



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
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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/m² 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
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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/m² 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/m ² IV on day 1, cisplatin (C) 60 mg/m ² IV on day 1, and capecitabine (X) 625 mg/m ² 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/m ² IV on day 1, cisplatin (C) 60 mg/m ² IV on day 1, and capecitabine (X) 625 mg/m ² 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
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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/m² 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
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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/m² 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
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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
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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
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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
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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
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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
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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
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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 < 1.0 indicates a lower average event rate and a longer time to progression for Rilotumumab + ECX relative to 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 RECIST 1.1, 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 \geq 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
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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
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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
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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
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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
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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
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End point description:

End point type	Secondary
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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
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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
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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
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End point description:

End point type	Secondary
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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]
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End point description:

End point type	Secondary
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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]
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo + ECX
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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/m² 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
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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/m² 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 erythrodysesthesia 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 occurrences (all)	6 / 299 (2.01%) 9	6 / 298 (2.01%) 8
Amylase increased subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	13 / 299 (4.35%) 15	7 / 298 (2.35%) 8
Blood albumin decreased subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 5	3 / 298 (1.01%) 4
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	9 / 299 (3.01%) 12	7 / 298 (2.35%) 10
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0
Blood bilirubin subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0
Blood bilirubin abnormal subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0
Blood bilirubin increased subjects affected / exposed occurrences (all)	6 / 299 (2.01%) 9	0 / 298 (0.00%) 0
Blood calcium decreased subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0
Blood creatine abnormal subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 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 occurrences (all)	1 / 299 (0.33%) 1	2 / 298 (0.67%) 2
Capillary fragility increased subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0
Clostridium test positive subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Creatinine renal clearance decreased subjects affected / exposed occurrences (all)	21 / 299 (7.02%) 33	15 / 298 (5.03%) 20
Creatinine renal clearance increased subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Eastern Cooperative Oncology Group performance status worsened subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Ejection fraction decreased subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 2	2 / 298 (0.67%) 2
Fibrin D dimer increased subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 2	1 / 298 (0.34%) 1
Glomerular filtration rate subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Glomerular filtration rate abnormal subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 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 occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Renal function test abnormal subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	2 / 298 (0.67%) 2	
Transaminases increased subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Troponin I increased subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Urine output increased subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	49 / 299 (16.39%) 63	23 / 298 (7.72%) 33	
Weight increased subjects affected / exposed occurrences (all)	3 / 299 (1.00%) 3	1 / 298 (0.34%) 1	
White blood cell count decreased subjects affected / exposed occurrences (all)	14 / 299 (4.68%) 28	13 / 298 (4.36%) 42	
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 2	1 / 298 (0.34%) 1	
Dumping syndrome subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Eye injury subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 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	
Phimosi			
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 occurrences (all)	3 / 299 (1.00%) 3	1 / 298 (0.34%) 1	
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Visual impairment subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 2	1 / 298 (0.34%) 1	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 1	
Abdominal distension subjects affected / exposed occurrences (all)	9 / 299 (3.01%) 10	10 / 298 (3.36%) 10	
Abdominal pain subjects affected / exposed occurrences (all)	49 / 299 (16.39%) 56	43 / 298 (14.43%) 64	
Abdominal pain lower subjects affected / exposed occurrences (all)	3 / 299 (1.00%) 3	1 / 298 (0.34%) 1	
Abdominal pain upper subjects affected / exposed occurrences (all)	22 / 299 (7.36%) 27	16 / 298 (5.37%) 17	
Anal fissure subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Anorectal discomfort subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	2 / 298 (0.67%) 2	
Aphagia subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Aphthous stomatitis subjects affected / exposed occurrences (all)	3 / 299 (1.00%) 3	4 / 298 (1.34%) 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 occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 2	1 / 298 (0.34%) 1	
Vomiting subjects affected / exposed occurrences (all)	94 / 299 (31.44%) 153	94 / 298 (31.54%) 149	
Hepatobiliary disorders			
Biliary colic subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Cholelithiasis subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Cholestasis subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Hepatic pain subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Hepatomegaly subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Hepatotoxicity subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	11 / 299 (3.68%) 16	9 / 298 (3.02%) 9	
Jaundice subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 3	1 / 298 (0.34%) 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

Onychoclasia		
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 erythrodysesthesia 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 occurrences (all)	3 / 299 (1.00%) 3	3 / 298 (1.01%) 3	
Skin hyperpigmentation subjects affected / exposed occurrences (all)	7 / 299 (2.34%) 7	2 / 298 (0.67%) 2	
Skin irritation subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 2	0 / 298 (0.00%) 0	
Skin lesion subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Skin reaction subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 1	
Skin ulcer subjects affected / exposed occurrences (all)	3 / 299 (1.00%) 3	0 / 298 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 1	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	2 / 298 (0.67%) 2	
Bladder pain subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Bladder stenosis subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Chromaturia subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 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 occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 1	
Urethritis noninfective subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Urinary retention subjects affected / exposed occurrences (all)	3 / 299 (1.00%) 3	4 / 298 (1.34%) 4	
Urine odour abnormal subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	7 / 299 (2.34%) 8	2 / 298 (0.67%) 2	
Back pain subjects affected / exposed occurrences (all)	25 / 299 (8.36%) 30	14 / 298 (4.70%) 16	
Bone pain subjects affected / exposed occurrences (all)	4 / 299 (1.34%) 4	0 / 298 (0.00%) 0	
Flank pain subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 3	3 / 298 (1.01%) 3	
Gouty arthritis subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Groin pain subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Joint effusion subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 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 occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Spinal pain subjects affected / exposed occurrences (all)	3 / 299 (1.00%) 4	2 / 298 (0.67%) 2	
Tendonitis subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Infections and infestations			
Anorectal infection subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Arthritis infective subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Asymptomatic bacteriuria subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 2	0 / 298 (0.00%) 0	
Bacteraemia subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Bacterial infection subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	2 / 298 (0.67%) 2	
Bacteriuria subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 2	
Biliary sepsis subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 2	4 / 298 (1.34%) 4	
Candida infection subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 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 occurrences (all)	4 / 299 (1.34%) 4	3 / 298 (1.01%) 3
Mucosal infection subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Nail bed infection subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0
Nail infection subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 299 (1.34%) 6	11 / 298 (3.69%) 12
Oesophageal candidiasis subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0
Onychomycosis subjects affected / exposed occurrences (all)	2 / 299 (0.67%) 2	2 / 298 (0.67%) 2
Oral candidiasis subjects affected / exposed occurrences (all)	8 / 299 (2.68%) 10	4 / 298 (1.34%) 5
Oral fungal infection subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	2 / 298 (0.67%) 4
Oral herpes subjects affected / exposed occurrences (all)	4 / 299 (1.34%) 4	1 / 298 (0.34%) 2
Otitis media subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1
Paronychia subjects affected / exposed occurrences (all)	4 / 299 (1.34%) 5	7 / 298 (2.35%) 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 occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Wound infection subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 2	
Wound infection staphylococcal subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Metabolism and nutrition disorders			
Abnormal loss of weight subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Cachexia subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	3 / 298 (1.01%) 3	
Decreased appetite subjects affected / exposed occurrences (all)	72 / 299 (24.08%) 99	72 / 298 (24.16%) 106	
Dehydration subjects affected / exposed occurrences (all)	10 / 299 (3.34%) 14	14 / 298 (4.70%) 23	
Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Electrolyte imbalance subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 1	
Feeding disorder subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	0 / 298 (0.00%) 0	
Fluid retention subjects affected / exposed occurrences (all)	1 / 299 (0.33%) 1	1 / 298 (0.34%) 7	
Folate deficiency subjects affected / exposed occurrences (all)	0 / 299 (0.00%) 0	1 / 298 (0.34%) 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 $\geq 25\%$ 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