Clinical trial results:
An Open-label, Multicenter, Randomized, Phase 2 Study of a Recombinant Human Anti-VEGFR-2 Monoclonal Antibody, IMC-1121B in Combination with Platinum-based Chemotherapy versus Platinum-based Chemotherapy Alone as First-line Treatment of Patients with Recurrent or Advanced Non-small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2009-016784-11
Trial protocol	DE GB BE
Global end of trial date	19 April 2018

Results information

Result version number	v1 (current)
This version publication date	03 May 2019
First version publication date	03 May 2019

Trial information

Trial identification

Sponsor protocol code	I4T-IE-JVBL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01160744
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 13916

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine if participants with Stage IV NSCLC have a better outcome when treated with IMC-1121B in combination with pemetrexed + carboplatin/cisplatin or gemcitabine + carboplatin/cisplatin than when treated with pemetrexed + carboplatin/cisplatin or gemcitabine + carboplatin/cisplatin alone.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 223
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	280
EEA total number of subjects	52

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)	137
From 65 to 84 years	143
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

Participants who died (any cause) or had disease progression were considered to be study completers.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pem + Carb or Cis (Non-Squamous)

Arm description:

Pemetrexed (Pem): 500 milligrams/square meter (mg/m²) on Day 1 of every 21-day cycle.
Carboplatin (Carb) [Area Under the Concentration Time Curve 6 (AUC 6)] : Day 1 of every 21-day cycle.
Cisplatin (Cis): 75 mg/m² intravenous (IV) on Day 1 of every 21-day cycle.
Participants were treated for up to 89 weeks.

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

Dosage and administration details:

Pemetrexed : 500 milligrams/square meter (mg/m²) on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Carboplatin [Area Under the Concentration Time Curve 6 (AUC 6)] : Day 1 of every 21-day cycle.

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

Dosage and administration details:

Cisplatin: 75 mg/m² intravenous (IV) on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.

Arm title	Ram + Pem + Carb or Cis (Non-Squamous)

Arm description:

Ramucirumab (Ram): 10 milligrams/kilogram (mg/kg) Day 1 of every 21-day cycle.
Pem: 500 mg/m² on Day 1 of every 21-day cycle.
Carb (AUC 6): Day 1 of every 21-day cycle.
Cis: 75 mg/m² IV on Day 1 of every 21-day cycle.
Participants were treated for up to 89 weeks.

Arm type	Active comparator
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	IMC-1121B, LY3009806
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ramucirumab : 10 milligrams/kilogram (mg/kg) Day 1 of every 21-day cycle.

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

Dosage and administration details:

Pemetrexed: 500 mg/m² on Day 1 of every 21-day cycle.

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

Dosage and administration details:

Carboplatin (AUC 6): Day 1 of every 21-day cycle.

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

Dosage and administration details:

Cisplatin : 75 mg/m² IV on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.

Arm title	Gem + Carb or Cis (Squamous)

Arm description:

Gemcitabine (Gem): 1000 mg/m² on Days 1 and 8 of every 21-day cycle.
Carb [Area Under the Concentration Time Curve 5 (AUC 5)]: Day 1 of every 21-day cycle.
Cis: 75 mg/m² IV on Day 1 of every 21-day cycle.
Participants were treated for up to 89 weeks.

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

Dosage and administration details:

Gemcitabine: 1000 mg/m² on Days 1 and 8 of every 21-day cycle.

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

Dosage and administration details:

Carboplatin[Area Under the Concentration Time Curve 5 (AUC 5)]: Day 1 of every 21-day cycle.

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

Dosage and administration details:

Cisplatin: 75 mg/m² IV on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.

Arm title	Ram + Gem + Carb or Cis (Squamous)

Arm description:

Ram: 10 mg/kg on Day 1 of each every 21-day cycle.
Gem: 1000 mg/m² on Days 1 and 8 of every 21-day cycle.
Carb (AUC 5): Day 1 of every 21-day cycle.
Cis: 75 mg/m² IV on Day 1 of each every 21-day cycle.
Participants were treated for up to 89 weeks.

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

Dosage and administration details:

Ramucirumab: 10 mg/kg on Day 1 of each every 21-day cycle.

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

Dosage and administration details:

Gemcitabine: 1000 mg/m² on Days 1 and 8 of every 21-day cycle.

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

Dosage and administration details:

Carboplatin (AUC 5): Day 1 of every 21-day cycle.

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

Dosage and administration details:

Cisplatin : 75 mg/m² IV on Day 1 of each every 21-day cycle.

Number of subjects in period 1	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)
Started	71	69	69
Received Study Drug	69	67	63
Completed	60	64	62
Not completed	11	5	7
Consent withdrawn by subject	11	5	6
Not meet inclusion/exclusion criteria	-	-	1

Number of subjects in period 1	Ram + Gem + Carb or Cis (Squamous)
Started	71
Received Study Drug	71
Completed	67
Not completed	4
Consent withdrawn by subject	4
Not meet inclusion/exclusion criteria	-

Baseline characteristics

Reporting groups	
Reporting group title	Pem + Carb or Cis (Non-Squamous)
Reporting group description:	
Pemetrexed (Pem): 500 milligrams/square meter (mg/m²) on Day 1 of every 21-day cycle. Carboplatin (Carb) [Area Under the Concentration Time Curve 6 (AUC 6)] : Day 1 of every 21-day cycle. Cisplatin (Cis): 75 mg/m² intravenous (IV) on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.	
Reporting group title	Ram + Pem + Carb or Cis (Non-Squamous)
Reporting group description:	
Ramucirumab (Ram): 10 milligrams/kilogram (mg/kg) Day 1 of every 21-day cycle. Pem: 500 mg/m² on Day 1 of every 21-day cycle. Carb (AUC 6): Day 1 of every 21-day cycle. Cis: 75 mg/m² IV on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.	
Reporting group title	Gem + Carb or Cis (Squamous)
Reporting group description:	
Gemcitabine (Gem): 1000 mg/m² on Days 1 and 8 of every 21-day cycle. Carb [Area Under the Concentration Time Curve 5 (AUC 5)]: Day 1 of every 21-day cycle. Cis: 75 mg/m² IV on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.	
Reporting group title	Ram + Gem + Carb or Cis (Squamous)
Reporting group description:	
Ram: 10 mg/kg on Day 1 of each every 21-day cycle. Gem: 1000 mg/m² on Days 1 and 8 of every 21-day cycle. Carb (AUC 5): Day 1 of every 21-day cycle. Cis: 75 mg/m² IV on Day 1 of each every 21-day cycle. Participants were treated for up to 89 weeks.	

Reporting group values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)
Number of subjects	71	69	69
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	37	37	27
>=65 years	34	32	40
Missing Data	0	0	2
Gender categorical Units: Subjects			
Female	26	33	26
Male	45	36	43
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	4	1
Not Hispanic or Latino	70	65	68
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	65	60	65
Black	2	8	1
Asian	4	1	1

Other	0	0	2
Region of Enrollment Units: Subjects			
United States	71	69	42
Canada	0	0	4
Belgium	0	0	5
Poland	0	0	4
Germany	0	0	14
United Kingdom	0	0	0

Reporting group values	Ram + Gem + Carb or Cis (Squamous)	Total	
Number of subjects	71	280	
Age categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	34	135	
>=65 years	37	143	
Missing Data	0	2	
Gender categorical Units: Subjects			
Female	16	101	
Male	55	179	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	6	
Not Hispanic or Latino	71	274	
Unknown or Not Reported	0	0	
Race/Ethnicity, Customized Units: Subjects			
White	67	257	
Black	4	15	
Asian	0	6	
Other	0	2	
Region of Enrollment Units: Subjects			
United States	41	223	
Canada	1	5	
Belgium	4	9	
Poland	12	16	
Germany	8	22	
United Kingdom	5	5	

End points

End points reporting groups

Reporting group title	Pem + Carb or Cis (Non-Squamous)

Reporting group description:

Pemetrexed (Pem): 500 milligrams/square meter (mg/m²) on Day 1 of every 21-day cycle.
Carboplatin (Carb) [Area Under the Concentration Time Curve 6 (AUC 6)] : Day 1 of every 21-day cycle.
Cisplatin (Cis): 75 mg/m² intravenous (IV) on Day 1 of every 21-day cycle.
Participants were treated for up to 89 weeks.

Reporting group title	Ram + Pem + Carb or Cis (Non-Squamous)

Reporting group description:

Ramucirumab (Ram): 10 milligrams/kilogram (mg/kg) Day 1 of every 21-day cycle.
Pem: 500 mg/m² on Day 1 of every 21-day cycle.
Carb (AUC 6): Day 1 of every 21-day cycle.
Cis: 75 mg/m² IV on Day 1 of every 21-day cycle.
Participants were treated for up to 89 weeks.

Reporting group title	Gem + Carb or Cis (Squamous)

Reporting group description:

Gemcitabine (Gem): 1000 mg/m² on Days 1 and 8 of every 21-day cycle.
Carb [Area Under the Concentration Time Curve 5 (AUC 5)]: Day 1 of every 21-day cycle.
Cis: 75 mg/m² IV on Day 1 of every 21-day cycle.
Participants were treated for up to 89 weeks.

Reporting group title	Ram + Gem + Carb or Cis (Squamous)

Reporting group description:

Ram: 10 mg/kg on Day 1 of each every 21-day cycle.
Gem: 1000 mg/m² on Days 1 and 8 of every 21-day cycle.
Carb (AUC 5): Day 1 of every 21-day cycle.
Cis: 75 mg/m² IV on Day 1 of each every 21-day cycle.
Participants were treated for up to 89 weeks.

Primary: Progression-Free survival (PFS)

End point title	Progression-Free survival (PFS)

End point description:

PFS was the time from randomization to the first objective progression as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v 1.1) or death from any cause, whichever occurred first. Progressive disease (PD) was defined as ≥20% increase in sum of diameter (SOD) of target lesions and short axes of target lymph nodes, taking as reference the smallest sum of the longest diameters recorded since treatment started and an absolute increase in sum diameter of ≥5 millimeters (mm); appearance of ≥1 new lesions and/or unequivocal progression of existing non-target lesions. Participants alive and without disease progression were censored at the time of the last objective tumor assessment. Participants who did not progress and were lost to follow-up were censored at their last radiographic assessment. If no baseline or post baseline radiologic assessments were available, participants were censored at date of randomization.

End point type	Primary

End point timeframe:

Randomization to PD or death (up to 24 months)

Analysis Population Description (APD): Intent-to-Treat (ITT) Population: All randomized participants.
Participants censored: Pem+Carb/Cis=14, Ram+Pem+Carb/Cis=13, Gem+Carb/Cis=14, Ram+Gem+Carb/Cis=18.

End point values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)	Ram + Gem + Carb or Cis (Squamous)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	69	69	71
Units: months				
median (confidence interval 90%)	5.6 (4.0 to 5.7)	7.2 (5.8 to 8.4)	5.4 (4.7 to 5.7)	5.6 (4.4 to 6.0)

Statistical analyses

Statistical analysis title	Progression-Free survival (PFS)
Comparison groups	Ram + Pem + Carb or Cis (Non-Squamous) v Pem + Carb or Cis (Non-Squamous)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1318
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.55
upper limit	1.03

Statistical analysis title	Progression-Free survival (PFS)
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5215
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.22

Secondary: Percentage of Participants with Best overall Response of complete response (CR) or partial response (PR) [Objective Response Rate (ORR)]

End point title	Percentage of Participants with Best overall Response of

	complete response (CR) or partial response (PR) [Objective Response Rate (ORR)]

End point description:

Best overall response of CR or PR was defined using RECIST v 1.1 criteria. CR was defined as the disappearance of all lesions, pathological lymph node reduction in short axis to <10 mm, and normalization of tumor marker levels of non-target lesions. PR was defined as ≥30% decrease in SOD of target lesions taking as reference the baseline sum diameter. PD was defined as ≥20% increase in SOD of target lesions and short axes of target lymph nodes, taking as reference the smallest sum of the longest diameters recorded since treatment started and an absolute increase in sum diameter of ≥5 mm; appearance of ≥1 new lesions and/or unequivocal progression of existing non-target lesions. Participants who had no post baseline tumor assessments were considered non-responders and included in the denominator when calculating response rate. Percentage of participants=(number of participants with CR+PR/total number of participants)*100.

APD: ITT Population: All randomized participants.

End point type	Secondary

End point timeframe:

Day 1, Cycle 1 (3-week cycles) and every 6 weeks thereafter to PD (up to 24 months)

End point values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)	Ram + Gem + Carb or Cis (Squamous)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	69	69	71
Units: percentage of participants				
number (not applicable)	38.0	49.3	24.6	46.5

Statistical analyses

Statistical analysis title	Percentage of Participants with Best overall Resp
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1797
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9
upper limit	2.78

Statistical analysis title	Percentage of Participants with Best overall Resp
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	2.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.45
upper limit	4.86

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. If the participant was alive at the end of the follow-up period or was lost to follow-up, OS was censored on the last date the participant was known to be alive.

Analysis Population Description: ITT Population: All randomized participants. Participants censored: Pem+Carb/Cis=22, Ram+Pem+Carb/Cis=16, Gem+Carb/Cis=32, Ram+Gem+Carb/Cis=32.

End point type	Secondary

End point timeframe:

Randomization to the date of death from any cause (up to 31.3 months)

End point values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)	Ram + Gem + Carb or Cis (Squamous)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	69	69	71
Units: months				
median (confidence interval 90%)	10.4 (8.2 to 15.9)	13.9 (10.0 to 17.8)	11.3 (9.7 to 13.3)	10.4 (7.8 to 14.8)

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8916
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	1.42

Statistical analysis title	Overall Survival (OS)
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6847
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.69
upper limit	1.27

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

DOR was measured from the time criteria were met for the first objectively recorded CR or PR until the first date criteria for PD were met or death. Response was defined using RECIST v 1.1 criteria. CR was defined as the disappearance of all lesions, pathological lymph node reduction in short axis to <10 mm, and normalization of tumor marker level of non-target lesions. PR was defined as ≥30% decrease SOD of target lesions taking as reference the baseline sum diameter. PD was defined as ≥20% increase in SOD of target lesions and short axes of target lymph nodes, taking as reference the smallest sum of the longest diameters recorded since treatment started and an absolute increase in sum diameter of ≥5 mm; appearance of ≥1 new lesions and/or unequivocal progression of existing non-target lesions. Participants who did not relapse were censored at the day of their last objective tumor assessment.

End point type	Secondary

End point timeframe:

Time of first response (CR or PR) until PD or death (up to 24 months)

APD:All randomized participants with a best overall response of CR or PR. Participants censored: Pem+Carb/Cis=44, Ram+Pem+Carb/Cis=35, Gem+Carb/Cis=50, Ram+Gem+Carb/Cis=37.

End point values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)	Ram + Gem + Carb or Cis (Squamous)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	34	17	33
Units: months				
median (confidence interval 90%)	4.5 (3.1 to 5.7)	5.5 (4.4 to 5.8)	4.3 (4.2 to 5.5)	4.3 (3.3 to 5.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Treatment-Emergent Adverse Events (TEAEs) and who Died

End point title	Number of Participants Reporting Treatment-Emergent Adverse Events (TEAEs) and who Died

End point description:

Data presented are the number of participants with at least 1 treatment-emergent adverse event (TEAE) and treatment-emergent serious adverse event (SAE), as well as, the number of participants who died during the study. TEAEs were defined as serious and other non-serious AEs that occurred or worsened after study treatment (regardless of causality). A summary of SAEs and other non-serious adverse events, regardless of causality, is located in the Reported Adverse Events module.

Analysis Population Description: All randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Day 1, Cycle 1 (3-week cycles) Up To 3 Years

End point values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)	Ram + Gem + Carb or Cis (Squamous)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	67	63	71
Units: participants				
number (not applicable)				
Treatment-Emergent SAE	38	44	29	39
Treatment-Emergent Adverse Event	68	67	63	71
Deaths	51	55	55	56

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants with CR, PR, or Stable Disease (SD) [Disease Control Rate (DCR)]

End point title	Percentage of Participants with CR, PR, or Stable Disease (SD) [Disease Control Rate (DCR)]

End point description:

DCR: percentage of participants with CR, PR, or SD using RECIST v 1.1 criteria. CR: disappearance of all lesions, pathological lymph node reduction in short axis to <10 mm, and normalization of tumor marker levels of non-target lesions. PR: ≥30% decrease in SOD of target lesions taking as reference baseline sum diameter. PD: ≥20% increase in SOD of target lesions and short axes of target lymph nodes, taking as reference smallest sum of longest diameters recorded since treatment started and an absolute increase in sum diameter ≥5 mm; appearance of ≥1 new lesions and/or unequivocal progression of existing non-target lesions. SD: neither sufficient shrinkage to qualify for PR nor increase to qualify for PD. Participants who had no post baseline tumor assessments were considered non-responders and included in the denominator when calculating response rate. Percentage of participants=(number of participants with CR+PR+SD/total number of participants)*100.

End point type	Other pre-specified

End point timeframe:

Day 1, Cycle 1 (3-week cycles) and every 6 weeks thereafter to PD (up to 24 months)

Analysis Population Description: ITT Population: All randomized participants.

End point values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)	Ram + Gem + Carb or Cis (Squamous)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	69	69	71
Units: percentage of participants				
number (confidence interval 90%)	70.4 (61.5 to 79.3)	85.5 (78.5 to 92.5)	66.7 (57.3 to 76.0)	73.2 (64.6 to 81.9)

Statistical analyses

Statistical analysis title	Percentage of Participants with CR, PR, or Stable
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0316
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	2.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.22
upper limit	5.02

Statistical analysis title	Percentage of Participants with CR, PR, or Stable
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3962
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	2.52

Other pre-specified: Change in Tumor Size (CTS)

End point title	Change in Tumor Size (CTS)

End point description:

CTS was defined as the log ratio of tumor size at 6 weeks to tumor size at baseline. CTS at 6 weeks=Log (Sum of Target Lesion Measurements at 6 Weeks)-Log (Sum of Target Lesion Measurements at Baseline).

Analysis Population Description: All randomized participants with results at baseline and 6 weeks.

End point type	Other pre-specified

End point timeframe:

Baseline, 6 weeks

End point values	Pem + Carb or Cis (Non-Squamous)	Ram + Pem + Carb or Cis (Non-Squamous)	Gem + Carb or Cis (Squamous)	Ram + Gem + Carb or Cis (Squamous)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	58	50	53
Units: log ratio				
arithmetic mean (standard deviation)	-0.2 (± 0.23)	-0.2 (± 0.22)	-0.3 (± 0.31)	-0.4 (± 0.39)

Statistical analyses

Statistical analysis title	Change in Tumor Size (CTS)
Comparison groups	Ram + Pem + Carb or Cis (Non-Squamous) v Pem + Carb or Cis (Non-Squamous)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1571
Method	t-test, 2-sided
Confidence interval	
sides	2-sided

Statistical analysis title	Change in Tumor Size (CTS)
Comparison groups	Pem + Carb or Cis (Non-Squamous) v Ram + Pem + Carb or Cis (Non-Squamous)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1597
Method	t-test, 2-sided
Confidence interval	
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

I4T-IE-JVBL

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Carb/Cis+Pem+Ram (non-SQ)

Reporting group description:

Ramucirumab (Ram): 10 milligrams/kilogram (mg/kg) Day 1 of every 21-day cycle. Pem: 500 mg/m² on Day 1 of every 21-day cycle. Carb (AUC 6): Day 1 of every 21-day cycle. Cis: 75 mg/m² IV on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.

Reporting group title	Carb/Cis+Pem (non-SQ)

Reporting group description:

Pemetrexed (Pem): 500 milligrams/square meter (mg/m²) on Day 1 of every 21-day cycle.

Carboplatin (Carb) [Area Under the Concentration Time Curve 6 (AUC 6)] : Day 1 of every 21-day cycle.

Cisplatin (Cis): 75 mg/m² intravenous (IV) on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.

Reporting group title	Carb/Cis+Gem+Ram (SQ)

Reporting group description:

Ram: 10 mg/kg on Day 1 of each every 21-day cycle. Gem: 1000 mg/m² on Days 1 and 8 of every 21-day cycle. Carb (AUC 5): Day 1 of every 21-day cycle. Cis: 75 mg/m² IV on Day 1 of each every 21-day cycle. Participants were treated for up to 89 weeks.

Reporting group title	Carb/Cis+Gem (SQ)

Reporting group description:

Gemcitabine (Gem): 1000 mg/m² on Days 1 and 8 of every 21-day cycle. Carb [Area Under the Concentration Time Curve 5 (AUC 5)]: Day 1 of every 21-day cycle.

Cis: 75 mg/m² IV on Day 1 of every 21-day cycle. Participants were treated for up to 89 weeks.

Serious adverse events	Carb/Cis+Pem+Ram (non-SQ)	Carb/Cis+Pem (non-SQ)	Carb/Cis+Gem+Ram (SQ)
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 67 (65.67%)	38 / 69 (55.07%)	39 / 71 (54.93%)
number of deaths (all causes)	4	6	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
malignant pleural effusion			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neoplasm progression			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
air embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
deep vein thrombosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
femoral artery occlusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haematoma			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypertension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypotension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
orthostatic hypotension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
venous thrombosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chest pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
death			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fatigue			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
general physical health deterioration			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
malaise			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
multi-organ failure			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

oedema peripheral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sudden death			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
acute respiratory failure			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
asphyxia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chronic obstructive pulmonary disease			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dyspnoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	1 / 69 (1.45%)	6 / 71 (8.45%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
epistaxis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemoptysis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemothorax			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
hiccups			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oesophagobronchial fistula			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
pleural effusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumothorax			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pulmonary embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
respiratory arrest			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
respiratory failure			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
stridor			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
confusional state			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
depression			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
mental status changes			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oxygen saturation decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
platelet count decreased			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
accidental overdose			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
drug administration error			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fall			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis radiation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hip fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
incorrect dose administered			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	2 / 67 (2.99%)	3 / 69 (4.35%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lumbar vertebral fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
medication error			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
overdose			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
radiation mucositis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
transfusion-related acute lung injury			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
underdose			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	2 / 69 (2.90%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
acute myocardial infarction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
angina pectoris			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial fibrillation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bradycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bundle branch block left			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardiac arrest			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
cardiac failure congestive			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardio-respiratory arrest			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
cardiovascular disorder			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
coronary artery occlusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
left ventricular dysfunction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

supraventricular tachycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tachycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
cerebral haemorrhage			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cerebrovascular accident			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
encephalopathy			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
facial paresis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic cerebral infarction			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lethargy			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
paraplegia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	5 / 71 (7.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
febrile neutropenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	1 / 69 (1.45%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
leukopenia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutropenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	1 / 69 (1.45%)	4 / 71 (5.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pancytopenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
thrombocytopenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	2 / 69 (2.90%)	8 / 71 (11.27%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
vision blurred			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
colitis ischaemic			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	2 / 69 (2.90%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
duodenal ulcer			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

intestinal ischaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intestinal perforation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lip haemorrhage			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	4 / 69 (5.80%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pancreatitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	4 / 69 (5.80%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
cholangitis acute			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholecystitis acute			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
rash papular			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nephrolithiasis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
renal failure			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary retention			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
inappropriate antidiuretic hormone secretion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
groin pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
muscular weakness			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
bacteraemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bronchitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cellulitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diverticulitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis viral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infection			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung abscess			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pharyngeal abscess			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	6 / 69 (8.70%)	7 / 71 (9.86%)
occurrences causally related to treatment / all	0 / 1	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia bacterial			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia pseudomonal			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyelonephritis acute			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

sepsis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
staphylococcal infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dehydration			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	2 / 69 (2.90%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
failure to thrive			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fluid overload			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyperglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	1 / 69 (1.45%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyponatraemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypovolaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Carb/Cis+Gem (SQ)		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 63 (46.03%)		
number of deaths (all causes)	4		
number of deaths resulting from	0		

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
malignant pleural effusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
neoplasm progression			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
air embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
deep vein thrombosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
embolism			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
femoral artery occlusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
haematoma			

alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
hypertension				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
hypotension				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
orthostatic hypotension				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
venous thrombosis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
asthenia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
chest pain				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
death				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
fatigue				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
general physical health deterioration				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
malaise				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
multi-organ failure				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
non-cardiac chest pain				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

oedema peripheral				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pyrexia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
sudden death				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
hypersensitivity				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
acute respiratory failure				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
asphyxia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
chronic obstructive pulmonary disease				

alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
dyspnoea				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
epistaxis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
haemoptysis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
haemothorax				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
hiccups				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
oesophagobronchial fistula				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pleural effusion				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pneumothorax				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pulmonary embolism				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
respiratory arrest				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
respiratory failure				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
stridor				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
confusional state			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
depression			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
mental status changes			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
oxygen saturation decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
platelet count decreased			

alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
accidental overdose				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
drug administration error				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
fall				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
gastroenteritis radiation				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
hip fracture				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
incorrect dose administered				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
lumbar vertebral fracture				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
medication error				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
overdose				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
radiation mucositis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
transfusion-related acute lung injury				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
underdose				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
acute myocardial infarction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
angina pectoris			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
atrial fibrillation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
bradycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
bundle branch block left			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cardiac arrest			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
cardiac failure congestive				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
cardio-respiratory arrest				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
cardiovascular disorder				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
coronary artery occlusion				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
left ventricular dysfunction				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
myocardial infarction				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

supraventricular tachycardia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
tachycardia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
cerebral haemorrhage				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
cerebrovascular accident				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
encephalopathy				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
facial paresis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ischaemic cerebral infarction				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
lethargy			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
paraplegia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
syncope			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
febrile neutropenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
leukopenia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
neutropenia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pancytopenia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
thrombocytopenia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
vision blurred				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
abdominal pain				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
abdominal pain upper				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
colitis ischaemic			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
duodenal ulcer			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
gastritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

intestinal ischaemia				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
intestinal perforation				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
lip haemorrhage				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
nausea				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
pancreatitis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
vomiting				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
cholangitis acute				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
cholecystitis acute				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
rash papular				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
acute kidney injury				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
nephrolithiasis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
renal failure				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
urinary retention				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
inappropriate antidiuretic hormone secretion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
groin pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
muscular weakness			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
bacteraemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
bronchitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cellulitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
diverticulitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
gastroenteritis viral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
infection			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
lung abscess			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pharyngeal abscess			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
pneumonia bacterial			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pneumonia pseudomonal			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pyelonephritis acute			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

sepsis				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
staphylococcal infection				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
upper respiratory tract infection				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
urinary tract infection				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
decreased appetite				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
dehydration				
alternative dictionary used: MedDRA 18.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
failure to thrive				
alternative dictionary used: MedDRA 18.1				

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
fluid overload			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
hyperglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
hypoglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
hyponatraemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
hypovolaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Carb/Cis+Pem+Ram (non-SQ)	Carb/Cis+Pem (non-SQ)	Carb/Cis+Gem+Ram (SQ)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 67 (98.51%)	67 / 69 (97.10%)	71 / 71 (100.00%)
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 67 (17.91%)	4 / 69 (5.80%)	8 / 71 (11.27%)
occurrences (all)	15	5	16
hypotension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	3 / 69 (4.35%)	3 / 71 (4.23%)
occurrences (all)	7	3	3
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	2 / 69 (2.90%)	5 / 71 (7.04%)
occurrences (all)	12	2	8
chills			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	5 / 69 (7.25%)	5 / 71 (7.04%)
occurrences (all)	1	5	6
fatigue			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	44 / 67 (65.67%)	43 / 69 (62.32%)	39 / 71 (54.93%)
occurrences (all)	97	85	79
infusion site pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	1 / 71 (1.41%)
occurrences (all)	1	0	1
mucosal inflammation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	6 / 69 (8.70%)	3 / 71 (4.23%)
occurrences (all)	14	11	3
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	4 / 67 (5.97%)	3 / 69 (4.35%)	4 / 71 (5.63%)
occurrences (all)	11	3	4
oedema peripheral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 67 (25.37%)	16 / 69 (23.19%)	14 / 71 (19.72%)
occurrences (all)	23	19	23
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	12 / 69 (17.39%)	6 / 71 (8.45%)
occurrences (all)	9	19	8
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	13 / 67 (19.40%)	11 / 69 (15.94%)	14 / 71 (19.72%)
occurrences (all)	15	18	21
dysphonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	5 / 69 (7.25%)	0 / 71 (0.00%)
occurrences (all)	4	5	0
dyspnoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 67 (25.37%)	16 / 69 (23.19%)	10 / 71 (14.08%)
occurrences (all)	29	24	19
dyspnoea exertional			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	3 / 71 (4.23%)
occurrences (all)	3	0	6
epistaxis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 67 (25.37%)	5 / 69 (7.25%)	12 / 71 (16.90%)
occurrences (all)	36	6	17
haemoptysis			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	3 / 67 (4.48%)	1 / 69 (1.45%)	4 / 71 (5.63%)
occurrences (all)	3	1	9
oropharyngeal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	2 / 69 (2.90%)	4 / 71 (5.63%)
occurrences (all)	10	2	6
productive cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	1 / 69 (1.45%)	6 / 71 (8.45%)
occurrences (all)	4	1	10
rhinorrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 67 (8.96%)	2 / 69 (2.90%)	3 / 71 (4.23%)
occurrences (all)	7	2	3
wheezing			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	4 / 69 (5.80%)	1 / 71 (1.41%)
occurrences (all)	3	4	1
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 67 (8.96%)	4 / 69 (5.80%)	1 / 71 (1.41%)
occurrences (all)	6	4	1
depression			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	6 / 69 (8.70%)	5 / 71 (7.04%)
occurrences (all)	5	7	5
insomnia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	15 / 67 (22.39%)	10 / 69 (14.49%)	5 / 71 (7.04%)
occurrences (all)	15	10	5
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	5 / 67 (7.46%)	7 / 69 (10.14%)	6 / 71 (8.45%)
occurrences (all)	10	10	17
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	4 / 69 (5.80%)	11 / 71 (15.49%)
occurrences (all)	8	6	24
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	3 / 69 (4.35%)	7 / 71 (9.86%)
occurrences (all)	1	6	12
blood creatinine increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 67 (8.96%)	7 / 69 (10.14%)	4 / 71 (5.63%)
occurrences (all)	7	8	6
neutrophil count decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	7 / 69 (10.14%)	6 / 71 (8.45%)
occurrences (all)	3	16	9
platelet count decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	4 / 69 (5.80%)	7 / 71 (9.86%)
occurrences (all)	10	7	31
weight decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 67 (17.91%)	11 / 69 (15.94%)	12 / 71 (16.90%)
occurrences (all)	17	15	16
white blood cell count decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	5 / 69 (7.25%)	5 / 71 (7.04%)
occurrences (all)	8	6	15
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 67 (1.49%)	0 / 69 (0.00%)	0 / 71 (0.00%)
occurrences (all)	1	0	0
tachycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	4 / 69 (5.80%)	3 / 71 (4.23%)
occurrences (all)	2	4	3
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	13 / 69 (18.84%)	4 / 71 (5.63%)
occurrences (all)	8	18	4
dysgeusia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 67 (17.91%)	6 / 69 (8.70%)	7 / 71 (9.86%)
occurrences (all)	16	10	7
headache			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	19 / 67 (28.36%)	8 / 69 (11.59%)	14 / 71 (19.72%)
occurrences (all)	33	12	20
hypoaesthesia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	4 / 69 (5.80%)	3 / 71 (4.23%)
occurrences (all)	6	8	3
neuropathy peripheral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	4 / 69 (5.80%)	0 / 71 (0.00%)
occurrences (all)	4	4	0
paraesthesia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	4 / 69 (5.80%)	2 / 71 (2.82%)
occurrences (all)	5	8	2
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	32 / 67 (47.76%)	37 / 69 (53.62%)	38 / 71 (53.52%)
occurrences (all)	95	103	111
leukopenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	4 / 69 (5.80%)	10 / 71 (14.08%)
occurrences (all)	20	14	36
neutropenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	22 / 67 (32.84%)	17 / 69 (24.64%)	52 / 71 (73.24%)
occurrences (all)	70	42	152
thrombocytopenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	22 / 67 (32.84%)	15 / 69 (21.74%)	36 / 71 (50.70%)
occurrences (all)	72	48	128
Ear and labyrinth disorders			
tinnitus			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	2 / 69 (2.90%)	1 / 71 (1.41%)
occurrences (all)	7	2	1
Eye disorders			
lacrimation increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	10 / 69 (14.49%)	0 / 71 (0.00%)
occurrences (all)	10	10	0
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	6 / 69 (8.70%)	0 / 71 (0.00%)
occurrences (all)	6	8	0
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 67 (17.91%)	7 / 69 (10.14%)	2 / 71 (2.82%)
occurrences (all)	17	9	3
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	3 / 67 (4.48%)	0 / 69 (0.00%)	4 / 71 (5.63%)
occurrences (all)	4	0	5
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	19 / 67 (28.36%)	21 / 69 (30.43%)	18 / 71 (25.35%)
occurrences (all)	27	29	29
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	19 / 67 (28.36%)	19 / 69 (27.54%)	9 / 71 (12.68%)
occurrences (all)	23	28	12
dry mouth			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	2 / 69 (2.90%)	0 / 71 (0.00%)
occurrences (all)	4	2	0
dyspepsia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 67 (8.96%)	5 / 69 (7.25%)	0 / 71 (0.00%)
occurrences (all)	8	6	0
dysphagia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	2 / 69 (2.90%)	1 / 71 (1.41%)
occurrences (all)	7	3	1
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	3 / 69 (4.35%)	4 / 71 (5.63%)
occurrences (all)	4	3	4
gingival bleeding			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	0 / 69 (0.00%)	2 / 71 (2.82%)
occurrences (all)	6	0	2
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	35 / 67 (52.24%)	39 / 69 (56.52%)	27 / 71 (38.03%)
occurrences (all)	65	71	44

stomatitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 67 (13.43%)	6 / 69 (8.70%)	3 / 71 (4.23%)
occurrences (all)	13	6	3
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	22 / 67 (32.84%)	24 / 69 (34.78%)	18 / 71 (25.35%)
occurrences (all)	35	34	23
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 67 (13.43%)	5 / 69 (7.25%)	5 / 71 (7.04%)
occurrences (all)	9	5	5
night sweats			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	3 / 69 (4.35%)	2 / 71 (2.82%)
occurrences (all)	4	3	2
pruritus			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	1 / 69 (1.45%)	3 / 71 (4.23%)
occurrences (all)	2	1	4
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	3 / 69 (4.35%)	9 / 71 (12.68%)
occurrences (all)	6	3	11
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	11 / 67 (16.42%)	7 / 69 (10.14%)	7 / 71 (9.86%)
occurrences (all)	16	10	16
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	14 / 67 (20.90%)	12 / 69 (17.39%)	10 / 71 (14.08%)
occurrences (all)	21	18	14

bone pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 67 (5.97%)	1 / 69 (1.45%)	5 / 71 (7.04%)
occurrences (all)	5	1	7
muscle spasms			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	1 / 69 (1.45%)	4 / 71 (5.63%)
occurrences (all)	5	1	4
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	4 / 69 (5.80%)	5 / 71 (7.04%)
occurrences (all)	10	6	5
musculoskeletal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 67 (10.45%)	2 / 69 (2.90%)	4 / 71 (5.63%)
occurrences (all)	11	2	5
myalgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 67 (8.96%)	3 / 69 (4.35%)	3 / 71 (4.23%)
occurrences (all)	6	4	5
pain in extremity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 67 (11.94%)	4 / 69 (5.80%)	2 / 71 (2.82%)
occurrences (all)	9	4	2
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	4 / 69 (5.80%)	0 / 71 (0.00%)
occurrences (all)	3	8	0
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	4 / 69 (5.80%)	3 / 71 (4.23%)
occurrences (all)	2	4	4
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	8 / 67 (11.94%)	5 / 69 (7.25%)	4 / 71 (5.63%)
occurrences (all)	13	6	4
urinary tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 67 (10.45%)	6 / 69 (8.70%)	3 / 71 (4.23%)
occurrences (all)	8	15	4
vulvovaginal mycotic infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed[1]	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	20 / 67 (29.85%)	18 / 69 (26.09%)	24 / 71 (33.80%)
occurrences (all)	30	27	35
dehydration			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 67 (8.96%)	12 / 69 (17.39%)	9 / 71 (12.68%)
occurrences (all)	6	12	9
hyperglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 67 (4.48%)	7 / 69 (10.14%)	6 / 71 (8.45%)
occurrences (all)	7	12	12
hypoalbuminaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 67 (1.49%)	7 / 69 (10.14%)	10 / 71 (14.08%)
occurrences (all)	1	12	23
hypocalcaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 67 (2.99%)	3 / 69 (4.35%)	6 / 71 (8.45%)
occurrences (all)	2	4	18
hypokalaemia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	8 / 67 (11.94%)	8 / 69 (11.59%)	9 / 71 (12.68%)
occurrences (all)	9	9	14
hypomagnesaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	10 / 67 (14.93%)	11 / 69 (15.94%)	14 / 71 (19.72%)
occurrences (all)	12	15	30
hyponatraemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 67 (7.46%)	8 / 69 (11.59%)	8 / 71 (11.27%)
occurrences (all)	11	10	12

Non-serious adverse events	Carb/Cis+Gem (SQ)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 63 (98.41%)		
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	4		
hypotension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	10		
chills			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
fatigue			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	34 / 63 (53.97%)		
occurrences (all)	62		
infusion site pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
mucosal inflammation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
oedema peripheral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	12		
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	9		
dysphonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
dyspnoea			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	11 / 63 (17.46%)		
occurrences (all)	19		
dyspnoea exertional			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
epistaxis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
haemoptysis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
oropharyngeal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
productive cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	9		
rhinorrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
wheezing			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
depression			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
insomnia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	7		
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	5		
blood creatinine increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
neutrophil count decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	10		
platelet count decreased			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	3		
weight decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
white blood cell count decreased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	10		
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
tachycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	7		
dysgeusia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	10		
headache			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
hypoaesthesia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
neuropathy peripheral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
paraesthesia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	40 / 63 (63.49%)		
occurrences (all)	94		
leukopenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	23		
neutropenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	35 / 63 (55.56%)		
occurrences (all)	94		
thrombocytopenia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	27 / 63 (42.86%)		
occurrences (all)	73		
Ear and labyrinth disorders			
tinnitus			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Eye disorders			
lacrimation increased			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	4		
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
constipation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	21 / 63 (33.33%)		
occurrences (all)	28		
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 63 (19.05%)		
occurrences (all)	14		
dry mouth			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
dyspepsia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
dysphagia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
gingival bleeding			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	36 / 63 (57.14%)		
occurrences (all)	51		
stomatitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	9		
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 63 (19.05%)		
occurrences (all)	15		
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	8		
night sweats			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
pruritus			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	8		
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	10		
bone pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	4		
muscle spasms			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
musculoskeletal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
myalgia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
pain in extremity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	4		
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
urinary tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	6		
vulvovaginal mycotic infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed[1]	0 / 24 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	15 / 63 (23.81%)		
occurrences (all)	17		
dehydration			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
hyperglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	9		
hypoalbuminaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	3		
hypocalcaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
hypokalaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	13		
hypomagnesaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 63 (26.98%)		
occurrences (all)	23		
hyponatraemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		

Notes:

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2012	Version 7: Upon annual review of safety data, the risk profile was revised to reflect the increases in the number of participants with cancer treated with ramucirumab and the number of adverse events reported in the clinical trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported