Clinical trial results:
A Randomized, Multicenter, Open-Label Phase 3 Study of Pemetrexed-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Pemetrexed-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2009-012574-12
Trial protocol	AT BE HU PT DE ES GR SK IT FR GB
Global end of trial date	23 December 2020

Results information

Result version number	v1 (current)
This version publication date	28 December 2021
First version publication date	28 December 2021

Trial information

Trial identification

Sponsor protocol code	I4X-IE-JFCB

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00982111
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 13908

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	23 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The research study is testing the investigational drug necitumumab in the treatment of advanced non-small cell lung cancer. The aim of this study is to determine if necitumumab, given together with a standard chemotherapy combination consisting of cisplatin and pemetrexed will be more effective in improving participant disease than the standard chemotherapy combination alone.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Romania: 52
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 67
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Brazil: 72
Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Australia: 14

Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 159
Country: Number of subjects enrolled	Croatia: 2
Worldwide total number of subjects	633
EEA total number of subjects	485

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)	416
From 65 to 84 years	216
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

Completers included participants who died from any cause and participants who were alive and on study at conclusion however were off treatment.

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	Necitumumab + Pemetrexed + Cisplatin

Arm description:

Necitumumab + Pemetrexed + Cisplatin

Necitumumab: 800 milligrams (mg) (absolute dose) on Days 1 and 8 of every 3-week cycle.

Pemetrexed: 500 mg/square meter (mg/m2) intravenous (I.V.) on Day 1 of every 3-week cycle, for a maximum of six cycles.

Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®,LY231514
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 milligram per square meter (mg/m2) administered Intravenously (I.V.) on Day 1 of every 3-week cycle, for a maximum of six cycles

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m2 administered I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles

Investigational medicinal product name	Necitumumab
Investigational medicinal product code	
Other name	IMC-11F8,LY3012211,Portrazza®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg (absolute dose) on Days 1 and 8 of every 3-week cycle, administered as an I.V.

Arm title	Pemetrexed + Cisplatin

Arm description:

Pemetrexed + Cisplatin

Pemetrexed: 500 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.

Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.

Arm type	Active comparator
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®,LY231514
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 milligram per square meter (mg/m2) administered Intravenously (I.V.) on Day 1 of every 3-week cycle, for a maximum of six cycles

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m2 administered I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles

Number of subjects in period 1	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin
Started	315	318
Received at least 1 dose of study drug	304	312
Death Due to Any Cause	236	246
Completed	236	246
Not completed	79	72
Consent withdrawn by subject	17	19
Sponsor's Decision	-	1
Adverse event, non-fatal	1	1
New Anti-Cancer Therapy	5	5
Progressive Disease	46	39
Global Study End	-	1
Medical Decision	1	-
Lost to follow-up	9	6

Baseline characteristics

Reporting groups	
Reporting group title	Necitumumab + Pemetrexed + Cisplatin
Reporting group description:	
Necitumumab + Pemetrexed + Cisplatin Necitumumab: 800 milligrams (mg) (absolute dose) on Days 1 and 8 of every 3-week cycle. Pemetrexed: 500 mg/square meter (mg/m2) intravenous (I.V.) on Day 1 of every 3-week cycle, for a maximum of six cycles. Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.	
Reporting group title	Pemetrexed + Cisplatin
Reporting group description:	
Pemetrexed + Cisplatin Pemetrexed: 500 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles. Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.	

Reporting group values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin	Total
Number of subjects	315	318	633
Age categorical Units: Subjects			
Age continuous Units: years			
median	61.0	60.0	
full range (min-max)	26 to 84	34 to 88	-
Gender categorical Units: Subjects			
Female	101	108	209
Male	214	210	424
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	47	46	93
Not Hispanic or Latino	268	272	540
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	9	17
White	292	298	590
More than one race	13	11	24
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			

Russian Federation	16	13	29
Romania	21	31	52
Hungary	23	22	45
United States	0	1	1
United Kingdom	11	11	22
Portugal	6	1	7
Spain	40	27	67
Greece	5	10	15
Canada	2	1	3
Austria	8	11	19
Belgium	8	9	17
Brazil	37	35	72
Poland	28	24	52
Italy	17	19	36
South Africa	2	5	7
Slovakia	3	1	4
Australia	6	8	14
France	7	3	10
Germany	75	84	159
Croatia	0	2	2
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at Baseline			
Classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death). 0 - Fully Active. 1 - Ambulatory, Restricted Strenuous Activity. 2 - Ambulatory, No Work Activities. 3 - Partially Confined to Bed, Limited Self Care. 4 - Completely Disabled. 5 - Death.			
Units: Subjects			
_0	115	132	247
_1	183	166	349
_2	16	20	36
Missing	1	0	1
Smoking Units: Subjects			
Ex-Light Smoker	26	27	53
Nonsmoker	51	53	104
Smoker	238	238	476
Disease Stage at Study Entry			
Stage means how big the tumor is and how far it has spread. Stages range from 0 (not spread) to IV (spread throughout the body). Stage IIIB - the cancer has spread to nearby tissue or spread to far away lymph nodes. Stage IV - the cancer has spread to other organs of the body such as the other lung, brain, or liver.			
Units: Subjects			
Stage IIIB	9	11	20
Stage IV	305	307	612
Missing	1	0	1
Disease Histology Units: Subjects			
Adenocarcinoma/Large Cell Carcinoma	307	311	618
Other	7	7	14
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Necitumumab + Pemetrexed + Cisplatin

Reporting group description:

Necitumumab + Pemetrexed + Cisplatin

Necitumumab: 800 milligrams (mg) (absolute dose) on Days 1 and 8 of every 3-week cycle.

Pemetrexed: 500 mg/square meter (mg/m2) intravenous (I.V.) on Day 1 of every 3-week cycle, for a maximum of six cycles.

Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.

Reporting group title	Pemetrexed + Cisplatin

Reporting group description:

Pemetrexed + Cisplatin

Pemetrexed: 500 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.

Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles.

Subject analysis set title	Necitumumab + Pemextrexed + Cisplatin
Subject analysis set type	Per protocol

Subject analysis set description:

Necitumumab + Pemetrexed + Cisplatin

Necitumumab: 800 mg (absolute dose) on Days 1 and 8 of every 3-week cycle, administered as an I.V. infusion

Pemetrexed: 500 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles

Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles

Primary: Overall survival time (OS)

End point title	Overall survival time (OS)

End point description:

OS is defined as the time from randomization to death from any cause. Participants who do not die at the end of the extended follow-up period, or were lost to follow-up during the study, were censored at the last date they were known to be alive. OS was estimated using the Kaplan-Meier method.

Analysis Population Description (APD): All randomized participants. Censored participants: Necitumumab + Pemetrexed + Cisplatin =79, Pemetrexed + Cisplatin=72

End point type	Primary

End point timeframe:

Randomization to Death from Any Cause (Up to 31.6 Months)

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	318		
Units: Months				
median (confidence interval 95%)	11.3 (9.5 to 13.4)	11.5 (10.1 to 13.1)		

Statistical analyses

Statistical analysis title	Overall survival time (OS)
Comparison groups	Necitumumab + Pemetrexed + Cisplatin v Pemetrexed + Cisplatin
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9561
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.21

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS is defined as the time from randomization until the first radiographic documentation of measured progressive disease as defined by RECIST (Version 1.0), or death from any cause. Participants who die without a reported prior progression will be considered to have progressed on the day of their death. Participants who did not progress or were lost to follow-up were censored at the day of their last radiographic tumor assessment. If no baseline or postbaseline radiologic assessment was available, the participant was censored at the date of randomization. If death or PD occurs after two or more consecutive missing radiographic visits, censoring occurred at the date of the last radiographic visit prior to the missed visits.

End point type	Secondary

End point timeframe:

Randomization to Measured Progressive Disease or Death from Any Cause (Up to 30.4 Months)

APD: All randomized participants. Censored participants: Necitumumab + Pemetrexed + Cisplatin=84, Pemetrexed + Cisplatin=79

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	318		
Units: Months				
median (confidence interval 95%)	5.6 (5.1 to 6.0)	5.6 (4.8 to 5.7)		

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)
Comparison groups	Necitumumab + Pemetrexed + Cisplatin v Pemetrexed + Cisplatin
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6647
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.16

Secondary: Percentage of Participants who Achieve Best Overall Tumor Response of Complete Response (CR) or Partial Response (PR) (Objective Tumor Response Rate [ORR])

End point title	Percentage of Participants who Achieve Best Overall Tumor Response of Complete Response (CR) or Partial Response (PR) (Objective Tumor Response Rate [ORR])

End point description:

ORR is confirmed best overall tumor response of CR or PR. According to RECIST v1.0, CR was defined as the disappearance of all target and non-target lesions; PR defined as a >30% decrease in the sum of the longest diameters (LD) of the target lesions, taking as reference the baseline sum of the LD. Percentage of participants was calculated as: (total number of participants with CR or PR from start of the treatment until disease progression or recurrence)/total number of participants treated) * 100.

APD: All randomized participants.

End point type	Secondary

End point timeframe:

Baseline to Measured Progressive Disease (Up to 30.4 Months)

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	318		
Units: percentage of participants				
number (confidence interval 95%)	31.1 (26.3 to 36.4)	32.1 (27.2 to 37.4)		

Statistical analyses

Statistical analysis title	ORR
Comparison groups	Necitumumab + Pemetrexed + Cisplatin v Pemetrexed + Cisplatin
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7945
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.34

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

TTF was defined as the time from study enrollment/randomization to the first observation of measured progressive disease, death from any cause, or early discontinuation of treatment or initiation of new anti-cancer therapies. Response was defined using Response Evaluation Criteria In Solid Tumors (RECIST, version 1.0) criteria. Progressive Disease (PD) was defined as having at least a 20% increase in sum of longest diameter of target lesions. Time to treatment failure was censored at the date of the last follow-up visit for participants who did not discontinue early, who were still alive, and who have not progressed.

APD: All randomized participants. Censored participants: Necitumumab + Pemetrexed + Cisplatin = 10, Pemetrexed + Cisplatin = 13

End point type	Secondary

End point timeframe:

Randomization to Measured Progressive Disease, Death from Any Cause, Discontinuation of Treatment or Initiation of New Anticancer Therapy (Up to 30.4 Months)

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	318		
Units: Months				
median (confidence interval 95%)	3.5 (3.2 to 3.9)	4.3 (3.3 to 4.8)		

Statistical analyses

Statistical analysis title	Time to Treatment Failure (TTF)
Comparison groups	Necitumumab + Pemetrexed + Cisplatin v Pemetrexed + Cisplatin
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0459
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.39

Secondary: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab	
End point title	Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab[1]
End point description:	
APD: Participants who were randomized to necitumumab and had evaluable PK data.	
End point type	Secondary
End point timeframe:	
Predose Day 1 of Cycle 2,3,4,5 and 6 Prior to Necitumumab Infusion, Up to 23 Weeks	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis were planned for participants who received Necitumumab only.	

End point values	Necitumumab + Pemetrexed + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	315			
Units: micrograms/milliliter (ug/ml)				
geometric mean (geometric coefficient of variation)				
Predose Cycle 2 Day 1	57.5 (± 84.5)			
Predose Cycle 3 Day 1	80.8 (± 89.3)			
Predose Cycle 4 Day 1	110 (± 82.9)			
Predose Cycle 5 Day 1	115 (± 81.8)			
Predose Cycle 6 Day 1	119 (± 68.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serum Anti-Necitumumab Antibody Assessment (Immunogenicity)

End point title	Number of Participants with Serum Anti-Necitumumab Antibody Assessment (Immunogenicity)

End point description:

A participant was considered to have an anti-Necitumumab antibody response if anti-drug antibodies (ADA) were confirmed positive. Treatment emergent antibodies were defined as any anti-Necitumumab antibody titer equal to or greater than 4-fold the participant's baseline titer.

APD: All randomized participants who received at least one dose of necitumumab and had evaluable antibody data.

End point type	Secondary

End point timeframe:

Baseline to Study Completion (Up to 31.6 Months)

End point values	Necitumumab + Pemextrexed + Cisplatin			
Subject group type	Subject analysis set			
Number of subjects analysed	301			
Units: participants				
number (not applicable)				
1 Positive Titer Antibodies Detected	37 18			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Patient Reported Outcomes (PRO) using the European Quality of Life-5 Dimensions (EQ-5D)

End point title	Mean Change from Baseline in Patient Reported Outcomes (PRO) using the European Quality of Life-5 Dimensions (EQ-5D)

End point description:

The EQ-5D is a generic, multidimensional, health-related, quality-of-life instrument. The profile allows participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a three level scale 1-3 (no problem, some problems, and major problems). These combinations of attributes were converted into a weighted health-state Index Score according to the United Kingdom (UK) population-based algorithm. The possible values for the

Index Score ranged from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension).

APD: All randomized participants who had evaluable baseline and postbaseline EQ-5D data

End point type	Secondary

End point timeframe:

Baseline, Cycle 6 (Cycle = 3 weeks)

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	147		
Units: units on a scale				
arithmetic mean (standard deviation)	0.0419 (± 0.28230)	0.0478 (± 0.22645)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in PRO as measured using the Lung Cancer Symptom Scale (LCSS)

End point title	Mean Change from Baseline in PRO as measured using the Lung Cancer Symptom Scale (LCSS)

End point description:

The LCSS consisted of 9 items: 6 items focused on lung cancer symptoms [loss of appetite, fatigue, cough, dyspnea (shortness of breath), hemoptysis (blood in sputum), and pain] and 3 items were global items (symptom distress, interference with activity level, and global quality of life). Participant responses to each item were measured using visual analogue scales (VAS) with 100-mm lines. A higher score for any item represented a higher level of symptoms/problems. Scores for each of the reported categories ranged from 0 (for best outcome) to 100 (for worst outcome). The Average Symptom Burden Index (ASBI) was the mean of the 6 symptom items of the LCSS, and the Total LCSS was the mean of all 9 LCSS items. ASBI and Total LCSS were not computed for a participant if he/she had 1 or more missing values for the 6 and 9 items, respectively.

End point type	Secondary

End point timeframe:

Baseline, Cycle 6 (Cycle =3 Weeks)

APD: All randomized participants who had evaluable baseline and postbaseline LCSS data.

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	318		
Units: millimeter (mm)				
arithmetic mean (standard deviation)				
Loss of Appetite	4.6 (± 46.18)	0.6 (± 27.52)		

Fatigue	4.5 (± 31.24)	1.6 (± 28.75)		
Cough	-9.1 (± 31.08)	-10.3 (± 27.88)		
Dyspnea	-2.8 (± 26.32)	-1.5 (± 23.67)		
Hemoptysis	-1.1 (± 11.92)	-1.1 (± 7.81)		
Pain	-4.2 (± 27.22)	-7.1 (± 26.64)		
Overall Symptoms	-3.1 (± 31.22)	-7.4 (± 27.11)		
Quality of Life	2.5 (± 26.01)	-3.3 (± 24.91)		
Interference	3.2 (± 27.15)	-4.0 (± 31.39)		
Average Symptom Burden Index (ASBI)	-0.9 (± 18.35)	-3.1 (± 13.11)		
LCSS Total Score	0.1 (± 17.59)	-4.3 (± 13.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Epidermal Growth Factor Hormone (EGFR) Protein Expression Measured by Immunohistochemistry (IHC)

End point title	Epidermal Growth Factor Hormone (EGFR) Protein Expression Measured by Immunohistochemistry (IHC)

End point description:

EGFR IHC H-score = weighted sum of % 1+ cells, twice % 2+ cells, and three times % 3+ cells. IHC H-score criteria assesses participants with a low EGFR expression defined by a H-score cutoff value of < 200 and participants with a high EGFR expression defined by a H-score of cutoff value of >=200.

APD: Translational research population included all participants who: (1) received at least one dose of study drug; (2) had a valid non-missing result for EGFR H-Score; and (3) were enrolled for more than 2 cycles prior to the decision to terminate enrollment.

End point type	Secondary

End point timeframe:

Baseline

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	245		
Units: H-Score				
arithmetic mean (standard deviation)				
H-score <200	69.06 (± 64.68)	66.23 (± 64.15)		
H-score >=200	259.35 (± 27.65)	256.26 (± 29.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with EGFR measured by IHC

End point title	Percentage of Participants with EGFR measured by IHC

End point description:

EGFR IHC H-score = weighted sum of % 1+ cells, twice % 2+ cells, and three times % 3+ cells. IHC H-score criteria assesses participants with a low EGFR expression defined by a H-score cutoff value of < 200 and participants with a high EGFR expression defined by a H-score of cutoff value of >=200.

APD: Translational research population included all participants who: (1) received at least one dose of study drug; (2) had a valid non-missing result for EGFR H-Score; and (3) were enrolled for more than 2 cycles prior to the decision to terminate enrollment

End point type	Secondary

End point timeframe:

Baseline

End point values	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	245		
Units: percentage of participants				
number (not applicable)				
H-score <200	58.8	59.6		
H-score >=200	41.2	40.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Entire Study	
Adverse event reporting additional description:	
I4X-IE-JFCB	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Pemetrexed+Cisplatin
Reporting group description:	
Pemetrexed + Cisplatin Pemetrexed: 500 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles	
Reporting group title	Necitumumab+Pemetrexed+Cisplatin
Reporting group description:	
Necitumumab + Pemetrexed + Cisplatin Necitumumab: 800 mg (absolute dose) on Days 1 and 8 of every 3-week cycle Pemetrexed: 500 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle, for a maximum of six cycles	

Serious adverse events	Pemetrexed+Cisplatin	Necitumumab+Pemetrexed+Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	130 / 312 (41.67%)	158 / 304 (51.97%)	
number of deaths (all causes)	35	53	
number of deaths resulting from adverse events	10	15	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
cancer pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant pleural effusion			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
metastases to central nervous system			

alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
metastatic pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-small cell lung cancer			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	10 / 312 (3.21%)	24 / 304 (7.89%)	
occurrences causally related to treatment / all	0 / 10	0 / 24	
deaths causally related to treatment / all	0 / 9	0 / 19	
tumour pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
aortic aneurysm rupture			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
arterial stenosis limb			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
arterial thrombosis limb			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
circulatory collapse			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
deep vein thrombosis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
hypertension			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
orthostatic hypotension			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral embolism			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

peripheral ischaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
poor venous access			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subclavian vein thrombosis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
superior vena caval occlusion			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombosis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
venous thrombosis limb			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
analgesic therapy			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
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			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	8 / 304 (2.63%)	
occurrences causally related to treatment / all	3 / 3	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
chest pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	1 / 1	1 / 3	
fatigue			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	7 / 312 (2.24%)	8 / 304 (2.63%)	
occurrences causally related to treatment / all	6 / 7	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 312 (1.28%)	6 / 304 (1.97%)	
occurrences causally related to treatment / all	4 / 5	6 / 7	
deaths causally related to treatment / all	1 / 2	1 / 1	
mucosal inflammation			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	4 / 304 (1.32%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
multi-organ failure			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
oedema peripheral			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
performance status decreased			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	4 / 304 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
systemic inflammatory response syndrome			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
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 pulmonary oedema			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
acute respiratory failure			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cough			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 312 (1.60%)	8 / 304 (2.63%)	
occurrences causally related to treatment / all	0 / 8	1 / 8	
deaths causally related to treatment / all	0 / 2	0 / 0	
epistaxis			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoptysis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
interstitial lung disease			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	3 / 312 (0.96%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
pneumonitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary artery thrombosis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

pulmonary embolism			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	11 / 312 (3.53%)	13 / 304 (4.28%)	
occurrences causally related to treatment / all	2 / 11	10 / 13	
deaths causally related to treatment / all	0 / 4	2 / 3	
pulmonary haemorrhage			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
pulmonary oedema			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory failure			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 1	1 / 3	
Psychiatric disorders			
agitation			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
confusional state			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
international normalised ratio increased			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
weight decreased			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
drug administration error			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
femur fracture			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip fracture			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
incorrect dose administered			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	2 / 312 (0.64%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar vertebral fracture			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
medication error			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	6 / 304 (1.97%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
procedural pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suture rupture			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acute myocardial infarction			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina pectoris			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
arrhythmia supraventricular			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
atrial fibrillation			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial flutter			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac failure			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac tamponade			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardio-respiratory arrest			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

cardiomyopathy			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiopulmonary failure			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
myocardial infarction			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
pericardial effusion			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
sinus tachycardia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tachycardia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral infarction			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	2 / 312 (0.64%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral ischaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
cerebrovascular accident			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	4 / 312 (1.28%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	1 / 3	0 / 0	
convulsion			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness postural			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hemiparesis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

hypotonia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ischaemic stroke			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
migraine			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
paraesthesia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal cord compression			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	13 / 312 (4.17%)	12 / 304 (3.95%)	
occurrences causally related to treatment / all	15 / 18	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
granulocytopenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	8 / 312 (2.56%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	8 / 8	5 / 5	
deaths causally related to treatment / all	1 / 1	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 312 (1.60%)	9 / 304 (2.96%)	
occurrences causally related to treatment / all	5 / 5	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancytopenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
splenic infarction			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

thrombocytopenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 312 (1.60%)	8 / 304 (2.63%)	
occurrences causally related to treatment / all	6 / 6	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dental caries			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 312 (1.60%)	10 / 304 (3.29%)	
occurrences causally related to treatment / all	3 / 5	9 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
duodenal ulcer			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
duodenal ulcer haemorrhage			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysphagia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocolitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal disorder			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus paralytic			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
inguinal hernia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal infarction			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

intestinal perforation			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
intra-abdominal haemorrhage			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestine perforation			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	6 / 312 (1.92%)	8 / 304 (2.63%)	
occurrences causally related to treatment / all	6 / 6	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal ulcer			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophagitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumatosis intestinalis			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal haemorrhage			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stomatitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	3 / 312 (0.96%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
volvulus			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	7 / 312 (2.24%)	9 / 304 (2.96%)	
occurrences causally related to treatment / all	7 / 7	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
biliary colic			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic failure			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
rash			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	5 / 304 (1.64%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
rash maculo-papular			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
toxic skin eruption			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urticaria			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
nephropathy toxic			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	6 / 312 (1.92%)	4 / 304 (1.32%)	
occurrences causally related to treatment / all	6 / 7	5 / 5	
deaths causally related to treatment / all	2 / 2	0 / 0	
renal failure acute			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal impairment			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
back pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
bone pain			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
flank pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
musculoskeletal chest pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
musculoskeletal pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myalgia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain in extremity			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pathological fracture			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
abscess limb			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
device related infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
diverticulitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
erysipelas			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatitis b			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
herpes dermatitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
herpes oesophagitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal gangrene			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
neutropenic sepsis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	2 / 2	

oral candidiasis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritoneal infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	6 / 312 (1.92%)	14 / 304 (4.61%)	
occurrences causally related to treatment / all	3 / 7	4 / 14	
deaths causally related to treatment / all	1 / 2	1 / 2	
pyelonephritis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (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			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	3 / 312 (0.96%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	4 / 304 (1.32%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	3 / 3	
septic shock			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 312 (0.32%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
skin bacterial infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
staphylococcal infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
staphylococcal sepsis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
anorexia			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	3 / 312 (0.96%)	6 / 304 (1.97%)	
occurrences causally related to treatment / all	3 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
cachexia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
dehydration			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 312 (1.60%)	4 / 304 (1.32%)	
occurrences causally related to treatment / all	8 / 8	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
electrolyte imbalance			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fluid retention			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperglycaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperkalaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

hyperuricaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypomagnesaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 312 (0.32%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 312 (0.64%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pemetrexed+Cisplatin	Necitumumab+Pemetrexed+Cisplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	303 / 312 (97.12%)	296 / 304 (97.37%)	
Vascular disorders			

hypertension			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	29 / 312 (9.29%)	17 / 304 (5.59%)	
occurrences (all)	41	24	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	68 / 312 (21.79%)	88 / 304 (28.95%)	
occurrences (all)	146	192	
fatigue			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	95 / 312 (30.45%)	87 / 304 (28.62%)	
occurrences (all)	171	164	
mucosal inflammation			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	27 / 312 (8.65%)	50 / 304 (16.45%)	
occurrences (all)	36	104	
non-cardiac chest pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	16 / 312 (5.13%)	11 / 304 (3.62%)	
occurrences (all)	22	16	
oedema peripheral			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	41 / 312 (13.14%)	40 / 304 (13.16%)	
occurrences (all)	51	52	
pyrexia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	22 / 312 (7.05%)	46 / 304 (15.13%)	
occurrences (all)	32	57	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	48 / 312 (15.38%)	56 / 304 (18.42%)	
occurrences (all)	59	75	

dyspnoea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	41 / 312 (13.14%)	46 / 304 (15.13%)	
occurrences (all)	52	62	
epistaxis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	9 / 312 (2.88%)	21 / 304 (6.91%)	
occurrences (all)	9	30	
haemoptysis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	10 / 312 (3.21%)	21 / 304 (6.91%)	
occurrences (all)	12	30	
productive cough			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	7 / 312 (2.24%)	16 / 304 (5.26%)	
occurrences (all)	9	17	
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	10 / 312 (3.21%)	18 / 304 (5.92%)	
occurrences (all)	11	20	
insomnia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	15 / 312 (4.81%)	17 / 304 (5.59%)	
occurrences (all)	20	23	
Investigations			
blood creatinine increased			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	18 / 312 (5.77%)	21 / 304 (6.91%)	
occurrences (all)	23	34	
weight decreased			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	24 / 312 (7.69%)	39 / 304 (12.83%)	
occurrences (all)	28	53	
Nervous system disorders			

dizziness			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	26 / 312 (8.33%)	38 / 304 (12.50%)	
occurrences (all)	37	52	
dysgeusia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	32 / 312 (10.26%)	21 / 304 (6.91%)	
occurrences (all)	43	27	
headache			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	27 / 312 (8.65%)	30 / 304 (9.87%)	
occurrences (all)	32	41	
paraesthesia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	8 / 312 (2.56%)	16 / 304 (5.26%)	
occurrences (all)	9	20	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	91 / 312 (29.17%)	72 / 304 (23.68%)	
occurrences (all)	200	155	
leukopenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	36 / 312 (11.54%)	45 / 304 (14.80%)	
occurrences (all)	61	92	
lymphopenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	17 / 312 (5.45%)	16 / 304 (5.26%)	
occurrences (all)	26	53	
neutropenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	99 / 312 (31.73%)	92 / 304 (30.26%)	
occurrences (all)	217	179	
thrombocytopenia			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	23 / 312 (7.37%)	22 / 304 (7.24%)	
occurrences (all)	42	43	
Ear and labyrinth disorders			
tinnitus			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	16 / 312 (5.13%)	15 / 304 (4.93%)	
occurrences (all)	18	18	
Eye disorders			
conjunctivitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	6 / 312 (1.92%)	31 / 304 (10.20%)	
occurrences (all)	6	46	
lacrimation increased			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	17 / 312 (5.45%)	4 / 304 (1.32%)	
occurrences (all)	17	4	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	15 / 312 (4.81%)	19 / 304 (6.25%)	
occurrences (all)	15	25	
abdominal pain upper			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	25 / 312 (8.01%)	26 / 304 (8.55%)	
occurrences (all)	29	36	
constipation			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	83 / 312 (26.60%)	91 / 304 (29.93%)	
occurrences (all)	124	133	
diarrhoea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	51 / 312 (16.35%)	90 / 304 (29.61%)	
occurrences (all)	78	148	
dyspepsia			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	18 / 312 (5.77%)	16 / 304 (5.26%)	
occurrences (all)	28	21	
nausea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	183 / 312 (58.65%)	174 / 304 (57.24%)	
occurrences (all)	403	392	
stomatitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	12 / 312 (3.85%)	30 / 304 (9.87%)	
occurrences (all)	22	41	
vomiting			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	104 / 312 (33.33%)	105 / 304 (34.54%)	
occurrences (all)	180	213	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	18 / 312 (5.77%)	29 / 304 (9.54%)	
occurrences (all)	20	31	
dermatitis acneiform			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	42 / 304 (13.82%)	
occurrences (all)	0	119	
dry skin			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	11 / 312 (3.53%)	43 / 304 (14.14%)	
occurrences (all)	13	62	
hirsutism			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed[1]	0 / 107 (0.00%)	5 / 95 (5.26%)	
occurrences (all)	0	5	
pruritus			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	8 / 312 (2.56%)	31 / 304 (10.20%)	
occurrences (all)	9	48	
rash			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	20 / 312 (6.41%)	125 / 304 (41.12%)	
occurrences (all)	23	346	
rash generalised			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 312 (1.60%)	28 / 304 (9.21%)	
occurrences (all)	5	62	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	20 / 312 (6.41%)	33 / 304 (10.86%)	
occurrences (all)	24	40	
musculoskeletal pain			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	15 / 312 (4.81%)	19 / 304 (6.25%)	
occurrences (all)	21	26	
pain in extremity			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	17 / 312 (5.45%)	18 / 304 (5.92%)	
occurrences (all)	19	22	
Infections and infestations			
oral candidiasis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	5 / 312 (1.60%)	18 / 304 (5.92%)	
occurrences (all)	5	22	
paronychia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 312 (0.00%)	28 / 304 (9.21%)	
occurrences (all)	0	67	
urinary tract infection			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	16 / 312 (5.13%)	19 / 304 (6.25%)	
occurrences (all)	21	21	
Metabolism and nutrition disorders			
anorexia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	97 / 312 (31.09%)	110 / 304 (36.18%)	
occurrences (all)	171	174	
fluid retention			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	12 / 312 (3.85%)	17 / 304 (5.59%)	
occurrences (all)	22	39	
hyperglycaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	10 / 312 (3.21%)	16 / 304 (5.26%)	
occurrences (all)	15	34	
hypocalcaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	13 / 312 (4.17%)	30 / 304 (9.87%)	
occurrences (all)	16	51	
hypomagnesaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	36 / 312 (11.54%)	75 / 304 (24.67%)	
occurrences (all)	66	185	
hypokalaemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	23 / 312 (7.37%)	20 / 304 (6.58%)	
occurrences (all)	33	34	
hyponatraemia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	20 / 312 (6.41%)	23 / 304 (7.57%)	
occurrences (all)	30	36	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2011	Amendment v.5.0: The enrollment for this study was early terminated following Independent Data Monitoring Committee (IDMC) recommendations, due to an increased rate of serious thromboembolic (TE) events in the treatment arm with Necitumumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported