Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo Controlled Study of Rilotumumab (AMG 102) with Epirubicin, Cisplatin, and Capecitabine (ECX) as First-line Therapy in Advanced MET-positive Gastric or Gastroesophageal Junction Adenocarcinoma

Summary

EudraCT number	2011-004923-11
Trial protocol	GR IT CZ BE PT AT GB DE SE HU ES DK BG PL SK RO
Global end of trial date	07 August 2015

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	20070622

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01697072
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine if the treatment of rilotumumab in combination with ECX significantly improves overall survival (OS) as compared with rilotumumab-placebo in combination with ECX in subjects with unresectable, locally advanced or metastatic, mesenchymal epithelial transition factor (MET)-positive, gastric, or gastroesophageal junction (GEJ).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and country-specific regulations/guidelines.
The investigator was responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified screening procedures or any investigational products are administered.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.
An independent Data Monitoring Committee (DMC) external to Amgen conducted planned safety reviews and one interim efficacy review.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 34

Country: Number of subjects enrolled	United Kingdom: 56
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Russian Federation: 63
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	Ukraine: 43
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	609
EEA total number of subjects	360

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)	404
From 65 to 84 years	205
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 152 centers across Australia, Europe, South Africa, North America, and South America.

Pre-assignment

Screening details:

Eligible subjects were randomized in a 1:1 ratio to either of 2 treatment arms. Randomization was stratified by 2 factors; extent of the disease (locally advanced vs metastatic disease) and the Eastern Cooperative Oncology Group (ECOG) status (0 vs 1).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + ECX

Arm description:

Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Arm type	Placebo
Investigational medicinal product name	Placebo to rilotumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as an intravenous (IV) infusion through a peripheral line or indwelling catheter on day 1 of each cycle before dosing of ECX.

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

Dosage and administration details:

50 mg/m² IV on day 1 of every 21 day cycle.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg/m² IV on day 1 of every 21-day cycle

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

625 mg/m² orally twice a day on days 1-21 of every 21 day cycle

Arm title	Rilotumumab + ECX

Arm description:

Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Arm type	Experimental
Investigational medicinal product name	Rilotumumab
Investigational medicinal product code	AMG 102
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as an intravenous (IV) infusion through a peripheral line or indwelling catheter on day 1 of each cycle before dosing of ECX.

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

Dosage and administration details:

50 mg/m² IV on day 1 of every 21 day cycle.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg/m² IV on day 1 of every 21-day cycle

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

625 mg/m² orally twice a day on days 1-21 of every 21 day cycle

Number of subjects in period 1	Placebo + ECX	Rilotumumab + ECX
Started	305	304
Received Study Drug	300	297
Completed	0	0
Not completed	305	304
Consent withdrawn by subject	8	16
Death	196	217
Lost to follow-up	10	7
Subjects continuing study	2	1
Decision by sponsor	89	63

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + ECX

Reporting group description:

Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Reporting group title	Rilotumumab + ECX

Reporting group description:

Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Reporting group values	Placebo + ECX	Rilotumumab + ECX	Total
Number of subjects	305	304	609
Age Categorical Units: Subjects			
< 65 years	211	193	404
≥ 65 years	94	111	205
Age Continuous Units: years			
arithmetic mean	58.4	59.5	
standard deviation	± 11.2	± 11.3	-
Gender Categorical Units: Subjects			
Female	85	99	184
Male	220	205	425
Race Units: Subjects			
Asian	2	4	6
Black or African American	5	3	8
Native Hawaiian or Other Pacific Islander	0	1	1
Other	10	6	16
White	288	290	578
Region Units: Subjects			
Western Europe, South Africa and Australia	129	121	250
Eastern Europe (Including Turkey)	130	141	271
North America	27	26	53
South America	19	16	35
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Scale used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50%			

of waking hours; 3 = Capable of only limited self care, confined to a bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	122	122	244
Grade 1	183	182	365
Disease Extent Units: Subjects			
Locally advanced	31	30	61
Metastatic disease	274	274	548

End points

End points reporting groups

Reporting group title	Placebo + ECX

Reporting group description:

Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Reporting group title	Rilotumumab + ECX

Reporting group description:

Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) is defined as the time from randomization to death due to any cause. Subjects who had not died by the analysis data cut-off or were lost to follow-up were censored at their last contact date, subjects who withdrew consent were censored at the date of withdrawal. OS was analyzed using Kaplan-Meier methods.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	304		
Units: months				
median (confidence interval 95%)	10.74 (9.63 to 12.35)	8.84 (7.72 to 10.15)		

Statistical analyses

Statistical analysis title	Primary Analysis of Overall Survival

Statistical analysis description:

A log-rank test stratified by the randomization factors was used for the primary comparison.

Comparison groups	Placebo + ECX v Rilotumumab + ECX

Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [1]
Method	Logrank

Notes:

[1] - 1-sided p-value stratified by disease extent and ECOG performance status.

Statistical analysis title	Additional Analysis of Overall Survival

Statistical analysis description:

A Cox proportional hazards regression model was used to provide the hazard ratio and 2-sided 95% CI for rilotumumab + ECX relative to placebo + ECX, stratified by disease extent and ECOG performance status. A hazard ratio < 1.0 indicates a lower average event rate and a longer overall survival for Rilotumumab + ECX relative to Placebo + ECX.

Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.339
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.103
upper limit	1.627

Notes:

[2] - 2-sided p-value stratified by disease extent and ECOG performance status.

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) was defined as the time from the date of randomization to either disease progression or death. PFS was based upon the investigators assessment of disease progression, per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. If a subject's disease did not progress and the subject was alive, PFS was censored at the last evaluable radiological assessment. If a subject had no tumor evaluation in the study, the PFS time was censored at the date of randomization. PFS was analyzed using Kaplan-Meier methods.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	304		
Units: months				
median (confidence interval 95%)	5.98 (5.65 to 7.2)	5.62 (5.32 to 5.91)		

Statistical analyses

Statistical analysis title	Primary Analysis of Progression-free Survival

Statistical analysis description:

A log-rank test stratified by the randomization factors was used for the primary comparison.

Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99 [3]
Method	Logrank

Notes:

[3] - 1-sided p-value stratified by disease extent and ECOG performance status

Statistical analysis title	Additional Analysis of Progression-free Survival

Statistical analysis description:

The hazard ratio estimates were from a Cox proportional hazard model stratified by disease extent and ECOG performance status. A hazard ratio < 1.0 indicates a lower average event rate and a longer progression-free survival for Rilotumumab + ECX relative to Placebo + ECX.

Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.256
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.043
upper limit	1.512

Notes:

[4] - 2-sided

Secondary: Survival Rate at 12 Months

End point title	Survival Rate at 12 Months

End point description:

Survival rate at 12 months was defined as the stratified Kaplan-Meier (K-M) estimate of the percentage of subjects alive at 12 months.

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	304		
Units: percentage of participants				
number (confidence interval 95%)	45.1 (39.2 to 50.8)	36 (30.3 to 41.7)		

Statistical analyses

Statistical analysis title	Primary Analysis of Survival Rate at 12 Months
Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	-0.7

Notes:

[5] - Stratified by disease extent and ECOG performance status.

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression (TTP) was defined as the time from the date of randomization to disease progression (per RECIST 1.1). If a subject's disease did not progress, TTP was censored at the last evaluable radiological assessment, surgical resection date or the start of new anti-cancer therapy (if available) date. If a subject had no tumor evaluation in the study, the TTP time was censored at the date of randomization. If a subject died without radiological progression, TTP was censored at the last evaluable radiological assessment date. TTP was analyzed using Kaplan-Meier methods.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	304		
Units: months				
median (confidence interval 95%)	7.06 (5.88 to 7.85)	6.05 (5.68 to 7.95)		

Statistical analyses

Statistical analysis title	Primary Analysis of Time to Progression
Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95 [6]
Method	Logrank

Notes:

[6] - 1-sided p-value stratified by disease extent and ECOG performance status

Statistical analysis title	Additional Analysis of Time to Progression
Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.097 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.237
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.961
upper limit	1.591

Notes:

[7] - The hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0indicates a lower average event rate and a longer time to progression for Rilotumumab + ECX relativeto Placebo + ECX.

[8] - 2-sided

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate was defined as the incidence rate of either complete response (CR) or partial response (PR) per RECIST 1.1 criteria. Best Overall Response for a subject is the best observed disease response per RECIST1.1, excluding tumor assessments after initiation of new anti-cancer therapy, surgical resection or an assessment of disease progression. Overall response was analyzed in the Response Analysis Set, defined as the subset of subjects in the Full Analysis Set with at least 1 uni-dimensionally measurable lesion at baseline, per RECIST 1.1.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267[9]	262[10]		
Units: percentage of participants				
number (confidence interval 95%)	44.6 (38.5 to 50.8)	29.8 (24.3 to 35.7)		

Notes:

[9] - Response Analysis Set

[10] - Response Analysis Set

Statistical analyses

Statistical analysis title	Analysis of Best Overall Response

Statistical analysis description:

A Cochran-Mantel–Haenszel test stratified by extent of disease and ECOG performance status was used to provide the adjusted common odds ratio.

Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.76

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate was defined as the incidence rate of either a CR, PR or stable disease (SD) per RECIST 1.1. The SD classification required subjects to have a response of SD ≥ 11 weeks after the date of the first dose of rilotumumab.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267[11]	262[12]		
Units: percentage of participants				
number (confidence interval 95%)	70.8 (64.9 to 76.2)	53.4 (47.2 to 59.6)		

Notes:

[11] - Response Analysis Set

[12] - Response Analysis Set

Statistical analyses

Statistical analysis title	Analysis of Disease Control Rate

Statistical analysis description:

A Cochran-Mantel–Haenszel test stratified by extent of disease and ECOG performance status was used to provide the adjusted common odds ratio.

Comparison groups	Placebo + ECX v Rilotumumab + ECX
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.68

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR) was defined as time from the date of first response (PR or CR) to disease progression (per RECIST 1.1) or death. If a subject's disease did not progress and the subject was alive, DOR was censored at the last evaluable radiological assessment. DOR was analyzed using Kaplan-Meier methods.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119[13]	78[14]		
Units: months				
median (confidence interval 95%)	5.29 (4.5 to 6.08)	5.65 (4.6 to 6.51)		

Notes:

[13] - Response Analysis Set with CR or PR

[14] - Response Analysis Set with CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initial Objective Response

End point title	Time to Initial Objective Response

End point description:

Time to initial response is calculated as the time from randomization to the first tumor response assessment with an outcome indicating an objective response (CR or PR) as classified by RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119[15]	78[16]		
Units: months				
median (inter-quartile range (Q1-Q3))	2.76 (2.628 to 2.957)	2.793 (2.694 to 2.99)		

Notes:

[15] - Response Analysis Set with CR or PR

[16] - Response Analysis Set with CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

End point type	Secondary

End point timeframe:

From the date of first administration of protocol specified treatment through 30 days after the last administration of protocol specified treatment.

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299[17]	298[18]		
Units: participants				
Any adverse event	288	283		
Serious adverse events	149	142		
Leading to discontinuation of study drug	30	41		
Leading to discontinuation of Epirubicin	53	57		
Leading to discontinuation of Cisplatin	48	52		
Leading to discontinuation of Capecitabine	48	57		
Leading to discontinuation of all treatments	21	30		
Fatal adverse events	31	42		

Notes:

[17] - Subjects who received at least 1 dose of study drug, analyzed according to the treatment received.
[18] - Subjects who received at least 1 dose of study drug, analyzed according to the treatment received.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Antibodies to Rilotumumab

End point title	Number of Participants who Developed Antibodies to Rilotumumab

End point description:

participants who were binding antibody positive post baseline with a negative or no result at baseline. The analysis was performed using the Antibody Analysis Set which includes all randomized subjects with evaluable antibody data.

End point type	Secondary

End point timeframe:

Day 1 of cycles 1, 3 & 7, and every 8 cycles thereafter (prior to study drug administration).

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259[19]	228[20]		
Units: participants	0	0		

Notes:

[19] - Subjects with a postbaseline result

[20] - Subjects with a postbaseline result

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment

End point title	Duration of Treatment

End point description:

End point type	Secondary

End point timeframe:

Day 1 until end of treatment

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299	298		
Units: months				
median (inter-quartile range (Q1-Q3))				
Placebo to Rilotumumab/Rilotumumab	3.7 (1.6 to 6.4)	2.5 (1 to 5.1)		
Epirubicin	4.1 (2.1 to 6.2)	2.4 (1 to 4.8)		
Cisplatin	4.2 (2.1 to 6.2)	2.6 (1 to 4.9)		
Capecitabine	4.8 (2.8 to 6.9)	2.9 (1.4 to 5.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration of Rilotumumab in Cycle 1

End point title	Maximum Observed Serum Concentration of Rilotumumab in Cycle 1[21]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1: Pre-dose, and within 5 min before end of infusion , 2 hours, 24 hours, 168 hours, and 336 hours after start of infusion and predose on day 1 of cycle 2

Notes:

[21] - 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: Rilotumumab pharmacokinetic (PK) parameters were only analyzed for subjects in the Rilotumumab + ECX treatment arm.

End point values	Rilotumumab + ECX			
Subject group type	Reporting group			
Number of subjects analysed	48[22]			
Units: µg/mL				
arithmetic mean (standard deviation)	227 (± 59.1)			

Notes:

[22] - Subjects who participated in the intensive PK assessment with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of Rilotumumab in Cycle 1

End point title	Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of Rilotumumab in Cycle 1[23]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 predose and within 5 minutes before end of infusion, 2 hours, 24 hours, 168 hours, and 336 hours after start of infusion and Cycle 2, predose on day 1

Notes:

[23] - 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: Rilotumumab pharmacokinetic (PK) parameters were only analyzed for subjects in the Rilotumumab + ECX treatment arm.

End point values	Rilotumumab + ECX			
Subject group type	Reporting group			
Number of subjects analysed	43[24]			
Units: hr*µg/mL				
arithmetic mean (standard deviation)	54200 (± 12200)			

Notes:

[24] - Subjects who participated in the intensive PK assessment with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration of ECX in Cycle 3

End point title	Maximum Observed Concentration of ECX in Cycle 3

End point description:

End point type	Secondary

End point timeframe:

Cycle 3 (week 7) day 1 predose to 24 hours post infusion

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[25]	37[26]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Epirubicin (N = 21, 23)	1.15 (± 0.948)	0.973 (± 0.799)		

Total Platinum (N = 26, 19)	2.39 (± 0.531)	2.42 (± 0.508)		
Unbound Platinum (N = 26, 19)	0.636 (± 0.41)	0.814 (± 0.458)		
Capecitabine (N = 21, 14)	2.82 (± 4.01)	2.37 (± 2.56)		
5-Fluorouracil (N = 21, 12)	0.0765 (± 0.0479)	0.1 (± 0.0513)		

Notes:

[25] - Subjects who participated in the intensive PK assessment with ECX samples

[26] - Subjects who participated in the intensive PK assessment with ECX samples

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of ECX in Cycle 3

End point title	Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of ECX in Cycle 3

End point description:

End point type	Secondary

End point timeframe:

Cycle 3

End point values	Placebo + ECX	Rilotumumab + ECX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[27]	37[28]		
Units: hr*µg/mL				
arithmetic mean (standard deviation)				
Epirubicin (N = 19, 18)	0.777 (± 0.322)	0.66 (± 0.372)		
Total Platinum (N = 26, 14)	38.3 (± 8.35)	39.6 (± 5.18)		
Unbound Platinum (N = 26, 14)	4.11 (± 3.21)	4.11 (± 1.79)		
Capecitabine (N = 21, 13)	4.29 (± 5.37)	4.47 (± 4.92)		
5-Fluorouracil (N = 21, 12)	0.13 (± 0.0558)	0.205 (± 0.0975)		

Notes:

[27] - Subjects who participated in the intensive PK assessment with ECX samples

[28] - Subjects who participated in the intensive PK assessment with ECX samples

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Median duration of exposure to study treatment was 3.7 months and 2.5 months for the placebo and rilotumumab arms respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo + ECX

Reporting group description:

Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Reporting group title	Rilotumumab + ECX

Reporting group description:

Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m² IV on day 1, cisplatin (C) 60 mg/m2² IV on day 1, and capecitabine (X) 625 mg/m² orally twice a day on days 1 to 21 for a maximum of 10 cycles.

Serious adverse events	Placebo + ECX	Rilotumumab + ECX	
Total subjects affected by serious adverse events			
subjects affected / exposed	149 / 299 (49.83%)	142 / 298 (47.65%)	
number of deaths (all causes)	194	213	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Adenocarcinoma gastric			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cancer pain			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	2 / 299 (0.67%)	8 / 298 (2.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 7	
Gastric cancer stage IV			
subjects affected / exposed	4 / 299 (1.34%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (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			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal cancer metastatic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Signet-ring cell carcinoma			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tumour haemorrhage			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 299 (0.67%)	8 / 298 (2.68%)	
occurrences causally related to treatment / all	0 / 2	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			

subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 299 (2.34%)	8 / 298 (2.68%)	
occurrences causally related to treatment / all	5 / 8	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain death			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 299 (0.67%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Device dislocation			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 299 (1.34%)	5 / 298 (1.68%)	
occurrences causally related to treatment / all	1 / 6	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			

subjects affected / exposed	3 / 299 (1.00%)	4 / 298 (1.34%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 299 (0.33%)	4 / 298 (1.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 1	1 / 4	
Non-cardiac chest pain			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 299 (0.33%)	4 / 298 (1.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organ failure			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 299 (2.68%)	4 / 298 (1.34%)	
occurrences causally related to treatment / all	2 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 2	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
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			
Balanoposthitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
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 distress syndrome			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 299 (0.33%)	4 / 298 (1.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	4 / 299 (1.34%)	12 / 298 (4.03%)	
occurrences causally related to treatment / all	3 / 4	6 / 12	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood altered			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium increased			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Cervical vertebral fracture			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding tube complication			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 299 (1.00%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	2 / 3	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Myocardial infarction			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (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			
Brain oedema			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous thrombosis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coma hepatic			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Presyncope			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 299 (7.02%)	7 / 298 (2.35%)	
occurrences causally related to treatment / all	13 / 29	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	11 / 299 (3.68%)	12 / 298 (4.03%)	
occurrences causally related to treatment / all	6 / 12	6 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	6 / 299 (2.01%)	10 / 298 (3.36%)	
occurrences causally related to treatment / all	2 / 6	4 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 299 (1.67%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 299 (2.68%)	7 / 298 (2.35%)	
occurrences causally related to treatment / all	1 / 9	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	11 / 299 (3.68%)	7 / 298 (2.35%)	
occurrences causally related to treatment / all	2 / 11	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysphagia			
subjects affected / exposed	7 / 299 (2.34%)	7 / 298 (2.35%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 299 (0.33%)	4 / 298 (1.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastric perforation			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 299 (1.00%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	5 / 299 (1.67%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 299 (1.00%)	5 / 298 (1.68%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	1 / 3	
Jejunal perforation			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 299 (1.67%)	7 / 298 (2.35%)	
occurrences causally related to treatment / all	3 / 5	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Obstruction gastric			
subjects affected / exposed	3 / 299 (1.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal obstruction			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	12 / 299 (4.01%)	14 / 298 (4.70%)	
occurrences causally related to treatment / all	8 / 15	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	3 / 299 (1.00%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation bile duct			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
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			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephropathy toxic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (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			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 299 (0.33%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph gland infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 299 (1.00%)	5 / 298 (1.68%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 299 (0.33%)	4 / 298 (1.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mycosis			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 299 (2.01%)	10 / 298 (3.36%)	
occurrences causally related to treatment / all	3 / 8	2 / 12	
deaths causally related to treatment / all	0 / 2	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperosmolar hyperglycaemic state			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 299 (1.34%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	5 / 299 (1.67%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	8 / 11	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 299 (1.34%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo + ECX	Rilotumumab + ECX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	281 / 299 (93.98%)	268 / 298 (89.93%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Mycosis fungoides			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Axillary vein thrombosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Deep vein thrombosis			
subjects affected / exposed	10 / 299 (3.34%)	21 / 298 (7.05%)	
occurrences (all)	11	21	
Embolism			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Hot flush			

subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences (all)	2	2	
Hypertension			
subjects affected / exposed	12 / 299 (4.01%)	1 / 298 (0.34%)	
occurrences (all)	14	2	
Hypotension			
subjects affected / exposed	7 / 299 (2.34%)	18 / 298 (6.04%)	
occurrences (all)	9	22	
Intermittent claudication			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	3	
Orthostatic hypotension			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences (all)	2	2	
Pallor			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Peripheral venous disease			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	2 / 299 (0.67%)	5 / 298 (1.68%)	
occurrences (all)	2	7	
Phlebitis superficial			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Thrombophlebitis			

subjects affected / exposed	1 / 299 (0.33%)	6 / 298 (2.01%)	
occurrences (all)	1	7	
Thrombophlebitis superficial			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Thrombosis			
subjects affected / exposed	2 / 299 (0.67%)	5 / 298 (1.68%)	
occurrences (all)	2	5	
Vascular insufficiency			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Vena cava thrombosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Venous thrombosis			
subjects affected / exposed	2 / 299 (0.67%)	5 / 298 (1.68%)	
occurrences (all)	2	5	
Venous thrombosis limb			
subjects affected / exposed	0 / 299 (0.00%)	5 / 298 (1.68%)	
occurrences (all)	0	6	
Surgical and medical procedures			
Abdominal cavity drainage			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Dental operation			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	52 / 299 (17.39%)	52 / 298 (17.45%)	
occurrences (all)	107	112	
Catheter site related reaction			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	0 / 299 (0.00%)	4 / 298 (1.34%)	
occurrences (all)	0	4	
Chest pain			
subjects affected / exposed	4 / 299 (1.34%)	8 / 298 (2.68%)	
occurrences (all)	5	9	
Chills			
subjects affected / exposed	4 / 299 (1.34%)	8 / 298 (2.68%)	
occurrences (all)	4	8	
Device issue			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Device occlusion			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Extravasation			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Face oedema			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	98 / 299 (32.78%)	103 / 298 (34.56%)	
occurrences (all)	218	199	
Feeling abnormal			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Feeling hot			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Generalised oedema			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Hyperpyrexia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	
Hyperthermia			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Hypothermia			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Inflammation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Injection site bruising			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Injection site phlebitis			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Injection site reaction			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Localised oedema			
subjects affected / exposed	0 / 299 (0.00%)	6 / 298 (2.01%)	
occurrences (all)	0	13	
Malaise			
subjects affected / exposed	4 / 299 (1.34%)	1 / 298 (0.34%)	
occurrences (all)	7	1	
Medical device pain			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			

subjects affected / exposed	15 / 299 (5.02%)	21 / 298 (7.05%)	
occurrences (all)	22	30	
Non-cardiac chest pain			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	3	
Oedema			
subjects affected / exposed	13 / 299 (4.35%)	19 / 298 (6.38%)	
occurrences (all)	15	26	
Oedema peripheral			
subjects affected / exposed	38 / 299 (12.71%)	86 / 298 (28.86%)	
occurrences (all)	54	130	
Pain			
subjects affected / exposed	8 / 299 (2.68%)	14 / 298 (4.70%)	
occurrences (all)	9	17	
Peripheral swelling			
subjects affected / exposed	1 / 299 (0.33%)	4 / 298 (1.34%)	
occurrences (all)	1	4	
Pyrexia			
subjects affected / exposed	17 / 299 (5.69%)	20 / 298 (6.71%)	
occurrences (all)	23	21	
Swelling			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Thrombosis in device			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences (all)	2	2	
Xerosis			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Multiple allergies			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

Social circumstances			
Sight disability			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Genital erythema			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Haematospermia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Oedema genital			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Penile oedema			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Penile pain			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Prostatomegaly			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Vulvovaginal rash			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	

Bronchopneumopathy				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Cough				
subjects affected / exposed	23 / 299 (7.69%)	10 / 298 (3.36%)		
occurrences (all)	25	10		
Dysphonia				
subjects affected / exposed	4 / 299 (1.34%)	0 / 298 (0.00%)		
occurrences (all)	7	0		
Dyspnoea				
subjects affected / exposed	20 / 299 (6.69%)	23 / 298 (7.72%)		
occurrences (all)	25	30		
Dyspnoea exertional				
subjects affected / exposed	1 / 299 (0.33%)	6 / 298 (2.01%)		
occurrences (all)	1	6		
Epistaxis				
subjects affected / exposed	3 / 299 (1.00%)	5 / 298 (1.68%)		
occurrences (all)	3	5		
Haemoptysis				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Hiccups				
subjects affected / exposed	13 / 299 (4.35%)	8 / 298 (2.68%)		
occurrences (all)	18	10		
Hypoxia				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Increased upper airway secretion				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Lung consolidation				

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Nasal discomfort			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Obstructive airways disorder			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	6 / 299 (2.01%)	3 / 298 (1.01%)	
occurrences (all)	6	3	
Pharyngeal erythema			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	3 / 299 (1.00%)	3 / 298 (1.01%)	
occurrences (all)	3	4	
Pleurisy			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Pleuritic pain			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Pneumonia aspiration			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Pneumonitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Pulmonary artery thrombosis			

subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Pulmonary embolism			
subjects affected / exposed	13 / 299 (4.35%)	15 / 298 (5.03%)	
occurrences (all)	13	17	
Pulmonary thrombosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 299 (0.33%)	3 / 298 (1.01%)	
occurrences (all)	1	3	
Throat tightness			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	11 / 299 (3.68%)	13 / 298 (4.36%)	
occurrences (all)	11	14	
Bradyphrenia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences (all)	0	3	
Depressed mood			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences (all)	0	4	

Depression			
subjects affected / exposed	9 / 299 (3.01%)	7 / 298 (2.35%)	
occurrences (all)	10	8	
Disorientation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	19 / 299 (6.35%)	19 / 298 (6.38%)	
occurrences (all)	19	22	
Irritability			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Libido decreased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Mood altered			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Nervousness			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Phobia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Sleep disorder due to a general medical condition			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	6 / 299 (2.01%)	6 / 298 (2.01%)		
occurrences (all)	9	8		
Amylase increased				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Aspartate aminotransferase increased				
subjects affected / exposed	13 / 299 (4.35%)	7 / 298 (2.35%)		
occurrences (all)	15	8		
Blood albumin decreased				
subjects affected / exposed	2 / 299 (0.67%)	3 / 298 (1.01%)		
occurrences (all)	5	4		
Blood alkaline phosphatase increased				
subjects affected / exposed	9 / 299 (3.01%)	7 / 298 (2.35%)		
occurrences (all)	12	10		
Blood bicarbonate decreased				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Blood bilirubin				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Blood bilirubin abnormal				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Blood bilirubin increased				
subjects affected / exposed	6 / 299 (2.01%)	0 / 298 (0.00%)		
occurrences (all)	9	0		
Blood calcium decreased				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Blood creatine abnormal				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Blood creatine increased				

subjects affected / exposed	4 / 299 (1.34%)	4 / 298 (1.34%)	
occurrences (all)	4	5	
Blood creatinine increased			
subjects affected / exposed	7 / 299 (2.34%)	9 / 298 (3.02%)	
occurrences (all)	8	12	
Blood glucose increased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Blood iron decreased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Blood magnesium decreased			
subjects affected / exposed	4 / 299 (1.34%)	1 / 298 (0.34%)	
occurrences (all)	7	1	
Blood phosphorus decreased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Blood potassium decreased			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	2	2	
Blood sodium decreased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Blood testosterone decreased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Body temperature increased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

C-reactive protein increased			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Capillary fragility increased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Clostridium test positive			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Creatinine renal clearance decreased			
subjects affected / exposed	21 / 299 (7.02%)	15 / 298 (5.03%)	
occurrences (all)	33	20	
Creatinine renal clearance increased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Ejection fraction decreased			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences (all)	2	2	
Fibrin D dimer increased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Glomerular filtration rate			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Glomerular filtration rate abnormal			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Glomerular filtration rate decreased			

subjects affected / exposed	2 / 299 (0.67%)	9 / 298 (3.02%)		
occurrences (all)	2	16		
Granulocyte count decreased				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Haemoglobin				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Haemoglobin abnormal				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Haemoglobin decreased				
subjects affected / exposed	8 / 299 (2.68%)	3 / 298 (1.01%)		
occurrences (all)	11	16		
Heart rate increased				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
International normalised ratio increased				
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)		
occurrences (all)	1	1		
Neutrophil count				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	5	0		
Neutrophil count decreased				
subjects affected / exposed	11 / 299 (3.68%)	11 / 298 (3.69%)		
occurrences (all)	42	24		
Platelet count decreased				
subjects affected / exposed	11 / 299 (3.68%)	11 / 298 (3.69%)		
occurrences (all)	18	22		
Platelet count increased				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Prothrombin time shortened				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		

Red blood cell count decreased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Renal function test abnormal			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Transaminases increased			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Troponin I increased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Urine output increased			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	49 / 299 (16.39%)	23 / 298 (7.72%)	
occurrences (all)	63	33	
Weight increased			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
White blood cell count decreased			
subjects affected / exposed	14 / 299 (4.68%)	13 / 298 (4.36%)	
occurrences (all)	28	42	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Dumping syndrome			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Eye injury			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Face injury			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	5 / 299 (1.67%)	2 / 298 (0.67%)	
occurrences (all)	5	2	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Infusion related reaction			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Joint injury			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Nail injury			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences (all)	0	4	
Rib fracture			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Urethral injury			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Vascular injury			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Congenital, familial and genetic			

disorders			
Epidermolysis bullosa			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	
Phimosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	4 / 299 (1.34%)	0 / 298 (0.00%)	
occurrences (all)	4	0	
Bradycardia			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Bundle branch block left			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Cardiomyopathy			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Cardiovascular disorder			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Cyanosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	
Myocardial fibrosis			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 299 (0.00%)	4 / 298 (1.34%)	
occurrences (all)	0	4	
Pericardial effusion			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	
Right ventricular dysfunction			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Tachycardia			
subjects affected / exposed	3 / 299 (1.00%)	5 / 298 (1.68%)	
occurrences (all)	4	5	
Ventricular extrasystoles			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Altered state of consciousness			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Amnesia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Anaesthesia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	

Aphasia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Ataxia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Balance disorder			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Cerebrovascular accident			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Disturbance in attention			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	26 / 299 (8.70%)	32 / 298 (10.74%)	
occurrences (all)	32	39	
Dizziness postural			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	19 / 299 (6.35%)	16 / 298 (5.37%)	
occurrences (all)	24	23	
Headache			
subjects affected / exposed	23 / 299 (7.69%)	18 / 298 (6.04%)	
occurrences (all)	28	21	
Hypoaesthesia			
subjects affected / exposed	5 / 299 (1.67%)	4 / 298 (1.34%)	
occurrences (all)	5	4	
Hypotonia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

Lethargy			
subjects affected / exposed	6 / 299 (2.01%)	2 / 298 (0.67%)	
occurrences (all)	8	2	
Memory impairment			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Mental retardation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	33 / 299 (11.04%)	24 / 298 (8.05%)	
occurrences (all)	52	34	
Neurotoxicity			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	2	
Paraesthesia			
subjects affected / exposed	11 / 299 (3.68%)	5 / 298 (1.68%)	
occurrences (all)	13	5	
Parkinson's disease			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Parosmia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Peripheral motor neuropathy			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	4	2	
Peripheral sensory neuropathy			
subjects affected / exposed	11 / 299 (3.68%)	8 / 298 (2.68%)	
occurrences (all)	13	10	
Polyneuropathy			
subjects affected / exposed	4 / 299 (1.34%)	7 / 298 (2.35%)	
occurrences (all)	5	11	
Post herpetic neuralgia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	

Presyncope			
subjects affected / exposed	3 / 299 (1.00%)	0 / 298 (0.00%)	
occurrences (all)	3	0	
Sciatica			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Seizure			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Sensory disturbance			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	3 / 299 (1.00%)	3 / 298 (1.01%)	
occurrences (all)	3	3	
Speech disorder			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	5 / 299 (1.67%)	8 / 298 (2.68%)	
occurrences (all)	6	8	
Tension headache			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	4 / 299 (1.34%)	0 / 298 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	117 / 299 (39.13%)	92 / 298 (30.87%)	
occurrences (all)	256	203	
Anaemia macrocytic			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Bone marrow failure			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Coagulopathy			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Febrile neutropenia			
subjects affected / exposed	4 / 299 (1.34%)	3 / 298 (1.01%)	
occurrences (all)	4	3	
Haemorrhagic disorder			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Hypofibrinogenaemia			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	7	
Leukocytosis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	31 / 299 (10.37%)	22 / 298 (7.38%)	
occurrences (all)	68	40	
Lymphadenopathy			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Lymphopenia			
subjects affected / exposed	5 / 299 (1.67%)	2 / 298 (0.67%)	
occurrences (all)	13	2	
Neutropenia			
subjects affected / exposed	122 / 299 (40.80%)	105 / 298 (35.23%)	
occurrences (all)	314	245	
Pancytopenia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	3	3	
Thrombocytopenia			
subjects affected / exposed	16 / 299 (5.35%)	19 / 298 (6.38%)	
occurrences (all)	37	40	
Ear and labyrinth disorders			

Deafness			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Deafness neurosensory			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Ear congestion			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	1 / 299 (0.33%)	4 / 298 (1.34%)	
occurrences (all)	1	4	
Hearing impaired			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Hypoacusis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Ototoxicity			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	12 / 299 (4.01%)	6 / 298 (2.01%)	
occurrences (all)	14	6	
Vertigo			
subjects affected / exposed	2 / 299 (0.67%)	6 / 298 (2.01%)	
occurrences (all)	2	6	
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Cataract			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Diplopia			

subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Dry eye			
subjects affected / exposed	1 / 299 (0.33%)	3 / 298 (1.01%)	
occurrences (all)	1	3	
Eye irritation			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Eye oedema			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Foreign body sensation in eyes			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	6 / 299 (2.01%)	5 / 298 (1.68%)	
occurrences (all)	6	7	
Periorbital oedema			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Photophobia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Photopsia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Uveitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Vision blurred			

subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Visual acuity reduced			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Abdominal distension			
subjects affected / exposed	9 / 299 (3.01%)	10 / 298 (3.36%)	
occurrences (all)	10	10	
Abdominal pain			
subjects affected / exposed	49 / 299 (16.39%)	43 / 298 (14.43%)	
occurrences (all)	56	64	
Abdominal pain lower			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Abdominal pain upper			
subjects affected / exposed	22 / 299 (7.36%)	16 / 298 (5.37%)	
occurrences (all)	27	17	
Anal fissure			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Anorectal discomfort			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Aphagia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Aphthous stomatitis			
subjects affected / exposed	3 / 299 (1.00%)	4 / 298 (1.34%)	
occurrences (all)	3	4	

Ascites			
subjects affected / exposed	11 / 299 (3.68%)	10 / 298 (3.36%)	
occurrences (all)	13	10	
Chapped lips			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Colitis			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	61 / 299 (20.40%)	67 / 298 (22.48%)	
occurrences (all)	86	81	
Diarrhoea			
subjects affected / exposed	78 / 299 (26.09%)	59 / 298 (19.80%)	
occurrences (all)	115	80	
Dry mouth			
subjects affected / exposed	6 / 299 (2.01%)	5 / 298 (1.68%)	
occurrences (all)	8	5	
Duodenal obstruction			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	18 / 299 (6.02%)	9 / 298 (3.02%)	
occurrences (all)	19	12	
Dysphagia			
subjects affected / exposed	16 / 299 (5.35%)	18 / 298 (6.04%)	
occurrences (all)	19	23	
Eructation			
subjects affected / exposed	3 / 299 (1.00%)	0 / 298 (0.00%)	
occurrences (all)	3	0	
Faecaloma			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

Faeces discoloured			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Faeces hard			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Faeces soft			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	6 / 299 (2.01%)	3 / 298 (1.01%)	
occurrences (all)	6	4	
Gastritis			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Gastrointestinal fistula			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 299 (1.34%)	7 / 298 (2.35%)	
occurrences (all)	6	7	
Gingival pain			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Haematochezia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	6 / 299 (2.01%)	3 / 298 (1.01%)	
occurrences (all)	6	4	

Lip swelling			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Lip ulceration			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Malignant dysphagia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	2	
Melaena			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Mouth ulceration			
subjects affected / exposed	5 / 299 (1.67%)	3 / 298 (1.01%)	
occurrences (all)	5	3	
Nausea			
subjects affected / exposed	152 / 299 (50.84%)	128 / 298 (42.95%)	
occurrences (all)	315	241	
Obstruction gastric			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Odynophagia			
subjects affected / exposed	4 / 299 (1.34%)	0 / 298 (0.00%)	
occurrences (all)	4	0	
Oesophageal disorder			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Oesophageal stenosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Oesophagitis			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	

Oral pain			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	3	
Pancreatitis chronic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Reflux gastritis			
subjects affected / exposed	3 / 299 (1.00%)	0 / 298 (0.00%)	
occurrences (all)	3	0	
Retching			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	6	
Small intestinal obstruction			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	25 / 299 (8.36%)	27 / 298 (9.06%)	
occurrences (all)	38	34	
Subileus			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	2	
Teething			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Tongue discolouration			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

Tooth loss			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	94 / 299 (31.44%)	94 / 298 (31.54%)	
occurrences (all)	153	149	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Cholelithiasis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Cholestasis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Hepatic pain			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Hepatomegaly			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Hepatotoxicity			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
subjects affected / exposed	11 / 299 (3.68%)	9 / 298 (3.02%)	
occurrences (all)	16	9	
Jaundice			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Jaundice cholestatic			

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	94 / 299 (31.44%)	74 / 298 (24.83%)	
occurrences (all)	120	88	
Alopecia totalis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Alopecia universalis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Dermatitis			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	4	1	
Dermatitis acneiform			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Dermatosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	12 / 299 (4.01%)	14 / 298 (4.70%)	
occurrences (all)	14	16	
Ecchymosis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	5 / 299 (1.67%)	4 / 298 (1.34%)	
occurrences (all)	7	5	

Exfoliative rash			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Hyperkeratosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Ingrowing nail			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Miliaria			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Nail discolouration			
subjects affected / exposed	2 / 299 (0.67%)	3 / 298 (1.01%)	
occurrences (all)	2	3	
Nail disorder			
subjects affected / exposed	8 / 299 (2.68%)	6 / 298 (2.01%)	
occurrences (all)	8	8	
Nail dystrophy			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Nail ridging			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Nail toxicity			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	4	
Night sweats			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Onychalgia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

Onychoclasis				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Onycholysis				
subjects affected / exposed	4 / 299 (1.34%)	1 / 298 (0.34%)		
occurrences (all)	6	2		
Onychomadesis				
subjects affected / exposed	3 / 299 (1.00%)	2 / 298 (0.67%)		
occurrences (all)	3	2		
Pain of skin				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Palmar erythema				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	81 / 299 (27.09%)	59 / 298 (19.80%)		
occurrences (all)	161	144		
Petechiae				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Photosensitivity reaction				
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)		
occurrences (all)	1	1		
Pigmentation disorder				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Plantar erythema				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Pruritus				
subjects affected / exposed	2 / 299 (0.67%)	4 / 298 (1.34%)		
occurrences (all)	2	4		
Pruritus generalised				

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	3	
Rash			
subjects affected / exposed	11 / 299 (3.68%)	9 / 298 (3.02%)	
occurrences (all)	11	14	
Rash erythematous			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Rash generalised			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Rash macular			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	2	
Rash maculo-papular			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Rash papular			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Skin depigmentation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Skin discolouration			
subjects affected / exposed	0 / 299 (0.00%)	2 / 298 (0.67%)	
occurrences (all)	0	3	
Skin disorder			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	
Skin exfoliation			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	2	
Skin fissures			

subjects affected / exposed	3 / 299 (1.00%)	3 / 298 (1.01%)	
occurrences (all)	3	3	
Skin hyperpigmentation			
subjects affected / exposed	7 / 299 (2.34%)	2 / 298 (0.67%)	
occurrences (all)	7	2	
Skin irritation			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Skin lesion			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Skin reaction			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Skin ulcer			
subjects affected / exposed	3 / 299 (1.00%)	0 / 298 (0.00%)	
occurrences (all)	3	0	
Urticaria			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Bladder pain			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Bladder stenosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Chromaturia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Chronic kidney disease			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	

Dysuria			
subjects affected / exposed	3 / 299 (1.00%)	2 / 298 (0.67%)	
occurrences (all)	3	2	
Haematuria			
subjects affected / exposed	3 / 299 (1.00%)	4 / 298 (1.34%)	
occurrences (all)	3	5	
Hydronephrosis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Nephropathy toxic			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Nocturia			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Pollakiuria			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	4	1	
Polyuria			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Renal colic			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	2 / 299 (0.67%)	3 / 298 (1.01%)	
occurrences (all)	2	6	
Renal impairment			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	

Ureteric obstruction			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Urethritis noninfective			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	3 / 299 (1.00%)	4 / 298 (1.34%)	
occurrences (all)	3	4	
Urine odour abnormal			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 299 (2.34%)	2 / 298 (0.67%)	
occurrences (all)	8	2	
Back pain			
subjects affected / exposed	25 / 299 (8.36%)	14 / 298 (4.70%)	
occurrences (all)	30	16	
Bone pain			
subjects affected / exposed	4 / 299 (1.34%)	0 / 298 (0.00%)	
occurrences (all)	4	0	
Flank pain			
subjects affected / exposed	1 / 299 (0.33%)	3 / 298 (1.01%)	
occurrences (all)	3	3	
Gouty arthritis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Joint effusion			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Joint range of motion decreased			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	7 / 299 (2.34%)	5 / 298 (1.68%)	
occurrences (all)	7	7	
Muscular weakness			
subjects affected / exposed	1 / 299 (0.33%)	3 / 298 (1.01%)	
occurrences (all)	1	4	
Musculoskeletal chest pain			
subjects affected / exposed	8 / 299 (2.68%)	4 / 298 (1.34%)	
occurrences (all)	8	4	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 299 (0.33%)	3 / 298 (1.01%)	
occurrences (all)	1	4	
Musculoskeletal pain			
subjects affected / exposed	6 / 299 (2.01%)	1 / 298 (0.34%)	
occurrences (all)	6	1	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	5 / 299 (1.67%)	3 / 298 (1.01%)	
occurrences (all)	5	3	
Neck pain			
subjects affected / exposed	0 / 299 (0.00%)	3 / 298 (1.01%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	10 / 299 (3.34%)	11 / 298 (3.69%)	
occurrences (all)	13	15	
Pain in jaw			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Sjogren's syndrome			

subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	3 / 299 (1.00%)	2 / 298 (0.67%)	
occurrences (all)	4	2	
Tendonitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Arthritis infective			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Bacteraemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Bacterial infection			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Bacteriuria			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	2	
Biliary sepsis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	2 / 299 (0.67%)	4 / 298 (1.34%)	
occurrences (all)	2	4	
Candida infection			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	

Cellulitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences (all)	2	3	
Conjunctivitis bacterial			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	2	
Device related infection			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences (all)	2	2	
Ear infection			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Embolic pneumonia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Erysipelas			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Fungal skin infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

Gastroenteritis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal fungal infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Gastrointestinal infection			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Genital herpes			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Giardiasis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Herpes dermatitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	3 / 299 (1.00%)	0 / 298 (0.00%)	
occurrences (all)	4	0	
Infectious colitis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	3 / 299 (1.00%)	4 / 298 (1.34%)	
occurrences (all)	3	5	
Localised infection			
subjects affected / exposed	3 / 299 (1.00%)	1 / 298 (0.34%)	
occurrences (all)	3	1	

Lower respiratory tract infection			
subjects affected / exposed	4 / 299 (1.34%)	3 / 298 (1.01%)	
occurrences (all)	4	3	
Mucosal infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Nail bed infection			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Nail infection			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	4 / 299 (1.34%)	11 / 298 (3.69%)	
occurrences (all)	6	12	
Oesophageal candidiasis			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Onychomycosis			
subjects affected / exposed	2 / 299 (0.67%)	2 / 298 (0.67%)	
occurrences (all)	2	2	
Oral candidiasis			
subjects affected / exposed	8 / 299 (2.68%)	4 / 298 (1.34%)	
occurrences (all)	10	5	
Oral fungal infection			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	4	
Oral herpes			
subjects affected / exposed	4 / 299 (1.34%)	1 / 298 (0.34%)	
occurrences (all)	4	2	
Otitis media			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	4 / 299 (1.34%)	7 / 298 (2.35%)	
occurrences (all)	5	9	

Pharyngitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 299 (0.00%)	4 / 298 (1.34%)	
occurrences (all)	0	4	
Respiratory tract infection			
subjects affected / exposed	6 / 299 (2.01%)	2 / 298 (0.67%)	
occurrences (all)	6	2	
Respiratory tract infection viral			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	2 / 299 (0.67%)	3 / 298 (1.01%)	
occurrences (all)	2	3	
Sepsis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Skin bacterial infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	
Skin candida			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Soft tissue infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Sputum purulent			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	

Tinea cruris				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Tinea pedis				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Tooth infection				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	1		
Tracheobronchitis				
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)		
occurrences (all)	0	2		
Upper respiratory tract infection				
subjects affected / exposed	9 / 299 (3.01%)	6 / 298 (2.01%)		
occurrences (all)	9	7		
Upper respiratory tract infection bacterial				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Urinary tract infection				
subjects affected / exposed	16 / 299 (5.35%)	9 / 298 (3.02%)		
occurrences (all)	20	10		
Urinary tract infection enterococcal				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Urinary tract infection fungal				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Viral infection				
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)		
occurrences (all)	2	0		
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)		
occurrences (all)	1	0		
Vulvovaginal candidiasis				

subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	2	
Wound infection staphylococcal			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Cachexia			
subjects affected / exposed	1 / 299 (0.33%)	3 / 298 (1.01%)	
occurrences (all)	1	3	
Decreased appetite			
subjects affected / exposed	72 / 299 (24.08%)	72 / 298 (24.16%)	
occurrences (all)	99	106	
Dehydration			
subjects affected / exposed	10 / 299 (3.34%)	14 / 298 (4.70%)	
occurrences (all)	14	23	
Diabetes mellitus			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Electrolyte imbalance			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Feeding disorder			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	7	
Folate deficiency			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

Gout			
subjects affected / exposed	2 / 299 (0.67%)	0 / 298 (0.00%)	
occurrences (all)	2	0	
Hypercalcaemia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	
Hypercreatininaemia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	7 / 299 (2.34%)	7 / 298 (2.35%)	
occurrences (all)	11	10	
Hyperkalaemia			
subjects affected / exposed	6 / 299 (2.01%)	3 / 298 (1.01%)	
occurrences (all)	7	5	
Hypermagnesaemia			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	
Hyperphosphataemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	3	0	
Hyperuricaemia			
subjects affected / exposed	2 / 299 (0.67%)	1 / 298 (0.34%)	
occurrences (all)	2	1	
Hypoalbuminaemia			
subjects affected / exposed	10 / 299 (3.34%)	34 / 298 (11.41%)	
occurrences (all)	11	49	
Hypocalcaemia			
subjects affected / exposed	8 / 299 (2.68%)	29 / 298 (9.73%)	
occurrences (all)	12	56	
Hypochloraemia			
subjects affected / exposed	1 / 299 (0.33%)	1 / 298 (0.34%)	
occurrences (all)	1	1	

Hypokalaemia			
subjects affected / exposed	31 / 299 (10.37%)	32 / 298 (10.74%)	
occurrences (all)	50	63	
Hypokalaemic syndrome			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	33 / 299 (11.04%)	46 / 298 (15.44%)	
occurrences (all)	57	78	
Hyponatraemia			
subjects affected / exposed	6 / 299 (2.01%)	17 / 298 (5.70%)	
occurrences (all)	15	29	
Hypophosphataemia			
subjects affected / exposed	11 / 299 (3.68%)	9 / 298 (3.02%)	
occurrences (all)	27	14	
Hypoproteinaemia			
subjects affected / exposed	1 / 299 (0.33%)	5 / 298 (1.68%)	
occurrences (all)	1	7	
Magnesium deficiency			
subjects affected / exposed	1 / 299 (0.33%)	0 / 298 (0.00%)	
occurrences (all)	1	0	
Malnutrition			
subjects affected / exposed	1 / 299 (0.33%)	2 / 298 (0.67%)	
occurrences (all)	1	3	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 299 (0.00%)	1 / 298 (0.34%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	1. To clarify that when a subject's HER2 status is unknown at the time of screening, testing will be conducted at the central laboratory 2. To add that pregnancy testing can occur more frequently if required as part of standard of care or as required by local laws and regulations
10 February 2014	The 20070622 protocol enrolls subjects who are tumor MET-positive by centralized immunohistochemistry testing. MET-positive has been defined as ≥ 25% tumor membrane staining for MET. Amgen is amending the protocol to allow testing at a second pre-defined higher tumor MET-positive level if survival analysis based on the 25% level is not positive. The reasons for the proposed changes are: • Phase 2 data suggested a MET-positive rate of approximately 60% • Observed a higher than expected MET-positive rate in study 20070622 is higher than expected (approximately 80%) • Increased rate could result in including a MET insensitive population into the study In addition, the amendment includes updates, clarifications, and corrections of minor errors.
12 December 2014	As a result of the important information shared with investigators in a letter dated 21 November 2014, namely that an increase in the number of deaths in the rilotumumab and chemotherapy arm was observed when compared with the chemotherapy only arm, and that protocol-defined futility criteria would likely have been met at the planned interim analysis in March 2015, this protocol is being amended. The amendment reflects that subjects receiving rilotumumab in combination with chemotherapy were to discontinue all study treatments and to complete safety follow-up visits approximately 30 days after receipt of the last dose of the protocol-specified therapy. Subjects receiving chemotherapy and rilotumumab-placebo are permitted to continue treatment with chemotherapy according to physician discretion until other protocol specified stopping criteria occur at which time the subjects will complete safety follow-up visits. All subjects are to be followed in long-term safety follow-up for 6 months after the primary analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported