurrences (all)	50	38	
Pruritus			
subjects affected / exposed	89 / 503 (17.69%)	83 / 496 (16.73%)	
occurrences (all)	124	129	
Rash			
subjects affected / exposed	257 / 503 (51.09%)	249 / 496 (50.20%)	
occurrences (all)	530	494	
Skin fissures			
subjects affected / exposed	43 / 503 (8.55%)	42 / 496 (8.47%)	
occurrences (all)	55	66	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	47 / 503 (9.34%)	27 / 496 (5.44%)	
occurrences (all)	57	31	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	37 / 503 (7.36%)	35 / 496 (7.06%)	
occurrences (all)	50	44	
Infections and infestations			
Paronychia			
subjects affected / exposed	75 / 503 (14.91%)	58 / 496 (11.69%)	
occurrences (all)	150	116	
Upper respiratory tract infection			
subjects affected / exposed	28 / 503 (5.57%)	14 / 496 (2.82%)	
occurrences (all)	37	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	77 / 503 (15.31%)	70 / 496 (14.11%)	
occurrences (all)	102	84	
Hypocalcaemia			
subjects affected / exposed	17 / 503 (3.38%)	26 / 496 (5.24%)	
occurrences (all)	28	43	
Hypokalaemia			
subjects affected / exposed	23 / 503 (4.57%)	41 / 496 (8.27%)	
occurrences (all)	44	57	

Hypomagnesaemia subjects affected / exposed occurrences (all)	91 / 503 (18.09%) 184	135 / 496 (27.22%) 310	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2012	- clarified that crossover was not permitted on study while a subject was receiving study treatment - clarified that subjects were to be treated until disease progression, intolerability, withdrawal of consent, or death and were to be followed for survival until death, full withdrawal of consent, or end of the long term follow-up period - included definitions of primary completion (the time when the last subject was assessed or received an intervention for the purposes of final collection of data for the primary endpoint of OS) and end of study (the time when the last subject was assessed or received an intervention for evaluation in the study [eg, during follow-up]) - clarified rules for missed doses and dose withholding clarified that Amgen could do additional testing on samples collected (blood or tumor tissue) in the study for any of the tests outlined in the protocol, for any tests necessary to minimize risks to study subjects, and for other exploratory research (if consent was provided). - clarified that sites were allowed to conduct a search of public records, such as those establishing survival status, to obtain survival data for any subject for whom survival status was not known at time of data cutoff for the primary and/or final analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported