



Clinical trial results:

A Randomized, Open-label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Treatment of Physician's Choice in Subjects with Advanced Non-Small Cell Lung Cancer

Summary

EudraCT number	2011-000724-15
Trial protocol	DE GB ES PL IT
Global end of trial date	02 May 2016

Results information

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

Trial information

Trial identification

Sponsor protocol code	E7389-G000-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01454934
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	300 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.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	29 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, open-label, multicenter, Phase 3 study, comparing efficacy and safety of eribulin with treatment of physician's choice (TPC) in subjects with advanced and disease progression following at least two prior regimens for advanced disease, which should have included a platinum-based regimen.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Japan: 120
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	France: 98

Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Singapore: 15
Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Taiwan: 27
Worldwide total number of subjects	540
EEA total number of subjects	251

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)	338
From 65 to 84 years	201
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 735 subjects were screened. Of these, 195 screen failed due to failure to meet inclusion/exclusion criteria, adverse events, withdrawal of consent, or other reason and were not randomized into the study. A total of 540 subjects were randomized into the study. Of these, 3 were discontinued prior to treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Arm A: Eribulin Mesylate
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Arm description:

Eribulin mesylate (1.4 milligram per square meter [mg/m²]) was administered intravenously (IV) over 2 to 5 minutes on Day 1 and Day 8 of every cycle, where the duration of each cycle is 21 days.

Arm type	Experimental
Investigational medicinal product name	Eribulin mesylate
Investigational medicinal product code	E7389
Other name	Halaven
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate was administered as an intravenous infusion at a dose of 1.4 mg/m², over 2 to 5 minutes on Days 1 and 8 of every cycle, where the duration of each cycle was 21 days.

Arm title	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
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Arm description:

Treatment of Physician's Choice (TPC): Vinorelbine (30 mg/m²) was administered IV on Day 1 every 7 days, Gemcitabine (1250 mg/m²) was administered IV on Days 1 and 8 every 21 days (or 1000 mg/m² IV on Days 1, 8, and 15 every 28 days), Docetaxel (75 mg/m²) was administered IV on Day 1 every 21 days, or Pemetrexed (500 mg/m²) was administered IV on Day 1 every 21 days (nonsquamous histology only).

Arm type	Active comparator
Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	Navelbine
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vinorelbine (30 mg/m²) was administered by IV on Day 1, every 7 days.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (1250 mg/m²) was administered by IV on Days 1 and 8, every 21 days (or 1000 mg/m² on Days 1, 8, and 15 every 28 days)

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere, Docefrez
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel (75 mg/m²) was administered IV every 21 days

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Almita
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed (500 mg/m²) was administered IV on Day 1 every 21 days (nonsquamous histology only)

Number of subjects in period 1	Arm A: Eribulin Mesylate	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
Started	270	270
Completed	0	0
Not completed	270	270
Clinical progression	28	25
Consent withdrawn by subject	2	5
Disease progression	194	181
Adverse event, non-fatal	28	24
Other	6	17
Withdrawal by participant	11	15
Lost to follow-up	-	1
Not treated	1	2

Baseline characteristics

Reporting groups

Reporting group title	Arm A: Eribulin Mesylate
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Reporting group description:

Eribulin mesylate (1.4 milligram per square meter [mg/m²]) was administered intravenously (IV) over 2 to 5 minutes on Day 1 and Day 8 of every cycle, where the duration of each cycle is 21 days.

Reporting group title	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
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Reporting group description:

Treatment of Physician's Choice (TPC): Vinorelbine (30 mg/m²) was administered IV on Day 1 every 7 days, Gemcitabine (1250 mg/m²) was administered IV on Days 1 and 8 every 21 days (or 1000 mg/m² IV on Days 1, 8, and 15 every 28 days), Docetaxel (75 mg/m²) was administered IV on Day 1 every 21 days, or Pemetrexed (500 mg/m²) was administered IV on Day 1 every 21 days (nonsquamous histology only).

Reporting group values	Arm A: Eribulin Mesylate	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed	Total
Number of subjects	270	270	540
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	61.4	60.8	
standard deviation	± 9.62	± 9.32	-
Gender categorical Units: Subjects			
Female	107	101	208
Male	163	169	332

End points

End points reporting groups

Reporting group title	Arm A: Eribulin Mesylate
Reporting group description: Eribulin mesylate (1.4 milligram per square meter [mg/m ²]) was administered intravenously (IV) over 2 to 5 minutes on Day 1 and Day 8 of every cycle, where the duration of each cycle is 21 days.	
Reporting group title	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
Reporting group description: Treatment of Physician's Choice (TPC): Vinorelbine (30 mg/m ²) was administered IV on Day 1 every 7 days, Gemcitabine (1250 mg/m ²) was administered IV on Days 1 and 8 every 21 days (or 1000 mg/m ² IV on Days 1, 8, and 15 every 28 days), Docetaxel (75 mg/m ²) was administered IV on Day 1 every 21 days, or Pemetrexed (500 mg/m ²) was administered IV on Day 1 every 21 days (nonsquamous histology only).	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: The OS was defined as the time in months from the date of randomization to the date of death, regardless of cause. In the absence of confirmation of death, the subjects were censored either at the date that subject was last known to be alive or the date of study cut-off, whichever was earlier. The two treatment arms were compared using the log-rank test, stratified by histology, TPC option, and geographic region; and the treatment difference between eribulin and TPC was tested at a significance level of 0.05 (2-sided). Kaplan-Meier (K-M) survival probabilities for each arm were plotted over time. The treatment effect was estimated by fitting a Cox Proportional Hazards model to the OS times including treatment arm as a factor and histology, TPC option and geographic region as strata. Full analysis set (FAS) was the primary analysis set for all efficacy evaluations and included all randomized subjects.	
End point type	Primary
End point timeframe: Randomization (Day 1) until date of death from any cause, or 37 months	

End point values	Arm A: Eribulin Mesylate	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	270		
Units: months				
median (confidence interval 95%)	9.5 (7.4 to 11.4)	9.5 (8.5 to 11.3)		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description: OS was compared between eribulin and TPC testing the following null hypothesis: H0: OS in Arm A (eribulin) is equal to OS in Arm B (TPC) against the alternative: H1: OS in Arm A (eribulin) is not equal	

to OS in Arm B (TPC).

Comparison groups	Arm A: Eribulin Mesylate v Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1343 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.41

Notes:

[1] - P-value was calculated from a 2-sided log-rank test stratified by histology, TPC option, and geographic region.

Secondary: Progression Free Survival (PFS) by Response Evaluation Criteria in Solid Tumors (RECIST)

End point title	Progression Free Survival (PFS) by Response Evaluation Criteria in Solid Tumors (RECIST)
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End point description:

PFS was defined as the time from the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first. The difference in PFS (based on the tumor response evaluation as determined by the investigator) between eribulin and TPC was evaluated using the log rank test, stratified by histology, TPC option, and geographic region, tested at an alpha level of 0.05 (2-sided). PFS censoring rules will be defined in the SAP and follow Federal Department of Agriculture (FDA) guidance. FAS was the primary analysis set for all efficacy evaluations and included all randomized subjects.

End point type	Secondary
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End point timeframe:

Randomization (Day 1) until date of disease progression or death (whichever occurred first), or 37 months

End point values	Arm A: Eribulin Mesylate	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	270		
Units: months				
median (confidence interval 95%)	3 (2.6 to 3.9)	2.8 (2.6 to 3.6)		

Statistical analyses

Statistical analysis title	PFS by RECIST
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Statistical analysis description:

OS was compared between eribulin and TPC testing the following null hypothesis: H0: OS in Arm A

(eribulin) is equal to OS in Arm B (TPC) against the alternative: H1: OS in Arm A (eribulin) is not equal to OS in Arm B (TPC).

Comparison groups	Arm A: Eribulin Mesylate v Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3946 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.32

Notes:

[2] - P-value was calculated from a 2-sided long-rank test stratified by histology, TPC option, and geographic region.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description:	
<p>The ORR was defined as the proportion of subjects with best overall response of complete response (CR) or partial response (PR) per RECIST criteria. The ORR was estimated by study arm based on the tumor response evaluation as determined by the investigator, according to RECIST 1.1. Subjects with unknown response were treated as non-responders. The statistical difference in ORR between treatment arms was evaluated using the Cochran-Mantel-Haenszel (CMH) chi-square test with histology, TPC option, and geographic region as strata, tested at an alpha level of 0.05 (2-sided). The 95 percent CI was calculated using Clopper Pearson method. FAS was the primary analysis set for all efficacy evaluations and included all randomized subjects.</p>	
End point type	Secondary
End point timeframe:	
Randomization (Day 1) to CR or PR	

End point values	Arm A: Eribulin Mesylate	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	270		
Units: percentage of subjects				
number (confidence interval 95%)	12.2 (8.6 to 16.7)	15.2 (11.1 to 20)		

Statistical analyses

Statistical analysis title	ORR
Statistical analysis description:	
OS was compared between eribulin and TPC testing the following null hypothesis: H0: OS in Arm A	

(eribulin) is equal to OS in Arm B (TPC) against the alternative: H1: OS in Arm A (eribulin) is not equal to OS in Arm B (TPC).

Comparison groups	Arm A: Eribulin Mesylate v Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3034 ^[3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - The P-value was stratified by histology, TPC option, and geographic region.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose up to 30 days after the last dose of study treatment, or up to data cutoff date (30 May 2014), up to approximately 37 months

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) were reported. The safety analysis set included all randomized subjects who received at least one dose of study treatment. Adverse event severity was graded on a 5-point scale according to Common Terminology for Adverse Events (CTCAE) version 4.0. All AEs graded 4 or 5 were considered serious.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Arm A: Eribulin Mesylate
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Reporting group description:

Eribulin mesylate (1.4 mg/m²) was administered IV over 2 to 5 minutes on Day 1 and Day 8 of every cycle, where the duration of each cycle is 21 days.

Reporting group title	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed
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Reporting group description:

TPC: Vinorelbine (30 mg/m²) was administered IV on Day 1 every 7 days, Gemcitabine (1250 mg/m²) was administered IV on Days 1 and 8 every 21 days (or 1000 mg/m² IV on Days 1, 8, and 15 every 28 days), Docetaxel (75 mg/m²) was administered IV on Day 1 every 21 days, or Pemetrexed (500 mg/m²) was administered IV on Day 1 every 21 days (nonsquamous histology only).

Serious adverse events	Arm A: Eribulin Mesylate	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed	
Total subjects affected by serious adverse events			
subjects affected / exposed	97 / 269 (36.06%)	86 / 268 (32.09%)	
number of deaths (all causes)	28	21	
number of deaths resulting from adverse events	22	17	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant neoplasm progression subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant pleural effusion subjects affected / exposed	1 / 269 (0.37%)	4 / 268 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system subjects affected / exposed	2 / 269 (0.74%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to meninges subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain subjects affected / exposed	2 / 269 (0.74%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis subjects affected / exposed	1 / 269 (0.37%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Superior vena cava syndrome subjects affected / exposed	0 / 269 (0.00%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava stenosis subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia subjects affected / exposed	2 / 269 (0.74%)	3 / 268 (1.12%)	
occurrences causally related to treatment / all	2 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue subjects affected / exposed	0 / 269 (0.00%)	3 / 268 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

General physical health deterioration			
subjects affected / exposed	13 / 269 (4.83%)	12 / 268 (4.48%)	
occurrences causally related to treatment / all	1 / 21	0 / 18	
deaths causally related to treatment / all	0 / 7	0 / 7	
Non-cardiac chest pain			
subjects affected / exposed	2 / 269 (0.74%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 269 (1.12%)	3 / 268 (1.12%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 269 (0.74%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cough		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dyspnoea		
subjects affected / exposed	9 / 269 (3.35%)	10 / 268 (3.73%)
occurrences causally related to treatment / all	0 / 12	1 / 13
deaths causally related to treatment / all	0 / 1	0 / 1
Dyspnoea exertional		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemoptysis		
subjects affected / exposed	2 / 269 (0.74%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxia		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pharyngeal inflammation		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural effusion		
subjects affected / exposed	2 / 269 (0.74%)	2 / 268 (0.75%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Pneumonitis		

subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 269 (0.74%)	6 / 268 (2.24%)	
occurrences causally related to treatment / all	1 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary hypertension			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 269 (0.37%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 269 (0.74%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fear			

subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood phosphorus decreased			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 269 (0.37%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 269 (0.74%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebral infarction			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			

subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 269 (0.74%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 269 (1.12%)	7 / 268 (2.61%)	
occurrences causally related to treatment / all	3 / 3	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 269 (1.49%)	3 / 268 (1.12%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 269 (0.37%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 269 (0.74%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal obstruction		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestinal obstruction		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nausea		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal stenosis		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal varices haemorrhage		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Stomatitis		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vomiting		

subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Muscular weakness			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 269 (0.00%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 269 (0.00%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 269 (0.37%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 269 (0.74%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 269 (0.74%)	2 / 268 (0.75%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	12 / 269 (4.46%)	5 / 268 (1.87%)
occurrences causally related to treatment / all	4 / 13	1 / 6
deaths causally related to treatment / all	0 / 1	0 / 1
Pseudomembranous colitis		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection		
subjects affected / exposed	2 / 269 (0.74%)	3 / 268 (1.12%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	1 / 269 (0.37%)	2 / 268 (0.75%)
occurrences causally related to treatment / all	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0
Septic shock		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Staphylococcal sepsis		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection		
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Wound infection fungal		

subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 269 (0.37%)	3 / 268 (1.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	4 / 269 (1.49%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 268 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polydipsia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 269 (0.37%)	0 / 268 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: Eribulin Mesylate	Arm B: Vinorelbine, Gemcitabine, Docetaxel, or Pemetrexed	
Total subjects affected by non-serious adverse events subjects affected / exposed	254 / 269 (94.42%)	261 / 268 (97.39%)	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	19 / 269 (7.06%) 35	23 / 268 (8.58%) 35	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	17 / 269 (6.32%) 38	17 / 268 (6.34%) 24	
Neutrophil count decreased subjects affected / exposed occurrences (all)	60 / 269 (22.30%) 347	58 / 268 (21.64%) 237	
Weight decreased subjects affected / exposed occurrences (all)	20 / 269 (7.43%) 30	15 / 268 (5.60%) 18	
White blood cell count decreased subjects affected / exposed occurrences (all)	55 / 269 (20.45%) 320	57 / 268 (21.27%) 208	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	14 / 269 (5.20%) 17	19 / 268 (7.09%) 26	
Dysgeusia subjects affected / exposed occurrences (all)	25 / 269 (9.29%) 27	16 / 268 (5.97%) 25	
Headache subjects affected / exposed occurrences (all)	35 / 269 (13.01%) 57	21 / 268 (7.84%) 27	
Paraesthesia subjects affected / exposed occurrences (all)	21 / 269 (7.81%) 33	6 / 268 (2.24%) 6	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	44 / 269 (16.36%) 69	24 / 268 (8.96%) 29	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	59 / 269 (21.93%)	72 / 268 (26.87%)	
occurrences (all)	153	157	
Leukopenia			
subjects affected / exposed	27 / 269 (10.04%)	28 / 268 (10.45%)	
occurrences (all)	101	60	
Neutropenia			
subjects affected / exposed	92 / 269 (34.20%)	74 / 268 (27.61%)	
occurrences (all)	262	187	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	59 / 269 (21.93%)	56 / 268 (20.90%)	
occurrences (all)	112	89	
Fatigue			
subjects affected / exposed	66 / 269 (24.54%)	62 / 268 (23.13%)	
occurrences (all)	135	149	
Malaise			
subjects affected / exposed	22 / 269 (8.18%)	29 / 268 (10.82%)	
occurrences (all)	29	70	
Oedema peripheral			
subjects affected / exposed	40 / 269 (14.87%)	31 / 268 (11.57%)	
occurrences (all)	54	40	
Pyrexia			
subjects affected / exposed	47 / 269 (17.47%)	50 / 268 (18.66%)	
occurrences (all)	79	59	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	17 / 269 (6.32%)	17 / 268 (6.34%)	
occurrences (all)	21	21	
Constipation			
subjects affected / exposed	63 / 269 (23.42%)	63 / 268 (23.51%)	
occurrences (all)	92	81	
Diarrhoea			
subjects affected / exposed	38 / 269 (14.13%)	45 / 268 (16.79%)	
occurrences (all)	50	65	

Nausea subjects affected / exposed occurrences (all)	73 / 269 (27.14%) 111	78 / 268 (29.10%) 152	
Stomatitis subjects affected / exposed occurrences (all)	43 / 269 (15.99%) 83	34 / 268 (12.69%) 54	
Vomiting subjects affected / exposed occurrences (all)	29 / 269 (10.78%) 44	38 / 268 (14.18%) 45	
Abdominal pain subjects affected / exposed occurrences (all)	13 / 269 (4.83%) 26	19 / 268 (7.09%) 24	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	42 / 269 (15.61%) 49	42 / 268 (15.67%) 51	
Dyspnoea subjects affected / exposed occurrences (all)	57 / 269 (21.19%) 81	52 / 268 (19.40%) 71	
Haemoptysis subjects affected / exposed occurrences (all)	19 / 269 (7.06%) 25	20 / 268 (7.46%) 22	
Productive cough subjects affected / exposed occurrences (all)	16 / 269 (5.95%) 18	14 / 268 (5.22%) 14	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	81 / 269 (30.11%) 106	42 / 268 (15.67%) 47	
Rash subjects affected / exposed occurrences (all)	17 / 269 (6.32%) 21	24 / 268 (8.96%) 27	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	16 / 269 (5.95%) 17	20 / 268 (7.46%) 28	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 269 (5.58%)	18 / 268 (6.72%)	
occurrences (all)	25	20	
Back pain			
subjects affected / exposed	24 / 269 (8.92%)	21 / 268 (7.84%)	
occurrences (all)	32	31	
Muscle Spasms			
subjects affected / exposed	14 / 269 (5.20%)	7 / 268 (2.61%)	
occurrences (all)	16	8	
Muscular Weakness			
subjects affected / exposed	14 / 269 (5.20%)	9 / 268 (3.36%)	
occurrences (all)	15	18	
Musculoskeletal chest pain			
subjects affected / exposed	19 / 269 (7.06%)	24 / 268 (8.96%)	
occurrences (all)	20	27	
Musculoskeletal pain			
subjects affected / exposed	22 / 269 (8.18%)	14 / 268 (5.22%)	
occurrences (all)	27	30	
Myalgia			
subjects affected / exposed	28 / 269 (10.41%)	26 / 268 (9.70%)	
occurrences (all)	48	47	
Pain in extremity			
subjects affected / exposed	13 / 269 (4.83%)	14 / 268 (5.22%)	
occurrences (all)	17	16	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 269 (4.83%)	14 / 268 (5.22%)	
occurrences (all)	17	14	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	98 / 269 (36.43%)	68 / 268 (25.37%)	
occurrences (all)	148	129	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2012	<ul style="list-style-type: none">• Any hypokalemia or hypomagnesemia should be corrected before eribulin administration• Addition of a recommendation to monitor the QT interval during the treatment period• Introduction of an option to delay administration of eribulin for up to 2 weeks, to allow for resolution of any effects which would normally prevent eribulin dosing• Addition of an alternative dosing schedule for gemcitabine and clarification that the doses given for all treating physician choice (TPC) options were for reference only and country/regional Prescribing Information was to be followed.• Removal of the requirement to administer anti-emetic prophylaxis with eribulin mesylate.• Removal of the requirement for brain and bone scans to be conducted within 1 week of achieving a complete response (CR) or partial response (PR) in line with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported