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

Summary

EudraCT number	2009-013838-25
Trial protocol	BE AT DE HU PT ES GR SK IT GB
Global end of trial date	30 May 2024

Results information

Result version number	v1 (current)
This version publication date	15 June 2025
First version publication date	15 June 2025

Trial information

Trial identification

Sponsor protocol code	I4X-IE-JFCC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00981058
WHO universal trial number (UTN)	-
Other trial identifiers	Additional Identifier: IMCLCP11-0806

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Clinical Trial Information, Eli Lilly and Company, 1 08772854559, EU_Lilly_Clinical_Trials@lilly.com
Scientific contact	Clinical Trial Information, Eli Lilly and Company, 1 877CTLilly, EU_Lilly_Clinical_Trials@lilly.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	30 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2024
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 evaluate the overall survival (OS) in patients with Stage IV squamous NSCLC (per the AJCC Staging Manual, Seventh Edition) treated with IMC-11F8 plus gemcitabine-cisplatin chemotherapy (Arm A) versus gemcitabine-cisplatin chemotherapy alone (Arm B) in the first-line metastatic setting.

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	07 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 128
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Romania: 91
Country: Number of subjects enrolled	Slovakia: 19
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 73
Country: Number of subjects enrolled	Germany: 108
Country: Number of subjects enrolled	Greece: 32
Country: Number of subjects enrolled	Hungary: 84
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Russian Federation: 195
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	Brazil: 58
Country: Number of subjects enrolled	Korea, Republic of: 47

Country: Number of subjects enrolled	Serbia: 24
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Philippines: 20
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Australia: 10
Worldwide total number of subjects	1093
EEA total number of subjects	657

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)	668
From 65 to 84 years	424
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Not applicable.

Pre-assignment

Screening details:

Completers are defined as those participants who died due to any cause in this study.

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 + Gemcitabine + Cisplatin

Arm description:

Necitumumab + Gemcitabine + Cisplatin
Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle.
Continues until progressive disease, toxicity, noncompliance, or withdrawal.
Gemcitabine: 1250 milligrams/square meter (mg/m2) on Days 1 and 8 of every 3 week cycle.
Continues for a maximum of six cycles.
Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle.
Continues for a maximum of six cycles.

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

Dosage and administration details:

Administered intravenously.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	LY2334737
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously.

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

Dosage and administration details:

Administered intravenously.

Arm title	Gemcitabine + Cisplatin

Arm description:

Gemcitabine + Cisplatin
Gemcitabine: 1250 mg/m2 on Days 1 and 8 of every 3 week cycle.
Continues for a maximum of six cycles.

Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle.
Continues for a maximum of six cycles.

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	LY2334737
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously.

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

Dosage and administration details:

Administered intravenously.

Number of subjects in period 1	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin
Started	545	548
Received at Least 1 Dose of Study Drug	538	541
Completed	476	487
Not completed	69	61
Physician decision	4	5
Consent withdrawn by subject	24	22
Progressive Disease	38	31
Lost to follow-up	3	2
Randomization Error	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Necitumumab + Gemcitabine + Cisplatin
Reporting group description:	
Necitumumab + Gemcitabine + Cisplatin Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle. Continues until progressive disease, toxicity, noncompliance, or withdrawal. Gemcitabine: 1250 milligrams/square meter (mg/m2) on Days 1 and 8 of every 3 week cycle. Continues for a maximum of six cycles. Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle. Continues for a maximum of six cycles.	
Reporting group title	Gemcitabine + Cisplatin
Reporting group description:	
Gemcitabine + Cisplatin Gemcitabine: 1250 mg/m2 on Days 1 and 8 of every 3 week cycle. Continues for a maximum of six cycles. Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle. Continues for a maximum of six cycles.	

Reporting group values	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin	Total
Number of subjects	545	548	1093
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	62	62	
full range (min-max)	32 to 84	32 to 86	-
Gender categorical Units: Subjects			
Female	95	90	185
Male	450	458	908
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	55	56	111
Not Hispanic or Latino	489	490	979
Unknown or Not Reported	1	2	3
Race/Ethnicity Units: Subjects			
American Indian or Alaska Native	1	0	1

Asian	43	42	85
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	5	6	11
White	457	456	913
More than one race	1	0	1
Other	38	43	81
Region of Enrollment Units: Subjects			
Russian Federation	94	101	195
Singapore	1	2	3
United States	20	16	36
Thailand	3	6	9
Portugal	8	9	17
Greece	18	14	32
Austria	4	4	8
Brazil	28	30	58
Republic of Korea	24	23	47
Poland	69	59	128
Slovakia	9	10	19
France	34	39	73
Serbia	11	13	24
Croatia	2	4	6
Romania	46	45	91
Hungary	43	41	84
Philippines	12	8	20
United Kingdom	9	10	19
Spain	33	25	58
Canada	2	4	6
Belgium	4	4	8
Taiwan	3	2	5
Italy	13	12	25
South Africa	2	2	4
Australia	4	6	10
Germany	49	59	108

End points

End points reporting groups

Reporting group title	Necitumumab + Gemcitabine + Cisplatin

Reporting group description:

Necitumumab + Gemcitabine + Cisplatin
Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle.
Continues until progressive disease, toxicity, noncompliance, or withdrawal.
Gemcitabine: 1250 milligrams/square meter (mg/m2) on Days 1 and 8 of every 3 week cycle.
Continues for a maximum of six cycles.
Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle.
Continues for a maximum of six cycles.

Reporting group title	Gemcitabine + Cisplatin

Reporting group description:

Gemcitabine + Cisplatin
Gemcitabine: 1250 mg/m2 on Days 1 and 8 of every 3 week cycle.
Continues for a maximum of six cycles.
Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle.
Continues for a maximum of six cycles.

Primary: Overall Survival Time (OS)

End point title	Overall Survival Time (OS)

End point description:

Overall survival 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 by the Kaplan-Meier method.

Analysis Population Description (APD): All randomized participants. Censored participants: Necitumumab + Gemcitabine + Cisplatin = 127, Gemcitabine + Cisplatin = 106

End point type	Primary

End point timeframe:

Randomization to Death from Any Cause (Up to 31 Months)

End point values	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	545	548		
Units: Months				
median (confidence interval 95%)	11.5 (10.4 to 12.6)	9.9 (8.9 to 11.1)		

Statistical analyses

Statistical analysis title	Outcome Measure No. 1
Comparison groups	Necitumumab + Gemcitabine + Cisplatin v Gemcitabine + Cisplatin

Number of subjects included in analysis	1093
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.012
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.736
upper limit	0.962

Notes:

[1] - Superiority or Other (legacy)

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 objective measured progressive disease as defined by RECIST (Version 1.0), or death from any cause. Progressive Disease (PD) was defined as having at least a 20% increase in the sum of the longest diameter of target lesions. Participants who die without a reported prior progression were 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 participants were 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 31 Months).

APD: All randomized participants. Censored participants: Necitumumab + Gemcitabine + Cisplatin = 114, Gemcitabine + Cisplatin = 131

End point values	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	545	548		
Units: Months				
median (confidence interval 95%)	5.7 (5.6 to 6.0)	5.5 (4.8 to 5.6)		

Statistical analyses

Statistical analysis title	Outcome Measure No. 2
Comparison groups	Gemcitabine + Cisplatin v Necitumumab + Gemcitabine + Cisplatin

Number of subjects included in analysis	1093
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0201
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.851
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.743
upper limit	0.975

Notes:

[2] - Superiority or Other (legacy)

Secondary: Percentage of Participants Achieving Complete Response (CR) and Partial Response (PR) (Objective Response Rate [ORR])

End point title	Percentage of Participants Achieving Complete Response (CR) and Partial Response (PR) (Objective 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 31 Months)

End point values	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	545	548		
Units: Percentage of participants				
number (confidence interval 95%)	31.2 (27.4 to 35.2)	28.8 (25.2 to 32.8)		

Statistical analyses

Statistical analysis title	Outcome Measure No. 3
Comparison groups	Necitumumab + Gemcitabine + Cisplatin v Gemcitabine + Cisplatin

Number of subjects included in analysis	1093
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.3997
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.45

Notes:

[3] - Superiority or Other (legacy)

Secondary: Mean Change From Baseline in Patient Reported Outcomes (PRO) Using the European Quality of Life-5 Dimension (EQ-5D)

End point title	Mean Change From Baseline in Patient Reported Outcomes (PRO) Using the European Quality of Life-5 Dimension (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 + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	245		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.0053 (± 0.23626)	-0.0083 (± 0.23866)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

TTF is defined as the time from the date of randomization until the date of the first radiographic documentation of PD, death from any cause, discontinuation of treatment for any reason, or initiation of new cancer therapy. Participants who withdrew from the study for reasons other than progression or death were censored at the date of study withdrawal. Participants who did not meet any of the criteria for treatment failure were censored at their date of last contact in the study.

APD: All randomized participants. Censored participants: Necitumumab + Gemcitabine + Cisplatin = 16, Gemcitabine + Cisplatin =20

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 31 Months)

End point values	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	545	548		
Units: Months				
median (confidence interval 95%)	4.3 (4.2 to 4.8)	3.6 (3.3 to 4.1)		

Statistical analyses

Statistical analysis title	Outcome Measure No. 5
Comparison groups	Necitumumab + Gemcitabine + Cisplatin v Gemcitabine + Cisplatin
Number of subjects included in analysis	1093
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0061
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.844
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.747
upper limit	0.943

Notes:

[4] - Superiority or Other (legacy)

Secondary: Mean Change From Baseline in PRO Using the Outcomes Lung Cancer Symptom Scale (LCSS)

End point title	Mean Change From Baseline in PRO Using the Outcomes 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.

APD: All randomized participants who had evaluable data for LCSS.

End point type	Secondary

End point timeframe:

Baseline, Cycle 6 (Cycle = 3 Weeks)

End point values	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	545	548		
Units: millimeter (mm)				
arithmetic mean (standard deviation)				
Loss of Appetite (n=304, 242)	1.8 (± 31.84)	1.5 (± 29.30)		
Fatigue (n=302, 242)	6.3 (± 29.15)	3.5 (± 25.29)		
Cough (n=303, 243)	-7.8 (± 28.05)	-9.1 (± 25.74)		
Dyspnea (n=305, 244)	-2.8 (± 26.52)	-1.8 (± 25.27)		
Pain (n=302, 243)	-3.3 (± 17.98)	-2.2 (± 17.22)		
Overall Symptoms (n=303, 242)	-0.3 (± 26.19)	-0.6 (± 26.92)		
Interference (n=306,241)	3.8 (± 29.74)	2.2 (± 26.79)		
Quality of Life (n=305, 243)	-0.3 (± 27.35)	-1.6 (± 24.71)		
Average Symptom Burden Index (ASBI) (n=294, 234)	-1.9 (± 16.55)	-1.5 (± 16.52)		
LCSS Total Score (n=290, 228)	-0.8 (± 17.03)	-0.8 (± 16.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With an Epidermal Growth Factor Hormone (EGFR) Protein Expression Measured by Immunohistochemistry (IHC)

End point title	Number of Participants With an Epidermal Growth Factor Hormone (EGFR) Protein Expression Measured by Immunohistochemistry (IHC)

End point description:

EGFR IHC Histoscore H-score = weighted sum of % 1+ cells, twice % 2+ cells, and three times % 3+ cells. IHC H-score criteria was used to assess 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: All randomized participants who received at least one dose of study drug and had evaluable data for EGFR IHC.

End point type	Secondary

End point timeframe:

31 Months

End point values	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	496		
Units: Participants				
00	24	23		
>0	462	473		
<200	295	313		
>=200	191	183		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab

End point title	Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab[5]

End point description:

APD: All randomized participants who received at least one dose of study drug and had evaluable data for PK.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 2, 3, 4, 5 and 6 Prior to Necitumumab Drug Infusion, Up to 24 Months

Notes:

[5] - 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: All randomized participants who received at least one dose of study drug and had evaluable data for PK were included in this analysis. No inferential statistics was planned for this end point.

End point values	Necitumumab + Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	545			
Units: micrograms/milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Predose Cycle 2 Day 1 (n=419)	52.4 (± 95.9)			
Predose Cycle3 Day 1 (n=386)	76.6 (± 80.6)			
Predose Cycle 4 Day 1 (n=344)	94.5 (± 92.2)			
Predose Cycle 5 Day 1 (n=297)	101 (± 90)			
Predose Cycle 6 Day 1 (n=262)	98.5 (± 80)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Serum Anti-Necitumumab Antibody Assessment

End point title	Number of Participants With a Serum Anti-Necitumumab Antibody Assessment[6]

End point description:

A participant was considered to have an anti-Necitumumab antibody response if anti-drug antibodies (ADA) were detected at any time point.

APD: All randomized participants who received who received at least 1 dose of drug and had evaluable data for antibodies.

End point type	Secondary

End point timeframe:

Baseline through 31 Months

Notes:

[6] - 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: All randomized participants who received who received at least 1 dose of drug and had evaluable data for antibodies were included in this analysis. No inferential statistics was planned for this end point.

End point values	Necitumumab + Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	528			
Units: Participants				
Participants with at least 1 positive titer	81			
Neutralizing antibody detected	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Up To 156 Months

Adverse event reporting additional description:

All participants who received at least one dose of study drug. The adverse events were analyzed and reported according to the study treatments pre-specified in the statistical analysis plan.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Gemcitabine + Cisplatin

Reporting group description:

Gemcitabine: 1250 mg/m2 on Days 1 and 8 of every 3 week cycle. Continues for a maximum of six cycles.
Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle. Continues for a maximum of six cycles.

Reporting group title	Necitumumab + Gemcitabine + Cisplatin

Reporting group description:

Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle. Continues until progressive disease, toxicity, noncompliance, or withdrawal.
Gemcitabine: 1250 milligrams/square meter (mg/m2) on Days 1 and 8 of every 3 week cycle. Continues for a maximum of six cycles.
Cisplatin: 75 mg/m2 IV on Day 1 of every 3 week cycle. Continues for a maximum of six cycles.

Serious adverse events	Gemcitabine + Cisplatin	Necitumumab + Gemcitabine + Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	208 / 541 (38.45%)	262 / 538 (48.70%)	
number of deaths (all causes)	487	476	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
cancer pain			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to bone			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to central nervous system			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
non-small cell lung cancer			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	23 / 541 (4.25%)	26 / 538 (4.83%)	
occurrences causally related to treatment / all	0 / 23	1 / 26	
deaths causally related to treatment / all	0 / 19	1 / 24	
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertensive crisis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypotension			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypovolaemic shock			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
peripheral artery occlusion			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
orthostatic hypotension			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral venous disease			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral embolism			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral artery thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

superior vena cava syndrome			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
superior vena cava occlusion			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
superficial vein thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vena cava thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
venous thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
venous thrombosis limb			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	3 / 541 (0.55%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
chills			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	8 / 538 (1.49%)	
occurrences causally related to treatment / all	0 / 3	1 / 8	
deaths causally related to treatment / all	0 / 3	1 / 8	
fatigue			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	4 / 541 (0.74%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	7 / 541 (1.29%)	8 / 538 (1.49%)	
occurrences causally related to treatment / all	1 / 7	5 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
generalised oedema			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-cardiac chest pain			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

oedema			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oedema peripheral			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	4 / 541 (0.74%)	7 / 538 (1.30%)	
occurrences causally related to treatment / all	3 / 4	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
sudden death			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Immune system disorders			
drug hypersensitivity			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
social stay hospitalisation			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

pelvic pain			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
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			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
acute pulmonary oedema			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
bronchitis chronic			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
cough			
alternative dictionary used:			

MedDRA 27.1				
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
dyspnoea				
alternative dictionary used: MedDRA 27.1				
subjects affected / exposed	4 / 541 (0.74%)	3 / 538 (0.56%)		
occurrences causally related to treatment / all	4 / 4	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
epistaxis				
alternative dictionary used: MedDRA 27.1				
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
haemoptysis				
alternative dictionary used: MedDRA 27.1				
subjects affected / exposed	9 / 541 (1.66%)	11 / 538 (2.04%)		
occurrences causally related to treatment / all	2 / 9	4 / 11		
deaths causally related to treatment / all	0 / 5	1 / 4		
interstitial lung disease				
alternative dictionary used: MedDRA 27.1				
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	1 / 1		
lung infiltration				
alternative dictionary used: MedDRA 27.1				
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
pulmonary toxicity				
alternative dictionary used: MedDRA 27.1				

subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pharyngeal inflammation			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonitis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary artery thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	9 / 541 (1.66%)	19 / 538 (3.53%)	
occurrences causally related to treatment / all	5 / 9	14 / 19	
deaths causally related to treatment / all	0 / 0	1 / 1	
pulmonary haemorrhage			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	5 / 541 (0.92%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	

pulmonary hypertension			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
pulmonary oedema			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary venous thrombosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract haemorrhage			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
respiratory failure			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
abnormal behaviour			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
alcohol abuse			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
completed suicide			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
confusional state			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
delirium			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood creatinine increased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	6 / 538 (1.12%)	
occurrences causally related to treatment / all	1 / 1	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood phosphorus decreased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
c-reactive protein increased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ecg signs of myocardial ischaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
false positive investigation result			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoglobin decreased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
platelet count decreased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
femoral neck fracture			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
femur fracture			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
head injury			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
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 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (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 27.1			
subjects affected / exposed	21 / 541 (3.88%)	12 / 538 (2.23%)	
occurrences causally related to treatment / all	1 / 21	3 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
overdose			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
toxicity to various agents			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal compression fracture			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vascular graft occlusion			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

underdose			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
tracheo-oesophageal fistula			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute myocardial infarction			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	4 / 541 (0.74%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial flutter			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac arrest			

alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
cardiac failure			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
cardiac failure acute			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
cardiac failure congestive			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
cardiac tamponade			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardio-respiratory arrest			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
coronary artery disease			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial ischaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
pericarditis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericardial effusion malignant			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericardial effusion			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
supraventricular tachycardia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
ataxia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
brain oedema			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
cerebral haemorrhage			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral infarction			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral ischaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
encephalopathy			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	2 / 541 (0.37%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
epilepsy			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hydrocephalus			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
headache			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hemiplegia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
loss of consciousness			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (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 27.1			
subjects affected / exposed	0 / 541 (0.00%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

paraesthesia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral motor neuropathy			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
presyncope			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
radiculopathy			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
radial nerve palsy			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
seizure			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
sciatica			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
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 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
vocal cord paralysis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
agranulocytosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anaemia			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	17 / 541 (3.14%)	22 / 538 (4.09%)	
occurrences causally related to treatment / all	15 / 17	21 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	7 / 541 (1.29%)	6 / 538 (1.12%)	
occurrences causally related to treatment / all	7 / 7	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	4 / 541 (0.74%)	6 / 538 (1.12%)	
occurrences causally related to treatment / all	4 / 4	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	33 / 541 (6.10%)	20 / 538 (3.72%)	
occurrences causally related to treatment / all	31 / 33	20 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
myelosuppression			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancytopenia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	6 / 538 (1.12%)	
occurrences causally related to treatment / all	3 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
thrombocytosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
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 27.1			
subjects affected / exposed	20 / 541 (3.70%)	17 / 538 (3.16%)	
occurrences causally related to treatment / all	20 / 20	16 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
deafness bilateral			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ototoxicity			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
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 27.1			
subjects affected / exposed	1 / 541 (0.18%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain upper			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis ischaemic			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
duodenal ulcer			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
duodenal ulcer perforation			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysphagia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
enteritis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (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 27.1			
subjects affected / exposed	5 / 541 (0.92%)	8 / 538 (1.49%)	
occurrences causally related to treatment / all	3 / 5	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric haemorrhage			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

gastric ulcer			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroduodenal ulcer			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
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 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematemesis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematochezia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (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			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
intestinal obstruction			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatitis acute			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
small intestinal obstruction			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stomatitis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	12 / 538 (2.23%)	
occurrences causally related to treatment / all	2 / 2	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
bile duct stenosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholelithiasis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatorenal syndrome			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
dermatitis acneiform			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dermatitis allergic			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rash maculo-papular			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin fissures			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin toxicity			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin ulcer			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	5 / 541 (0.92%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	4 / 5	4 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
nephrotic syndrome			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
nephropathy toxic			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	6 / 541 (1.11%)	8 / 538 (1.49%)	
occurrences causally related to treatment / all	6 / 6	7 / 8	
deaths causally related to treatment / all	1 / 1	0 / 0	
renal infarct			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal tubular necrosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary retention			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
back pain			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	5 / 538 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
intervertebral disc protrusion			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteolysis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pathological fracture			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain in extremity			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bacterial infection			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	6 / 538 (1.12%)	
occurrences causally related to treatment / all	2 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
cystitis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dental gangrene			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
escherichia urinary tract infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

infectious pleural effusion			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
injection site abscess			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower respiratory tract infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	4 / 541 (0.74%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	1 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenic sepsis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
oral fungal infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
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 27.1			
subjects affected / exposed	20 / 541 (3.70%)	13 / 538 (2.42%)	
occurrences causally related to treatment / all	6 / 20	2 / 13	
deaths causally related to treatment / all	0 / 3	2 / 6	
pneumonia bacterial			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia necrotising			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyelonephritis acute			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary tuberculosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic shock			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
sepsis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	5 / 541 (0.92%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
respiratory tract infection bacterial			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

respiratory tract infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper respiratory tract infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper respiratory tract infection bacterial			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
urinary tract infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
urosepsis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	8 / 541 (1.48%)	5 / 538 (0.93%)	
occurrences causally related to treatment / all	7 / 8	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
diabetic ketoacidosis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
electrolyte imbalance			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypomagnesaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	2 / 538 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperuricaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperkalaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

hyperglycaemia alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypercreatininaemia alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypercalcaemia alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	6 / 541 (1.11%)	4 / 538 (0.74%)	
occurrences causally related to treatment / all	5 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypophosphataemia alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	1 / 538 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	2 / 541 (0.37%)	3 / 538 (0.56%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Gemcitabine + Cisplatin	Necitumumab + Gemcitabine + Cisplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	512 / 541 (94.64%)	518 / 538 (96.28%)	
Investigations			
blood creatinine increased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	41 / 541 (7.58%)	49 / 538 (9.11%)	
occurrences (all)	41	49	
weight decreased			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	36 / 541 (6.65%)	73 / 538 (13.57%)	
occurrences (all)	36	73	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	42 / 541 (7.76%)	55 / 538 (10.22%)	
occurrences (all)	42	55	
headache			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	32 / 541 (5.91%)	57 / 538 (10.59%)	
occurrences (all)	32	57	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	246 / 541 (45.47%)	221 / 538 (41.08%)	
occurrences (all)	246	221	
leukopenia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	85 / 541 (15.71%)	71 / 538 (13.20%)	
occurrences (all)	85	71	
neutropenia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	229 / 541 (42.33%)	220 / 538 (40.89%)	
occurrences (all)	229	220	
thrombocytopenia			

alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	124 / 541 (22.92%)	103 / 538 (19.14%)	
occurrences (all)	124	103	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	112 / 541 (20.70%)	125 / 538 (23.23%)	
occurrences (all)	112	125	
fatigue			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	121 / 541 (22.37%)	117 / 538 (21.75%)	
occurrences (all)	121	117	
oedema peripheral			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	42 / 541 (7.76%)	44 / 538 (8.18%)	
occurrences (all)	42	44	
pyrexia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	61 / 541 (11.28%)	70 / 538 (13.01%)	
occurrences (all)	61	70	
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	29 / 541 (5.36%)	31 / 538 (5.76%)	
occurrences (all)	29	31	
constipation			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	101 / 541 (18.67%)	111 / 538 (20.63%)	
occurrences (all)	101	111	
diarrhoea			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	60 / 541 (11.09%)	84 / 538 (15.61%)	
occurrences (all)	60	84	
dyspepsia			
alternative dictionary used:			

MedDRA 27.1			
subjects affected / exposed	22 / 541 (4.07%)	27 / 538 (5.02%)	
occurrences (all)	22	27	
nausea			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	284 / 541 (52.50%)	265 / 538 (49.26%)	
occurrences (all)	284	265	
stomatitis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	32 / 541 (5.91%)	58 / 538 (10.78%)	
occurrences (all)	32	58	
vomiting			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	134 / 541 (24.77%)	153 / 538 (28.44%)	
occurrences (all)	134	153	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	72 / 541 (13.31%)	93 / 538 (17.29%)	
occurrences (all)	72	93	
dyspnoea			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	79 / 541 (14.60%)	93 / 538 (17.29%)	
occurrences (all)	79	93	
epistaxis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	16 / 541 (2.96%)	40 / 538 (7.43%)	
occurrences (all)	16	40	
haemoptysis			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	22 / 541 (4.07%)	49 / 538 (9.11%)	
occurrences (all)	22	49	
productive cough			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	12 / 541 (2.22%)	29 / 538 (5.39%)	
occurrences (all)	12	29	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	70 / 541 (12.94%)	76 / 538 (14.13%)	
occurrences (all)	70	76	
dermatitis acneiform			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	80 / 538 (14.87%)	
occurrences (all)	3	80	
dry skin			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	8 / 541 (1.48%)	35 / 538 (6.51%)	
occurrences (all)	8	35	
acne			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	3 / 541 (0.55%)	47 / 538 (8.74%)	
occurrences (all)	3	47	
pruritus			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	5 / 541 (0.92%)	39 / 538 (7.25%)	
occurrences (all)	5	39	
rash			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	32 / 541 (5.91%)	252 / 538 (46.84%)	
occurrences (all)	32	252	
skin fissures			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	0 / 541 (0.00%)	27 / 538 (5.02%)	
occurrences (all)	0	27	
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	30 / 541 (5.55%)	29 / 538 (5.39%)	
occurrences (all)	30	29	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	31 / 541 (5.73%)	31 / 538 (5.76%)	
occurrences (all)	31	31	
back pain			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	30 / 541 (5.55%)	38 / 538 (7.06%)	
occurrences (all)	30	38	
pain in extremity			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	21 / 541 (3.88%)	27 / 538 (5.02%)	
occurrences (all)	21	27	
Infections and infestations			
paronychia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	1 / 541 (0.18%)	36 / 538 (6.69%)	
occurrences (all)	1	36	
urinary tract infection			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	13 / 541 (2.40%)	31 / 538 (5.76%)	
occurrences (all)	13	31	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	153 / 541 (28.28%)	162 / 538 (30.11%)	
occurrences (all)	153	162	
hyperglycaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	16 / 541 (2.96%)	28 / 538 (5.20%)	
occurrences (all)	16	28	
hyperkalaemia			
alternative dictionary used: MedDRA 27.1			

subjects affected / exposed	19 / 541 (3.51%)	27 / 538 (5.02%)	
occurrences (all)	19	27	
hypokalaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	27 / 541 (4.99%)	37 / 538 (6.88%)	
occurrences (all)	27	37	
hypomagnesaemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	82 / 541 (15.16%)	159 / 538 (29.55%)	
occurrences (all)	82	159	
hyponatraemia			
alternative dictionary used: MedDRA 27.1			
subjects affected / exposed	29 / 541 (5.36%)	23 / 538 (4.28%)	
occurrences (all)	29	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2010	- Updated secondary and exploratory objectives to reflect modification in the biomarker program; - Updated inclusion criteria for more clarity; - Updated efficacy and pharmacokinetic assessment data to reflect change in medical processes.
09 June 2011	-Serious adverse events reporting information was updated; - Thromboembolic events section was added;
28 May 2013	- A secondary objective was deleted, and some exploratory objectives were amended to reflect prioritization of biomarker analyses on current scientific data. - Changes made to tumor tissue collection and blood sampling collection to be consistent with changes made to objectives.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported