Clinical trial results:
A Phase II, Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Safety and Efficacy of Carboplatin/Paclitaxel and Carboplatin/Paclitaxel/Bevacizumab with and without GDC-0941 in Patients with Previously Untreated Advanced or Recurrent Non-Small Cell Lung Cancer

Summary

EudraCT number	2011-002893-21
Trial protocol	DE HU ES NL GB IT
Global end of trial date	30 March 2016

Results information

Result version number	v1 (current)
This version publication date	13 April 2017
First version publication date	13 April 2017

Trial information

Trial identification

Sponsor protocol code	GO27912

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01493843
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy (as measured by Progression Free Survival) of pictilisib in combination with carboplatin (C) + paclitaxel (P) in subjects with squamous non-small cell lung cancer (NSCLC) and in combination with carboplatin (C) + paclitaxel (P) + bevacizumab (B) in subjects with non-squamous NSCLC.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Brazil: 16
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Russian Federation: 90
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	United States: 155
Worldwide total number of subjects	501
EEA total number of subjects	165

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)	299
From 65 to 84 years	199
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

For Arms A and B subjects must have histologically documented advanced (Stage IV) or recurrent squamous NSCLC and for Arms C, D, E and F advanced (Stage IV) or recurrent non-squamous NSCLC.

Pre-assignment

Screening details:

Subjects with squamous NSCLC were checked for phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) amplification status and subjects with non-squamous NSCLC for phosphatase and tensin homolog (PTEN) loss/low status.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: 340 mg pictilisib + CP

Arm description:

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P).

Arm type	Experimental
Investigational medicinal product name	pictilisib
Investigational medicinal product code	
Other name	GDC-0941
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pictilisib, 340 mg, was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, pictilisib was taken once daily continuously.

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

Dosage and administration details:

Paclitaxel was administered 200 milligrams per square metre (mg/m^2) IV on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:

Carboplatin was administered intravenously (IV) to achieve an initial target area under the concentration curve (AUC) of
6 milligrams per millilitre per minute (mg/mL per min) on Day 1 of each 21-day cycle for a maximum of four cycles.

Arm title	Arm B: Placebo + CP

Arm description:

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle >/= 5).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo corresponding to 340 mg pictilisib was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, placebo was taken once daily continuously.

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

Dosage and administration details:

Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:

Paclitaxel was administered 200 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of four cycles.

Arm title	Arm C: 340 mg pictilisib + CPB

Arm description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).

Arm type	Experimental
Investigational medicinal product name	pictilisib
Investigational medicinal product code	
Other name	GDC-0941
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pictilisib, 340 mg, was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, pictilisib was taken once daily continuously.

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

Dosage and administration details:

Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:

Paclitaxel was administered 200 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:

Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.

Arm title	Arm D: Placebo + CPB

Arm description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo corresponding to 340 mg pictilisib was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, placebo was taken once daily continuously.

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

Dosage and administration details:

Carboplatin was administered IV to achieve an initial target AUC of
6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:

Paclitaxel was administered 200 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:
Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.

Arm title	Arm E: 260 mg pictilisib + CPB
Arm description:	
Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).	
Arm type	Experimental
Investigational medicinal product name	pictilisib
Investigational medicinal product code	
Other name	GDC-0941
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Pictilisib, 260 mg, was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, pictilisib was taken once daily continuously.	
Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.	
Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Paclitaxel was administered 200 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of four cycles.	
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.	
Arm title	Arm F: Placebo + CPB
Arm description:	
Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5).	
Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo corresponding to 260 mg pictilisib was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, placebo was taken once daily continuously.

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

Dosage and administration details:

Carboplatin was administered IV to achieve an initial target AUC of
6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:

Paclitaxel was administered 200 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of four cycles.

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

Dosage and administration details:

Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.

Number of subjects in period 1	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP	Arm C: 340 mg pictilisib + CPB
Started	126	125	79
Completed	0	0	0
Not completed	126	125	79
Other	15	7	5
Death	75	78	59
Unknown	1	-	1
Withdrawal by Subject	7	6	5
Study Terminated by Sponsor	24	30	8
Lost to follow-up	4	4	1

Number of subjects in period 1	Arm D: Placebo + CPB	Arm E: 260 mg pictilisib + CPB	Arm F: Placebo + CPB
Started	79	62	30

Completed	0	0	0
Not completed	79	62	30
Other	4	5	2
Death	57	43	21
Unknown	-	-	-
Withdrawal by Subject	3	3	1
Study Terminated by Sponsor	11	11	6
Lost to follow-up	4	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	501	501	
Age Categorical Units: Subjects			
Adults (18-64 years)	299	299	
From 65-84 years	199	199	
85 years and over	3	3	
Age Continuous Units: years			
arithmetic mean	62		
standard deviation	± 9.7	-	
Gender Categorical Units: Subjects			
Female	140	140	
Male	361	361	

End points

End points reporting groups

Reporting group title	Arm A: 340 mg pictilisib + CP
Reporting group description:	
Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P).	
Reporting group title	Arm B: Placebo + CP
Reporting group description:	
Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle >/= 5).	
Reporting group title	Arm C: 340 mg pictilisib + CPB
Reporting group description:	
Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).	
Reporting group title	Arm D: Placebo + CPB
Reporting group description:	
Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5).	
Reporting group title	Arm E: 260 mg pictilisib + CPB
Reporting group description:	
Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).	
Reporting group title	Arm F: Placebo + CPB
Reporting group description:	
Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5).	
Subject analysis set title	Arm A Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.	
Subject analysis set title	Arm B Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle >/= 5). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.	
Subject analysis set title	Arm C Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B). Safety population included all	

subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

Subject analysis set title	Arm D Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

Subject analysis set title	Arm E Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

Subject analysis set title	Arm F Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from randomisation to NSCLC disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause on study (</= 30 days after the last dose of study treatment), whichever occurs first. Progression according to RECIST v1.1 is defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 millimetre (mm) or the appearance of one or more new lesions. Tumor assessments were performed by computed tomography (CT) scan and/or magnetic resonance imaging (MRI). Intent-to-Treat (ITT) population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.

End point type	Primary

End point timeframe:

Up to approximately 2.5 years

End point values	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	90	79	79
Units: months				
median (confidence interval 90%)	5.45 (4.24 to 6.74)	5.49 (4.34 to 5.65)	6.87 (5.52 to 9.66)	6.08 (5.55 to 6.9)

End point values	Arm E: 260 mg pictilisib + CPB	Arm F: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	30		
Units: months				
median (confidence interval 90%)	6.93 (4.63 to 8.28)	6.6 (5.49 to 8.31)		

Statistical analyses

Statistical analysis title	Arm A versus Arm B
Statistical analysis description: Unstratified Analysis	
Comparison groups	Arm A: 340 mg pictilisib + CP v Arm B: Placebo + CP
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5327
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.66
upper limit	1.21

Statistical analysis title	Arm C versus Arm D
Statistical analysis description: Unstratified Analysis	
Comparison groups	Arm C: 340 mg pictilisib + CPB v Arm D: Placebo + CPB
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3496
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.6
upper limit	1.15

Statistical analysis title	Arm E versus Arm F

Statistical analysis description: Unstratified Analysis	
Comparison groups	Arm E: 260 mg pictilisib + CPB v Arm F: Placebo + CPB
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8866
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.66
upper limit	1.64

Primary: PFS in Subjects with PIK3CA Amplification

End point title	PFS in Subjects with PIK3CA Amplification[1]

End point description:

PFS was defined as the time from randomisation to NSCLC disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause on study (</= 30 days after the last dose of study treatment), whichever occurs first. Progression according to RECIST v1.1 is defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. PIK3CA amplified subjects in the ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised.

End point type	Primary

End point timeframe:

Up to approximately 2.5 years

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PIK3CA amplification were only represented in arms A and B. Therefore, only arms A and B were included in this endpoint.

End point values	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: months				
median (confidence interval 90%)	6.6 (4.5 to 6.93)	5.29 (4.27 to 5.55)		

Statistical analyses

Statistical analysis title	PIK3CA amplified subjects Arm A versus Arm B

Statistical analysis description:

Unstratified Analysis

Comparison groups	Arm A: 340 mg pictilisib + CP v Arm B: Placebo + CP

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5388
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.45
upper limit	1.44

Primary: PFS in Subjects with PTEN Loss/low	
End point title	PFS in Subjects with PTEN Loss/low[2]

End point description:

PFS was defined as the time from randomisation to NSCLC disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause on study (</= 30 days after the last dose of study treatment), whichever occurs first. Progression according to RECIST v1.1 is defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. Subjects with PTEN loss/low in the ITT population included all randomised subjects with PTEN loss/low with subjects allocated to the treatment arm to which they were randomised.

End point type	Primary

End point timeframe:

Up to approximately 2.5 years

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

End point values	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	46		
Units: months				
median (confidence interval 90%)	6.9 (5.52 to 9.69)	5.62 (5.13 to 6.08)		

Statistical analyses

Statistical analysis title	PTEN loss/low in Arm C versus Arm D

Statistical analysis description:

Unstratified Analysis

Comparison groups	Arm C: 340 mg pictilisib + CPB v Arm D: Placebo + CPB

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2199
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.45
upper limit	1.13

Secondary: Objective Tumor Response	
End point title	Objective Tumor Response
End point description: Objective tumor response was assessed by the investigator using RECIST v1.1 and had to be confirmed >/= 28 days after initial response. Objective tumor response was defined as percentage of subjects with partial response (PR) or complete response (CR). PR: >=30% decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.	
End point type	Secondary
End point timeframe: Up to approximately 2.5 years	

End point values	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	90	79	79
Units: Percentage of subjects				
number (not applicable)	24.5	30	36.7	29.1

End point values	Arm E: 260 mg pictilisib + CPB	Arm F: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	30		
Units: Percentage of subjects				
number (not applicable)	25.8	43.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Tumor Response in Subjects with PIK3CA Amplification

End point title	Objective Tumor Response in Subjects with PIK3CA Amplification[3]

End point description:

Objective tumor response was assessed by the investigator using RECIST v1.1 and had to be confirmed >/= 28 days after initial response. Objective tumor response was defined as percentage of subjects with partial response (PR) or complete response (CR). PR: >=30% decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 2.5 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PIK3CA amplification were only represented in arms A and B. Therefore, only arms A and B were included in this endpoint.

End point values	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: Percentage of subjects				
number (not applicable)	16.7	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Tumor Response in Subjects with PTEN Loss/low

End point title	Objective Tumor Response in Subjects with PTEN Loss/low[4]

End point description:

Objective tumor response was assessed by the investigator using RECIST v1.1 and had to be confirmed >/= 28 days after initial response. Objective tumor response was defined as percentage of subjects with partial response (PR) or complete response (CR). PR: >=30% decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with PTEN loss/low with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 2.5 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

End point values	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	46		
Units: Percentage of subjects				
number (not applicable)	39.3	28.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DoR)

End point title	Duration of Objective Response (DoR)

End point description:

DoR was defined as the time from first observation of an objective tumor response until first observation of disease progression as assessed by the investigator using RECIST v1.1. Objective tumor response was defined as percentage of participants with partial response (PR) or complete response (CR). PR: >=30% decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 2.5 years

End point values	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[5]	0[6]	0[7]	0[8]
Units: months				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[5] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[6] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[7] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[8] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

End point values	Arm E: 260 mg pictilisib + CPB	Arm F: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[9] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[10] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: DoR in Subjects with PIK3CA Amplification

End point title	DoR in Subjects with PIK3CA Amplification[11]

End point description:

DoR was defined as the time from first observation of an objective tumor response until first observation of disease progression as assessed by the investigator using RECIST v1.1. Objective tumor response was defined as percentage of participants with partial response (PR) or complete response (CR). PR: >=30% decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 2.5 years

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

End point values	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[15] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[16] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. 9999=NE=not estimable

End point type	Secondary

End point timeframe:

Up to approximately 2.5 years

End point values	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	90	79	79
Units: months				
median (confidence interval 90%)	12.16 (9.23 to 14.92)	12.39 (9.26 to 15.05)	13.57 (12.12 to 20.7)	16.07 (10.51 to 18.63)

End point values	Arm E: 260 mg pictilisib + CPB	Arm F: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	30		
Units: months				
median (confidence interval 90%)	11.47 (8.02 to 15.8)	14.23 (9 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in Subjects with PIK3CA Amplification

End point title	OS in Subjects with PIK3CA Amplification[17]

End point description:

OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised. 9999=NE=not estimable

End point type	Secondary

End point timeframe:

Up to approximately 2.5 years

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects with PIK3CA amplification were only represented in arms A and B. Therefore, only arms A and B were included in this endpoint.

End point values	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: months				
median (confidence interval 90%)	15.05 (9.46 to 20.37)	11.7 (8.51 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in Subjects with PTEN Loss/low

End point title	OS in Subjects with PTEN Loss/low[18]

End point description:

OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with PTEN loss/low with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 2.5 years

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

End point values	Arm C: 340 mg pictilisib + CPB	Arm D: Placebo + CPB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	46		
Units: months				
median (confidence interval 90%)	14.52 (12.12 to 20.86)	11.27 (8.28 to 18.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events

End point title	Percentage of Subjects with Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Secondary

End point timeframe:

Up to approximately 4 years

End point values	Arm A Safety Population	Arm B Safety Population	Arm C Safety Population	Arm D Safety Population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	133	115	82	73
Units: percentage of subjects				
number (not applicable)	94.7	97.4	98.8	100

End point values	Arm E Safety Population	Arm F Safety Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	26		
Units: percentage of subjects				
number (not applicable)	94.9	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4 years

Adverse event reporting additional description:

Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Arm A: 340 mg pictilisib + CP

Reporting group description:

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P).

Reporting group title	Arm B: Placebo + CP

Reporting group description:

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle >/= 5).

Reporting group title	Arm C: 340 mg pictilisib + CPB

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).

Reporting group title	Arm D: Placebo + CPB

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5).

Reporting group title	Arm E: 260 mg pictilisib + CPB

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).

Reporting group title	Arm F: Placebo + CPB

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle >/= 5).

Serious adverse events	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP	Arm C: 340 mg pictilisib + CPB
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 133 (36.09%)	34 / 115 (29.57%)	40 / 82 (48.78%)
number of deaths (all causes)	17	6	5

number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	5 / 133 (3.76%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 5	0 / 1	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to meninges			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Metastatic pain			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 133 (0.75%)	2 / 115 (1.74%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (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
Embolism			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Orthostatic hypotension			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Phlebitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	3 / 82 (3.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 133 (1.50%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (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
Chest pain			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Malaise			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Anaphylactic reaction			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Hypersensitivity			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 133 (3.01%)	1 / 115 (0.87%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	1 / 4	0 / 1	1 / 2
deaths causally related to treatment / all	1 / 2	0 / 1	1 / 1

Dyspnoea			
subjects affected / exposed	4 / 133 (3.01%)	0 / 115 (0.00%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Respiratory failure			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Epistaxis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	2 / 133 (1.50%)	0 / 115 (0.00%)	0 / 82 (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
Pulmonary oedema			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Acute respiratory failure			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Aspiration			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Interstitial lung disease			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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			

subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Confusional state			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Hallucination			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Eastern cooperative oncology group performance status worsened			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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

Blood bilirubin increased			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Neutrophil count decreased			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Infusion related reaction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Laceration			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Poisoning			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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 contusion			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Radiation necrosis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Toxicity to various agents			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all			0 / 0

subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (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
Cerebral amyloid angiopathy			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Decreased vibratory sense			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Loss of proprioception			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Neuralgia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic intolerance			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Seizure			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Syncope			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 133 (1.50%)	4 / 115 (3.48%)	3 / 82 (3.66%)
occurrences causally related to treatment / all	2 / 2	4 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 133 (0.75%)	2 / 115 (1.74%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	1 / 1	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	2 / 133 (1.50%)	1 / 115 (0.87%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 133 (1.50%)	0 / 115 (0.00%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 133 (1.50%)	1 / 115 (0.87%)	3 / 82 (3.66%)
occurrences causally related to treatment / all	2 / 2	0 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	3 / 82 (3.66%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			

subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Dysphagia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Diverticular perforation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Duodenal ulcer perforation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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 perforation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Haematemesis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Intestinal obstruction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Oesophageal mass			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Salivary gland calculus			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Cholelithiasis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	3 / 133 (2.26%)	0 / 115 (0.00%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	3 / 3	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	2 / 82 (2.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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 and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
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 kidney injury			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Acute prerenal failure			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Bladder perforation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Dysuria			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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 colic			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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 impairment			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Urinary retention			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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 and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
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			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Pain in extremity			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
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 chest pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Pathological fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 133 (6.02%)	7 / 115 (6.09%)	6 / 82 (7.32%)
occurrences causally related to treatment / all	0 / 9	2 / 7	2 / 6
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 133 (2.26%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung infection			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Abscess			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Anal abscess			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Appendicitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Arthropod-borne disease			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Cellulitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			

subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Cystitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Empyema			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Infectious pleural effusion			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Influenza			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Meningitis listeria			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Pleural infection			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Respiratory tract infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (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
Scrotal infection			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Septic shock			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Streptococcal sepsis			

subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Toxic shock syndrome			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (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
Urinary tract infection			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	2 / 133 (1.50%)	0 / 115 (0.00%)	0 / 82 (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
Hyponatraemia			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (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
Hypercalcaemia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (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
Hyperkalaemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D: Placebo +	Arm E: 260 mg	Arm F: Placebo +

subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Phlebitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 73 (5.48%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 73 (0.00%)	2 / 59 (3.39%)	0 / 26 (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
Fatigue			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
General physical health deterioration			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chest pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Disease progression			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Malaise			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Respiratory, thoracic and mediastinal disorders			

Pulmonary embolism			
subjects affected / exposed	1 / 73 (1.37%)	4 / 59 (6.78%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	1 / 1	3 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	1 / 73 (1.37%)	2 / 59 (3.39%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 73 (1.37%)	1 / 59 (1.69%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	2 / 73 (2.74%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Haemoptysis			
subjects affected / exposed	1 / 73 (1.37%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 73 (2.74%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epistaxis			

subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Pulmonary oedema			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Acute pulmonary oedema			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Aspiration			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Interstitial lung disease			

subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagobronchial fistula			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Pleural effusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 73 (2.74%)	0 / 59 (0.00%)	0 / 26 (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
Confusional state			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Hallucination			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Investigations			
Eastern cooperative oncology group performance status worsened			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 73 (2.74%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Infusion related reaction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Injury			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Laceration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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

Poisoning			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Pulmonary contusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Radiation necrosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Toxicity to various agents			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Myocardial infarction			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Atrial fibrillation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Cardiac arrest			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 73 (1.37%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Cerebral amyloid angiopathy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Decreased vibratory sense			

subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of proprioception			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Orthostatic intolerance			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Seizure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Syncope			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 73 (4.11%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	1 / 73 (1.37%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Leukopenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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			
Diarrhoea			
subjects affected / exposed	1 / 73 (1.37%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Nausea			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Abdominal pain			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Duodenal ulcer			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Dysphagia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Pneumatosis intestinalis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Constipation			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Diverticular perforation			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Duodenal ulcer perforation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Gastric perforation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / ')	1 / 59 (1.69%)	0 / 26 (0.00%)

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland calculus			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Cholelithiasis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Rash macular			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Dermatitis allergic			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Acute kidney injury			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Acute prerenal failure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Bladder perforation			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Dysuria			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Haematuria			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Renal colic			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Renal impairment			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Urinary retention			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 73 (0.00%)	2 / 59 (3.39%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Myalgia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Infections and infestations			

Pneumonia			
subjects affected / exposed	1 / 73 (1.37%)	5 / 59 (8.47%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Bronchitis			
subjects affected / exposed	3 / 73 (4.11%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Lung infection			
subjects affected / exposed	2 / 73 (2.74%)	0 / 59 (0.00%)	0 / 26 (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
Abscess			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Anal abscess			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Arthropod-borne disease			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Cellulitis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Cholecystitis infective			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Cystitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Empyema			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Meningitis listeria			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Otitis media			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Peritonitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Pleural infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Scrotal infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Septic shock			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Streptococcal sepsis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	0 / 26 (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
Toxic shock syndrome			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Urinary tract infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 73 (4.11%)	2 / 59 (3.39%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	3 / 5	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Hyponatraemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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
Hypercalcaemia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	0 / 26 (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
Hyperkalaemia			

subjects affected / exposed	0 / 73 (0.00%)	0 / 59 (0.00%)	0 / 26 (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

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

Non-serious adverse events	Arm A: 340 mg pictilisib + CP	Arm B: Placebo + CP	Arm C: 340 mg pictilisib + CPB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 133 (91.73%)	109 / 115 (94.78%)	81 / 82 (98.78%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 133 (6.02%)	7 / 115 (6.09%)	13 / 82 (15.85%)
occurrences (all)	10	10	20
Hypotension			
subjects affected / exposed	8 / 133 (6.02%)	4 / 115 (3.48%)	1 / 82 (1.22%)
occurrences (all)	8	7	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	33 / 133 (24.81%)	32 / 115 (27.83%)	30 / 82 (36.59%)
occurrences (all)	53	46	58
Asthenia			
subjects affected / exposed	22 / 133 (16.54%)	24 / 115 (20.87%)	26 / 82 (31.71%)
occurrences (all)	47	37	42
Pyrexia			
subjects affected / exposed	12 / 133 (9.02%)	9 / 115 (7.83%)	17 / 82 (20.73%)
occurrences (all)	20	10	27
Chest pain			
subjects affected / exposed	12 / 133 (9.02%)	8 / 115 (6.96%)	7 / 82 (8.54%)
occurrences (all)	12	10	10
Mucosal inflammation			
subjects affected / exposed	9 / 133 (6.77%)	1 / 115 (0.87%)	9 / 82 (10.98%)
occurrences (all)	11	1	17
Oedema peripheral			
subjects affected / exposed	5 / 133 (3.76%)	8 / 115 (6.96%)	9 / 82 (10.98%)
occurrences (all)	7	12	11

Pain			
subjects affected / exposed	6 / 133 (4.51%)	10 / 115 (8.70%)	5 / 82 (6.10%)
occurrences (all)	6	11	6
Chills			
subjects affected / exposed	3 / 133 (2.26%)	1 / 115 (0.87%)	6 / 82 (7.32%)
occurrences (all)	4	1	7
Non-cardiac chest pain			
subjects affected / exposed	0 / 133 (0.00%)	6 / 115 (5.22%)	1 / 82 (1.22%)
occurrences (all)	0	6	1
Influenza like illness			
subjects affected / exposed	3 / 133 (2.26%)	2 / 115 (1.74%)	1 / 82 (1.22%)
occurrences (all)	4	3	1
General physical health deterioration			
subjects affected / exposed	0 / 133 (0.00%)	2 / 115 (1.74%)	1 / 82 (1.22%)
occurrences (all)	0	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 133 (16.54%)	26 / 115 (22.61%)	21 / 82 (25.61%)
occurrences (all)	28	33	31
Dyspnoea			
subjects affected / exposed	20 / 133 (15.04%)	21 / 115 (18.26%)	18 / 82 (21.95%)
occurrences (all)	24	24	25
Epistaxis			
subjects affected / exposed	4 / 133 (3.01%)	5 / 115 (4.35%)	23 / 82 (28.05%)
occurrences (all)	4	5	34
Dysphonia			
subjects affected / exposed	4 / 133 (3.01%)	4 / 115 (3.48%)	8 / 82 (9.76%)
occurrences (all)	4	4	8
Haemoptysis			
subjects affected / exposed	5 / 133 (3.76%)	5 / 115 (4.35%)	3 / 82 (3.66%)
occurrences (all)	6	6	4
Productive cough			
subjects affected / exposed	2 / 133 (1.50%)	6 / 115 (5.22%)	3 / 82 (3.66%)
occurrences (all)	4	6	3
Oropharyngeal pain			

subjects affected / exposed	5 / 133 (3.76%)	1 / 115 (0.87%)	5 / 82 (6.10%)
occurrences (all)	9	1	5
Dyspnoea exertional			
subjects affected / exposed	2 / 133 (1.50%)	2 / 115 (1.74%)	3 / 82 (3.66%)
occurrences (all)	2	2	3
Pleural effusion			
subjects affected / exposed	3 / 133 (2.26%)	4 / 115 (3.48%)	0 / 82 (0.00%)
occurrences (all)	3	4	0
Hiccups			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	0 / 82 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	1 / 82 (1.22%)
occurrences (all)	0	1	1
Pulmonary embolism			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	2 / 82 (2.44%)
occurrences (all)	0	0	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 133 (6.77%)	11 / 115 (9.57%)	14 / 82 (17.07%)
occurrences (all)	9	13	14
Depression			
subjects affected / exposed	3 / 133 (2.26%)	7 / 115 (6.09%)	6 / 82 (7.32%)
occurrences (all)	3	7	6
Anxiety			
subjects affected / exposed	4 / 133 (3.01%)	4 / 115 (3.48%)	4 / 82 (4.88%)
occurrences (all)	4	4	4
Investigations			
Weight decreased			
subjects affected / exposed	13 / 133 (9.77%)	9 / 115 (7.83%)	18 / 82 (21.95%)
occurrences (all)	17	10	19
Platelet count decreased			
subjects affected / exposed	11 / 133 (8.27%)	4 / 115 (3.48%)	6 / 82 (7.32%)
occurrences (all)	17	12	7
Alanine aminotransferase increased			

subjects affected / exposed	10 / 133 (7.52%)	9 / 115 (7.83%)	1 / 82 (1.22%)
occurrences (all)	16	11	1
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 133 (5.26%)	7 / 115 (6.09%)	1 / 82 (1.22%)
occurrences (all)	9	11	1
Neutrophil count decreased			
subjects affected / exposed	7 / 133 (5.26%)	3 / 115 (2.61%)	2 / 82 (2.44%)
occurrences (all)	14	3	2
White blood cell count decreased			
subjects affected / exposed	2 / 133 (1.50%)	5 / 115 (4.35%)	2 / 82 (2.44%)
occurrences (all)	2	7	5
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 133 (2.26%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences (all)	3	0	2
Blood bilirubin increased			
subjects affected / exposed	3 / 133 (2.26%)	0 / 115 (0.00%)	3 / 82 (3.66%)
occurrences (all)	4	0	5
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 133 (1.50%)	1 / 115 (0.87%)	3 / 82 (3.66%)
occurrences (all)	2	1	3
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 133 (1.50%)	2 / 115 (1.74%)	1 / 82 (1.22%)
occurrences (all)	3	2	1
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	23 / 133 (17.29%)	18 / 115 (15.65%)	17 / 82 (20.73%)
occurrences (all)	32	21	25
Dizziness			
subjects affected / exposed	17 / 133 (12.78%)	11 / 115 (9.57%)	12 / 82 (14.63%)
occurrences (all)	18	12	14
Headache			
subjects affected / exposed	10 / 133 (7.52%)	10 / 115 (8.70%)	9 / 82 (10.98%)
occurrences (all)	13	16	20
Peripheral sensory neuropathy			

subjects affected / exposed	16 / 133 (12.03%)	13 / 115 (11.30%)	13 / 82 (15.85%)
occurrences (all)	20	17	22
Paraesthesia			
subjects affected / exposed			8 / 82 (9.76%)

subjects affected / exposed	1 / 133 (0.75%)	5 / 115 (4.35%)	4 / 82 (4.88%)
occurrences (all)	1	6	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	41 / 133 (30.83%)	19 / 115 (16.52%)	44 / 82 (53.66%)
occurrences (all)	85	28	120
Nausea			
subjects affected / exposed	35 / 133 (26.32%)	29 / 115 (25.22%)	46 / 82 (56.10%)
occurrences (all)	59	45	96
Vomiting			
subjects affected / exposed	27 / 133 (20.30%)	15 / 115 (13.04%)	28 / 82 (34.15%)
occurrences (all)	41	20	63
Constipation			
subjects affected / exposed	19 / 133 (14.29%)	22 / 115 (19.13%)	19 / 82 (23.17%)
occurrences (all)	22	32	24
Abdominal pain			
subjects affected / exposed	9 / 133 (6.77%)	3 / 115 (2.61%)	9 / 82 (10.98%)
occurrences (all)	10	3	26
Abdominal pain upper			
subjects affected / exposed	7 / 133 (5.26%)	5 / 115 (4.35%)	9 / 82 (10.98%)
occurrences (all)	8	5	10
Stomatitis			
subjects affected / exposed	11 / 133 (8.27%)	2 / 115 (1.74%)	11 / 82 (13.41%)
occurrences (all)	13	2	15
Dyspepsia			
subjects affected / exposed	7 / 133 (5.26%)	5 / 115 (4.35%)	8 / 82 (9.76%)
occurrences (all)	13	5	8
Dysphagia			
subjects affected / exposed	5 / 133 (3.76%)	2 / 115 (1.74%)	6 / 82 (7.32%)
occurrences (all)	5	3	6
Haemorrhoids			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	5 / 82 (6.10%)
occurrences (all)	0	1	7
Paraesthesia oral			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	42 / 133 (31.58%)	43 / 115 (37.39%)	34 / 82 (41.46%)
occurrences (all)	51	48	47
Pruritus			
subjects affected / exposed	14 / 133 (10.53%)	6 / 115 (5.22%)	14 / 82 (17.07%)
occurrences (all)	19	6	18
Rash maculo-papular			
subjects affected / exposed	18 / 133 (13.53%)	3 / 115 (2.61%)	14 / 82 (17.07%)
occurrences (all)	45	4	31
Dry skin			
subjects affected / exposed	7 / 133 (5.26%)	3 / 115 (2.61%)	13 / 82 (15.85%)
occurrences (all)	7	3	17
Rash macular			
subjects affected / exposed	11 / 133 (8.27%)	0 / 115 (0.00%)	13 / 82 (15.85%)
occurrences (all)	14	0	16
Rash papular			
subjects affected / exposed	13 / 133 (9.77%)	3 / 115 (2.61%)	7 / 82 (8.54%)
occurrences (all)	16	3	12
Erythema			
subjects affected / exposed	8 / 133 (6.02%)	2 / 115 (1.74%)	6 / 82 (7.32%)
occurrences (all)	9	2	6
Rash			
subjects affected / exposed	6 / 133 (4.51%)	1 / 115 (0.87%)	3 / 82 (3.66%)
occurrences (all)	8	1	4
Decubitus ulcer			
subjects affected / exposed	1 / 133 (0.75%)	2 / 115 (1.74%)	0 / 82 (0.00%)
occurrences (all)	1	2	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	5 / 82 (6.10%)
occurrences (all)	0	0	8
Renal failure			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	26 / 133 (19.55%)	22 / 115 (19.13%)	21 / 82 (25.61%)
occurrences (all)	33	35	28
Myalgia			
subjects affected / exposed	13 / 133 (9.77%)	15 / 115 (13.04%)	13 / 82 (15.85%)
occurrences (all)	17	15	16
Pain in extremity			
subjects affected / exposed	17 / 133 (12.78%)	9 / 115 (7.83%)	11 / 82 (13.41%)
occurrences (all)	29	14	13
Back pain			
subjects affected / exposed	6 / 133 (4.51%)	9 / 115 (7.83%)	14 / 82 (17.07%)
occurrences (all)	6	9	18
Musculoskeletal pain			
subjects affected / exposed	5 / 133 (3.76%)	3 / 115 (2.61%)	12 / 82 (14.63%)
occurrences (all)	5	3	14
Bone pain			
subjects affected / exposed	4 / 133 (3.01%)	4 / 115 (3.48%)	5 / 82 (6.10%)
occurrences (all)	5	8	6
Muscular weakness			
subjects affected / exposed	4 / 133 (3.01%)	5 / 115 (4.35%)	4 / 82 (4.88%)
occurrences (all)	5	5	7
Neck pain			
subjects affected / exposed	0 / 133 (0.00%)	1 / 115 (0.87%)	2 / 82 (2.44%)
occurrences (all)	0	1	2
Pain in jaw			
subjects affected / exposed	1 / 133 (0.75%)	0 / 115 (0.00%)	0 / 82 (0.00%)
occurrences (all)	1	0	0
Groin pain			
subjects affected / exposed	0 / 133 (0.00%)	0 / 115 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 133 (3.01%)	4 / 115 (3.48%)	11 / 82 (13.41%)
occurrences (all)	4	4	13
Nasopharyngitis			

subjects affected / exposed	1 / 133 (0.75%)	3 / 115 (2.61%)	4 / 82 (4.88%)
occurrences (all)	1	3	4
Bronchitis			
subjects affected / exposed	4 / 133 (3.01%)	5 / 115 (4.35%)	3 / 82 (3.66%)
occurrences (all)	5	6	8
Upper respiratory tract infection			
subjects affected / exposed	4 / 133 (3.01%)	4 / 115 (3.48%)	4 / 82 (4.88%)
occurrences (all)	5	4	5
Rhinitis			
subjects affected / exposed	3 / 133 (2.26%)	0 / 115 (0.00%)	5 / 82 (6.10%)
occurrences (all)	3	0	7
Pneumonia			
subjects affected / exposed	5 / 133 (3.76%)	4 / 115 (3.48%)	0 / 82 (0.00%)
occurrences (all)	5	4	0
Sinusitis			
subjects affected / exposed	1 / 133 (0.75%)	1 / 115 (0.87%)	4 / 82 (4.88%)
occurrences (all)	1	1	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 133 (21.80%)	20 / 115 (17.39%)	29 / 82 (35.37%)
occurrences (all)	34	27	36
Dehydration			
subjects affected / exposed	8 / 133 (6.02%)	12 / 115 (10.43%)	8 / 82 (9.76%)
occurrences (all)	10	16	8
Hyperglycaemia			
subjects affected / exposed	16 / 133 (12.03%)	14 / 115 (12.17%)	6 / 82 (7.32%)
occurrences (all)	26	23	16
Hypomagnesaemia			
subjects affected / exposed	10 / 133 (7.52%)	5 / 115 (4.35%)	5 / 82 (6.10%)
occurrences (all)	11	5	8
Hypokalaemia			
subjects affected / exposed	9 / 133 (6.77%)	3 / 115 (2.61%)	7 / 82 (8.54%)
occurrences (all)	14	4	12
Hyponatraemia			
subjects affected / exposed	5 / 133 (3.76%)	3 / 115 (2.61%)	3 / 82 (3.66%)
occurrences (all)	6	4	5

Hypocalcaemia			
subjects affected / exposed	2 / 133 (1.50%)	0 / 115 (0.00%)	3 / 82 (3.66%)
occurrences (all)	3	0	4

Non-serious adverse events	Arm D: Placebo + CPB	Arm E: 260 mg pictilisib + CPB	Arm F: Placebo + CPB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 73 (97.26%)	55 / 59 (93.22%)	25 / 26 (96.15%)
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 73 (15.07%)	11 / 59 (18.64%)	1 / 26 (3.85%)
occurrences (all)	14	12	1
Hypotension			
subjects affected / exposed	2 / 73 (2.74%)	2 / 59 (3.39%)	1 / 26 (3.85%)
occurrences (all)	2	6	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 73 (28.77%)	21 / 59 (35.59%)	9 / 26 (34.62%)
occurrences (all)	32	34	20
Asthenia			
subjects affected / exposed	20 / 73 (27.40%)	18 / 59 (30.51%)	5 / 26 (19.23%)
occurrences (all)	38	33	5
Pyrexia			
subjects affected / exposed	7 / 73 (9.59%)	11 / 59 (18.64%)	2 / 26 (7.69%)
occurrences (all)	7	14	2
Chest pain			
subjects affected / exposed	12 / 73 (16.44%)	0 / 59 (0.00%)	1 / 26 (3.85%)
occurrences (all)	13	0	1
Mucosal inflammation			
subjects affected / exposed	3 / 73 (4.11%)	5 / 59 (8.47%)	2 / 26 (7.69%)
occurrences (all)	3	5	2
Oedema peripheral			
subjects affected / exposed	2 / 73 (2.74%)	2 / 59 (3.39%)	3 / 26 (11.54%)
occurrences (all)	3	3	3
Pain			
subjects affected / exposed	2 / 73 (2.74%)	2 / 59 (3.39%)	2 / 26 (7.69%)
occurrences (all)	2	2	2

Chills			
subjects affected / exposed	5 / 73 (6.85%)	2 / 59 (3.39%)	0 / 26 (0.00%)
occurrences (all)	6	2	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 73 (2.74%)	2 / 59 (3.39%)	2 / 26 (7.69%)
occurrences (all)	2	4	2
Influenza like illness			
subjects affected / exposed	0 / 73 (0.00%)	3 / 59 (5.08%)	1 / 26 (3.85%)
occurrences (all)	0	3	1
General physical health deterioration			
subjects affected / exposed	0 / 73 (0.00%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 73 (21.92%)	11 / 59 (18.64%)	6 / 26 (23.08%)
occurrences (all)	21	15	7
Dyspnoea			
subjects affected / exposed	11 / 73 (15.07%)	9 / 59 (15.25%)	7 / 26 (26.92%)
occurrences (all)	17	12	11
Epistaxis			
subjects affected / exposed	18 / 73 (24.66%)	16 / 59 (27.12%)	7 / 26 (26.92%)
occurrences (all)	24	18	8
Dysphonia			
subjects affected / exposed	4 / 73 (5.48%)	4 / 59 (6.78%)	2 / 26 (7.69%)
occurrences (all)	6	4	2
Haemoptysis			
subjects affected / exposed	8 / 73 (10.96%)	1 / 59 (1.69%)	3 / 26 (11.54%)
occurrences (all)	10	1	3
Productive cough			
subjects affected / exposed	7 / 73 (9.59%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences (all)	14	1	0
Oropharyngeal pain			
subjects affected / exposed	3 / 73 (4.11%)	2 / 59 (3.39%)	0 / 26 (0.00%)
occurrences (all)	3	3	0
Dyspnoea exertional			

subjects affected / exposed	1 / 73 (1.37%)	2 / 59 (3.39%)	2 / 26 (7.69%)
occurrences (all)	1	2	2
Pleural effusion			
subjects affected / exposed	0 / 73 (0.00%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Hiccups			
subjects affected / exposed	3 / 73 (4.11%)	3 / 59 (5.08%)	1 / 26 (3.85%)
occurrences (all)	4	3	1
Rhinorrhoea			
subjects affected / exposed	2 / 73 (2.74%)	3 / 59 (5.08%)	1 / 26 (3.85%)
occurrences (all)	2	3	1
Pulmonary embolism			
subjects affected / exposed	4 / 73 (5.48%)	1 / 59 (1.69%)	0 / 26 (0.00%)
occurrences (all)	4	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 73 (13.70%)	5 / 59 (8.47%)	4 / 26 (15.38%)
occurrences (all)	13	6	5
Depression			
subjects affected / exposed	5 / 73 (6.85%)	6 / 59 (10.17%)	2 / 26 (7.69%)
occurrences (all)	6	6	2
Anxiety			
subjects affected / exposed	8 / 73 (10.96%)	3 / 59 (5.08%)	1 / 26 (3.85%)
occurrences (all)	10	6	1
Investigations			
Weight decreased			
subjects affected / exposed	10 / 73 (13.70%)	9 / 59 (15.25%)	5 / 26 (19.23%)
occurrences (all)	12	16	5
Platelet count decreased			
subjects affected / exposed	3 / 73 (4.11%)	3 / 59 (5.08%)	2 / 26 (7.69%)
occurrences (all)	4	6	2
Alanine aminotransferase increased			
subjects affected / exposed	2 / 73 (2.74%)	2 / 59 (3.39%)	3 / 26 (11.54%)
occurrences (all)	2	2	4
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 73 (2.74%)	2 / 59 (3.39%)	4 / 26 (15.38%)
occurrences (all)	6	2	5
Neutrophil count decreased			
subjects affected / exposed	1 / 73 (1.37%)	4 / 59 (6.78%)	1 / 26 (3.85%)
occurrences (all)	1	5	1
White blood cell count decreased			
subjects affected / exposed	0 / 73 (0.00%)	2 / 59 (3.39%)	2 / 26 (7.69%)
occurrences (all)	0	3	2
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 73 (2.74%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	2	3	0
Blood bilirubin increased			
subjects affected / exposed	0 / 73 (0.00%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 73 (6.85%)	2 / 59 (3.39%)	1 / 26 (3.85%)
occurrences (all)	6	2	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 73 (2.74%)	1 / 59 (1.69%)	2 / 26 (7.69%)
occurrences (all)	2	1	2
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	17 / 73 (23.29%)	6 / 59 (10.17%)	6 / 26 (23.08%)
occurrences (all)	19	8	8
Dizziness			
subjects affected / exposed	11 / 73 (15.07%)	7 / 59 (11.86%)	7 / 26 (26.92%)
occurrences (all)	12	10	9
Headache			
subjects affected / exposed	11 / 73 (15.07%)	15 / 59 (25.42%)	4 / 26 (15.38%)
occurrences (all)	15	18	7
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 73 (5.48%)	7 / 59 (11.86%)	3 / 26 (11.54%)
occurrences (all)	6	10	5
Paraesthesia			

subjects affected / exposed	7 / 73 (9.59%)	8 / 59 (13.56%)	1 / 26 (3.85%)
occurrences (all)	11	9	2
Dysgeusia			
subjects affected / exposed	4 / 73 (5.48%)	13 / 59 (22.03%)	0 / 26 (0.00%)
occurrences (all)	4	18	0
Hypoaesthesia			
subjects affected / exposed	1 / 73 (1.37%)	4 / 59 (6.78%)	0 / 26 (0.00%)
occurrences (all)	1	5	0
Polyneuropathy			
subjects affected / exposed	2 / 73 (2.74%)	6 / 59 (10.17%)	1 / 26 (3.85%)
occurrences (all)	4	8	1
Tremor			
subjects affected / exposed	1 / 73 (1.37%)	5 / 59 (8.47%)	0 / 26 (0.00%)
occurrences (all)	2	5	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 73 (15.07%)	9 / 59 (15.25%)	7 / 26 (26.92%)
occurrences (all)	23	20	15
Neutropenia			
subjects affected / exposed	15 / 73 (20.55%)	13 / 59 (22.03%)	8 / 26 (30.77%)
occurrences (all)	25	21	10
Thrombocytopenia			
subjects affected / exposed	7 / 73 (9.59%)	5 / 59 (8.47%)	3 / 26 (11.54%)
occurrences (all)	13	5	3
Leukopenia			
subjects affected / exposed	3 / 73 (4.11%)	2 / 59 (3.39%)	2 / 26 (7.69%)
occurrences (all)	4	2	2
Lymphopenia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	2 / 26 (7.69%)
occurrences (all)	0	3	4
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 73 (2.74%)	3 / 59 (5.08%)	1 / 26 (3.85%)
occurrences (all)	3	3	1
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	28 / 73 (38.36%)	29 / 59 (49.15%)	9 / 26 (34.62%)
occurrences (all)	39	48	11
Nausea			
subjects affected / exposed	23 / 73 (31.51%)	25 / 59 (42.37%)	6 / 26 (23.08%)
occurrences (all)	33	34	9
Vomiting			
subjects affected / exposed	18 / 73 (24.66%)	16 / 59 (27.12%)	4 / 26 (15.38%)
occurrences (all)	30	27	4
Constipation			
subjects affected / exposed	21 / 73 (28.77%)	14 / 59 (23.73%)	9 / 26 (34.62%)
occurrences (all)	27	17	9
Abdominal pain			
subjects affected / exposed	9 / 73 (12.33%)	3 / 59 (5.08%)	4 / 26 (15.38%)
occurrences (all)	12	3	5

subjects affected / exposed	27 / 73 (36.99%)	14 / 59 (23.73%)	10 / 26 (38.46%)
occurrences (all)	34	19	11
Pruritus			
subjects affected / exposed	10 / 73 (13.70%)	6 / 59 (10.17%)	2 / 26 (7.69%)
occurrences (all)	11	7	2
Rash maculo-papular			
subjects affected / exposed	4 / 73 (5.48%)	8 / 59 (13.56%)	0 / 26 (0.00%)
occurrences (all)	9	19	0
Dry skin			
subjects affected / exposed	4 / 73 (5.48%)	5 / 59 (8.47%)	2 / 26 (7.69%)
occurrences (all)	4	5	2
Rash macular			
subjects affected / exposed	1 / 73 (1.37%)	5 / 59 (8.47%)	2 / 26 (7.69%)
occurrences (all)	1	9	2
Rash papular			
subjects affected / exposed	0 / 73 (0.00%)	4 / 59 (6.78%)	2 / 26 (7.69%)
occurrences (all)	0	6	2
Erythema			
subjects affected / exposed	4 / 73 (5.48%)	4 / 59 (6.78%)	0 / 26 (0.00%)
occurrences (all)	5	4	0
Rash			
subjects affected / exposed	2 / 73 (2.74%)	9 / 59 (15.25%)	1 / 26 (3.85%)
occurrences (all)	2	11	1
Decubitus ulcer			
subjects affected / exposed	0 / 73 (0.00%)	4 / 59 (6.78%)	0 / 26 (0.00%)
occurrences (all)	0	4	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	5 / 73 (6.85%)	4 / 59 (6.78%)	4 / 26 (15.38%)
occurrences (all)	15	7	4
Renal failure			
subjects affected / exposed	1 / 73 (1.37%)	0 / 59 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	3
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	12 / 73 (16.44%)	15 / 59 (25.42%)	6 / 26 (23.08%)
occurrences (all)	21	16	9
Myalgia			
subjects affected / exposed	6 / 73 (8.22%)	8 / 59 (13.56%)	5 / 26 (19.23%)
occurrences (all)	15	9	6
Pain in extremity			
subjects affected / exposed	9 / 73 (12.33%)	11 / 59 (18.64%)	1 / 26 (3.85%)
occurrences (all)	13	17	2
Back pain			
subjects affected / exposed	9 / 73 (12.33%)	5 / 59 (8.47%)	4 / 26 (15.38%)
occurrences (all)	11	6	9
Musculoskeletal pain			
subjects affected / exposed	5 / 73 (6.85%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	6	3	0
Bone pain			
subjects affected / exposed	7 / 73 (9.59%)	5 / 59 (8.47%)	2 / 26 (7.69%)
occurrences (all)	12	5	4
Muscular weakness			
subjects affected / exposed	1 / 73 (1.37%)	6 / 59 (10.17%)	3 / 26 (11.54%)
occurrences (all)	3	9	3
Neck pain			
subjects affected / exposed	5 / 73 (6.85%)	0 / 59 (0.00%)	0 / 26 (0.00%)
occurrences (all)	5	0	0
Pain in jaw			
subjects affected / exposed	1 / 73 (1.37%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	1	4	0
Groin pain			
subjects affected / exposed	0 / 73 (0.00%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 73 (4.11%)	7 / 59 (11.86%)	0 / 26 (0.00%)
occurrences (all)	3	11	0
Nasopharyngitis			

subjects affected / exposed	4 / 73 (5.48%)	6 / 59 (10.17%)	4 / 26 (15.38%)
occurrences (all)	5	7	5
Bronchitis			
subjects affected / exposed	3 / 73 (4.11%)	2 / 59 (3.39%)	2 / 26 (7.69%)
occurrences (all)	3	2	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	4 / 59 (6.78%)	0 / 26 (0.00%)
occurrences (all)	0	4	0
Rhinitis			
subjects affected / exposed	2 / 73 (2.74%)	4 / 59 (6.78%)	0 / 26 (0.00%)
occurrences (all)	2	5	0
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 59 (1.69%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Sinusitis			
subjects affected / exposed	0 / 73 (0.00%)	3 / 59 (5.08%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 73 (21.92%)	23 / 59 (38.98%)	11 / 26 (42.31%)
occurrences (all)	16	32	14
Dehydration			
subjects affected / exposed	7 / 73 (9.59%)	10 / 59 (16.95%)	4 / 26 (15.38%)
occurrences (all)	10	17	7
Hyperglycaemia			
subjects affected / exposed	1 / 73 (1.37%)	6 / 59 (10.17%)	4 / 26 (15.38%)
occurrences (all)	1	15	8
Hypomagnesaemia			
subjects affected / exposed	2 / 73 (2.74%)	8 / 59 (13.56%)	0 / 26 (0.00%)
occurrences (all)	2	10	0
Hypokalaemia			
subjects affected / exposed	3 / 73 (4.11%)	5 / 59 (8.47%)	2 / 26 (7.69%)
occurrences (all)	3	8	2
Hyponatraemia			
subjects affected / exposed	4 / 73 (5.48%)	2 / 59 (3.39%)	3 / 26 (11.54%)
occurrences (all)	4	2	3

Hypocalcaemia			
subjects affected / exposed	2 / 73 (2.74%)	1 / 59 (1.69%)	2 / 26 (7.69%)
occurrences (all)	2	1	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2012	One inclusion criterion was modified to require all subjects to continue the use of contraception for 6 months after the last dose of paclitaxel and the duration of follow-up of female patients for pregnancy events was modified to be consistent with the use of contraception for 6 months after paclitaxel exposure. The schedule of assessments was changed to add pregnancy testing of female patients of childbearing potential prior to each cycle of study treatment. A criterion was added to exclude subjects with active inflammatory diseases that require immunosuppressants, including small or large intestine inflammation such as Crohn's disease or ulcerative colitis. The contraindication of therapeutic warfarin use with GDC-0941 and bevacizumab has been removed from the exclusion criterion and the list of excluded medications.
15 January 2013	The study design was modified to include the evaluation of pictilisib at a dose of 260 mg in subjects with non-squamous NSCLC. The risks associated with pictilisib was updated with new safety information. Modifications to the Inclusion/Exclusion criteria were added: 1) subjects with a history of carcinoma in situ were to be allowed to enroll in study, 2) exclusion of subjects with epidermal growth factor receptor (EGFR) mutation was limited to those whose mutation is associated with response to tyrosine kinase inhibitors. Triplicate 12-lead electrocardiogram (ECG) assessments were replaced with single 12-lead ECGs. Subjects with the following adverse events (AEs) of special interest were to be monitored and evaluated closely for their response to clinical intervention: Grade 4 or symptomatic Grade 3 hyperglycemia, Grade 3 rash, or Grade 2 pneumonitis. The statistical methods were modified to reflect the changes to the study design.
19 December 2013	In order to have sufficient number of subjects to assess PFS in the PIK3CA amplified subgroup (co-primary endpoint), the total number of subjects in Arms A and B was increased from 146 to approximately 250 subjects with squamous NSCLC to take into account a higher percentage of subject tumor samples being unevaluable with the phosphoinositide 3-kinase (PI3K) fluorescence in situ hybridisation (FISH) assay. Further clarification around exclusion criteria was provided as follows: Exclusion: Active inflammatory diseases that require immunosuppressants, including small or large intestine inflammation, such as Crohn’s or ulcerative colitis. Subjects receiving immunosuppressants were considered to have active disease and were not allowed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported