Clinical trial results:
A Randomized, Open-label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Dacarbazine in Subjects with Soft Tissue Sarcoma

Summary

EudraCT number	2010-024483-17
Trial protocol	BE DE CZ GB AT DK ES IT
Global end of trial date	10 August 2016

Results information

Result version number	v2 (current)
This version publication date	30 July 2020
First version publication date	27 February 2020
Version creation reason	• Correction of full data set Updates in adverse event section

Trial information

Trial identification

Sponsor protocol code	E7389-G000-309

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01327885
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Medical Research Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., +1 1-888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., +1 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	10 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare overall survival (OS) in subjects with advanced soft tissue sarcoma (STS) (one of two subtypes: adipocytic sarcoma [ADI] or leiomyosarcoma [LMS]) when treated with eribulin (Arm A) or dacarbazine (Arm B).

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	10 March 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	Spain: 23
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 157
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Brazil: 20

Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 65
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Singapore: 4
Worldwide total number of subjects	452
EEA total number of subjects	211

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)	356
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 594 subjects screened for entry into the study. Of these subjects, 452 were randomized into the study and 142 were identified as screen failures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Eribulin mesylate

Arm description:

Eribulin mesylate at a dose of 1.4 milligram per square meter (mg/m^2) was administered intravenously (IV) as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

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

Dosage and administration details:

Eribulin mesylate at a dose of 1.4 mg/m^2 was administered IV as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

Arm title	Arm B: Dacarbazine

Arm description:

Dacarbazine at a dose of 850 mg/m^2, 1000 mg/m^2, or 1200 mg/m^2 (as selected by the principal investigator [PI] or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

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

Dosage and administration details:

Dacarbazine at a dose of 850 mg/m^2, 1000 mg/m^2, or 1200 mg/m^2 (as selected by the PI or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

Number of subjects in period 1	Arm A: Eribulin mesylate	Arm B: Dacarbazine
Started	228	224
Completed	0	0
Not completed	228	224
Clinical progression	24	27
Participant choice	5	10
Disease progression-according to RECIST	173	165
Adverse event, non-fatal	14	10
Not specified	8	6
Study terminated by sponsor	-	1
Withdrawal of consent from study	3	4
Not treated	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Eribulin mesylate
Reporting group description:	
Eribulin mesylate at a dose of 1.4 milligram per square meter (mg/m^2) was administered intravenously (IV) as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.	
Reporting group title	Arm B: Dacarbazine
Reporting group description:	
Dacarbazine at a dose of 850 mg/m^2, 1000 mg/m^2, or 1200 mg/m^2 (as selected by the principal investigator [PI] or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.	

Reporting group values	Arm A: Eribulin mesylate	Arm B: Dacarbazine	Total
Number of subjects	228	224	452
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	55.6	55.7	
standard deviation	± 11.01	± 10.35	-
Gender categorical			
Units: Subjects			
Female	161	142	303
Male	67	82	149

End points

End points reporting groups

Reporting group title	Arm A: Eribulin mesylate

Reporting group description:

Eribulin mesylate at a dose of 1.4 milligram per square meter (mg/m^2) was administered intravenously (IV) as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

Reporting group title	Arm B: Dacarbazine

Reporting group description:

Dacarbazine at a dose of 850 mg/m^2, 1000 mg/m^2, or 1200 mg/m^2 (as selected by the principal investigator [PI] or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time in months from the date of treatment start until death, regardless of cause. In the absence of confirmation of death, participants were censored either at the date that participant was last known to be alive or the date of study cut-off, whichever was earlier. Participants who died on the date of randomization had a survival time of 0.5 day. Allocation of randomization numbers were performed based upon the following stratification factors: (a) Histology (adipocytic [ADI] or leiomyosarcoma [LMS]), (b) Region (Region 1: USA and Canada; or Region 2: Western Europe, Australia, Israel; or Region 3: Eastern Europe, Latin America, and Asia), and (c) Number of prior regimens for advanced soft tissue sarcoma (STS) (2 or greater than [>] 2 prior regimens).Full analysis set (FAS) (Intent-to-Treat [ITT] analysis set) included all subjects who were randomized.

End point type	Primary

End point timeframe:

From date of treatment start until date of death from any cause, up to 5 years 5 months

End point values	Arm A: Eribulin mesylate	Arm B: Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	224		
Units: Months				
median (confidence interval 95%)	13.5 (10.9 to 15.6)	11.5 (9.6 to 13.0)		

Statistical analyses

Statistical analysis title	OS

Statistical analysis description:

Statistical analysis was designed to detect superiority of Arm A (eribulin) over Arm B (dacarbazine). OS was compared between the two treatment arms using a two-sided stratified log-rank test at a nominal significance level of 0.0455 (adjusted for the interim analysis). This was the primary analysis that was performed when the target number of events (~353 deaths) was observed.

Comparison groups	Arm B: Dacarbazine v Arm A: Eribulin mesylate

Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0169 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.768
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.618
upper limit	0.954

Notes:

[1] - The P-value was calculated by 2-sided log-rank test as stratified by histology, geographic region, and number of prior regimens for advanced STS.

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

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 date of disease progression was defined as the date of radiologic disease progression as assessed by the investigator or designee based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Subjects who did not have an event (that is subjects who were lost to follow-up or who did not progress or die at the date of data cut-off), were censored. Subjects who discontinued study treatment without disease progression were censored on the date of their last radiological assessment (scan date). FAS (ITT analysis set) included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Randomization (day 1) to the date of first documentation of disease progression, or date of death (whichever occurred first), approximately up to 5 years 5 months.

End point values	Arm A: Eribulin mesylate	Arm B: Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	224		
Units: Months				
median (confidence interval 95%)	2.6 (1.9 to 2.8)	2.6 (1.8 to 2.7)		

Statistical analyses

Statistical analysis title	Progression-free Survival (PFS)

Statistical analysis description:

The PFS and PFS rate at 3, 6, and 12 months (95% confidence interval[CI]) was calculated using Kaplan-Meier (K-M) product-limit method and Greenwood Formula. PFS was compared between the treatment arms using two-sided stratified log-rank test, stratified by histology, geographic region, and number of prior regimens for advanced STS.

Comparison groups	Arm B: Dacarbazine v Arm A: Eribulin mesylate

Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2287 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.877
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.085

Notes:

[2] - P-value was calculated by 2-sided log-rank test, as stratified by histology, geographic region, and number of prior regimens for advanced STS.

Secondary: Progression-free Rate at 12 Weeks (PFR12wks)

End point title	Progression-free Rate at 12 Weeks (PFR12wks)

End point description:

The PFR12wks was defined as the percentage of subjects who were still alive without disease progression at 12 weeks from the date of randomization. Tumor assessment by the investigator or designee was based on RECIST 1.1. FAS (ITT analysis set) included all subjects who were randomized.

End point type	Secondary

End point timeframe:

From date of randomization start until Week 12

End point values	Arm A: Eribulin mesylate	Arm B: Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	224		
Units: Percentage of participants				
number (confidence interval 95%)	33.3 (27.2 to 39.9)	28.6 (22.8 to 35.0)		

Statistical analyses

Statistical analysis title	Progression-Free Rate at 12 Weeks (PFR12wks)

Statistical analysis description:

The PFR12wks was compared between the treatment arms using stratified Cochran-Mantel-Haenszel (CMH) chi-square test stratified by histology, geographic region, and number of prior regimens for advanced STS. The odds ratio between eribulin and dacarbazine was calculated by stratified CMH method. The stratified factors were as described above. The 2-sided 95% CI of the odds ratio is based on asymptotic normal approximation.

Comparison groups	Arm A: Eribulin mesylate v Arm B: Dacarbazine

Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.253 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.9

Notes:

[3] - The P-value was calculated using the stratified CMH method, the stratified factors included histology, geographic region, and number of prior regimens for advanced STS.

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR was defined as the percentage of subjects who have best overall response (BOR) of complete response (CR), or partial response (PR), or duration of stable disease (dSD) greater than or equal to 11 weeks, between Arm A and Arm B. CBR was estimated by treatment arm based on the tumor response evaluation performed by the PI or designee according to RECIST 1.1. CR was defined as disappearance of all target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter. FAS (ITT analysis set) included all subjects who were randomized.

End point type	Secondary

End point timeframe:

From date of treatment start (Day 1) until disease progression, development of unacceptable toxicity, withdrawal of consent, subject's choice to stop study treatment, up to approximately 5 years 5 months

End point values	Arm A: Eribulin mesylate	Arm B: Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	224		
Units: Percentage of participants				
number (confidence interval 95%)	46.1 (39.5 to 52.8)	47.8 (41.1 to 54.5)		

Statistical analyses

Statistical analysis title	Clinical Benefit Rate (CBR)

Statistical analysis description:

The CBR was compared between the treatment arms using stratified CMH chi-square test stratified by histology, geographic region, and number of prior regimens for advanced STS. The odds ratio between eribulin and dacarbazine was calculated by stratified CMH method. The stratified factors were as described above. The 2-sided 95% CI of odds ratio is based on asymptotic normal approximation.

Comparison groups	Arm A: Eribulin mesylate v Arm B: Dacarbazine

Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.741 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.4

Notes:

[4] - The P-value was calculated using the CMH method. The stratified factors were histology, geographic region, and number of prior regimens for advanced STS.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of signing of informed consent up to 30 days after the last dose of study treatment, up to 5 years 5 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Arm A: Eribulin mesylate

Reporting group description:

Eribulin mesylate at a dose of 1.4 mg/m^2 was administered IV as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

Reporting group title	Arm B: Dacarbazine

Reporting group description:

Dacarbazine at a dose of 850 mg/m^2, 1000 mg/m^2, or 1200 mg/m^2 (as selected by the PI or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

Serious adverse events	Arm A: Eribulin mesylate	Arm B: Dacarbazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 228 (33.33%)	71 / 224 (31.70%)	
number of deaths (all causes)	198	206	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 228 (0.88%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Metastases to neck			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myxoid liposarcoma			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyosarcoma			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
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 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 228 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 228 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 228 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 228 (4.39%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	4 / 13	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 228 (1.32%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	2 / 228 (0.88%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Fatigue			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 228 (1.75%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 228 (1.75%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Dyspnoea			
subjects affected / exposed	2 / 228 (0.88%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 228 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	7 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 228 (0.00%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
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			
Humerus fracture			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
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			
Neutropenia			
subjects affected / exposed	11 / 228 (4.82%)	10 / 224 (4.46%)	
occurrences causally related to treatment / all	18 / 18	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 228 (2.19%)	9 / 224 (4.02%)	
occurrences causally related to treatment / all	4 / 5	9 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 228 (1.32%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	4 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	2 / 228 (0.88%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 228 (0.00%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 228 (0.00%)	13 / 224 (5.80%)	
occurrences causally related to treatment / all	0 / 0	19 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 228 (1.75%)	4 / 224 (1.79%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	4 / 228 (1.75%)	5 / 224 (2.23%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 228 (0.88%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 228 (0.88%)	3 / 224 (1.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (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	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal fistula			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
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	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 228 (0.88%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			

subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 228 (0.88%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 228 (0.88%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal pain			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 228 (1.75%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 228 (1.32%)	2 / 224 (0.89%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 228 (0.88%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	2 / 228 (0.88%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 228 (0.44%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Serratia bacteraemia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	1 / 228 (0.44%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	3 / 3	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: Dacarbazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 228 (98.25%)	218 / 224 (97.32%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	13 / 228 (5.70%)	4 / 224 (1.79%)	
occurrences (all)	13	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	98 / 228 (42.98%)	86 / 224 (38.39%)	
occurrences (all)	191	127	
Pyrexia			
subjects affected / exposed	58 / 228 (25.44%)	28 / 224 (12.50%)	
occurrences (all)	85	35	
Asthenia			
subjects affected / exposed	46 / 228 (20.18%)	51 / 224 (22.77%)	
occurrences (all)	82	80	
Oedema peripheral			
subjects affected / exposed	27 / 228 (11.84%)	17 / 224 (7.59%)	
occurrences (all)	30	21	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 228 (17.11%)	28 / 224 (12.50%)	
occurrences (all)	50	33	
Dyspnoea			
subjects affected / exposed	34 / 228 (14.91%)	33 / 224 (14.73%)	
occurrences (all)	40	37	
Oropharyngeal pain			

subjects affected / exposed	12 / 228 (5.26%)	5 / 224 (2.23%)	
occurrences (all)	15	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 228 (9.65%)	10 / 224 (4.46%)	
occurrences (all)	24	10	
Anxiety			
subjects affected / exposed	12 / 228 (5.26%)	14 / 224 (6.25%)	
occurrences (all)	13	16	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 228 (9.21%)	5 / 224 (2.23%)	
occurrences (all)	53	6	
Neutrophil count decreased			
subjects affected / exposed	19 / 228 (8.33%)	12 / 224 (5.36%)	
occurrences (all)	90	34	
Alanine aminotransferase increased			
subjects affected / exposed	18 / 228 (7.89%)	8 / 224 (3.57%)	
occurrences (all)	57	10	
White blood cell count decreased			
subjects affected / exposed	16 / 228 (7.02%)	15 / 224 (6.70%)	
occurrences (all)	71	56	
Electrocardiogram QT prolonged			
subjects affected / exposed	14 / 228 (6.14%)	11 / 224 (4.91%)	
occurrences (all)	23	13	
Blood lactate dehydrogenase increased			
subjects affected / exposed	12 / 228 (5.26%)	7 / 224 (3.13%)	
occurrences (all)	20	8	
Platelet count decreased			
subjects affected / exposed	2 / 228 (0.88%)	17 / 224 (7.59%)	
occurrences (all)	8	45	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	46 / 228 (20.18%)	8 / 224 (3.57%)	
occurrences (all)	81	8	
Headache			

subjects affected / exposed	41 / 228 (17.98%)	21 / 224 (9.38%)	
occurrences (all)	55	25	
Dizziness			
subjects affected / exposed	21 / 228 (9.21%)	16 / 224 (7.14%)	
occurrences (all)	21	16	
Paraesthesia			
subjects affected / exposed	20 / 228 (8.77%)	7 / 224 (3.13%)	
occurrences (all)	28	11	
Dysgeusia			
subjects affected / exposed	18 / 228 (7.89%)	5 / 224 (2.23%)	
occurrences (all)	34	6	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	95 / 228 (41.67%)	51 / 224 (22.77%)	
occurrences (all)	234	139	
Anaemia			
subjects affected / exposed	66 / 228 (28.95%)	68 / 224 (30.36%)	
occurrences (all)	151	149	
Thrombocytopenia			
subjects affected / exposed	13 / 228 (5.70%)	60 / 224 (26.79%)	
occurrences (all)	27	191	
Leukopenia			
subjects affected / exposed	36 / 228 (15.79%)	22 / 224 (9.82%)	
occurrences (all)	109	65	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	18 / 228 (7.89%)	1 / 224 (0.45%)	
occurrences (all)	29	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	91 / 228 (39.91%)	106 / 224 (47.32%)	
occurrences (all)	138	153	
Constipation			
subjects affected / exposed	70 / 228 (30.70%)	58 / 224 (25.89%)	
occurrences (all)	102	69	
Abdominal pain			

subjects affected / exposed	42 / 228 (18.42%)	32 / 224 (14.29%)	
occurrences (all)	50	44	
Vomiting			
subjects affected / exposed	43 / 228 (18.86%)	50 / 224 (22.32%)	
occurrences (all)	52	60	
Diarrhoea			
subjects affected / exposed	38 / 228 (16.67%)	35 / 224 (15.63%)	
occurrences (all)	46	42	
Stomatitis			
subjects affected / exposed	31 / 228 (13.60%)	11 / 224 (4.91%)	
occurrences (all)	51	12	
Abdominal pain upper			
subjects affected / exposed	19 / 228 (8.33%)	13 / 224 (5.80%)	
occurrences (all)	22	15	
Dyspepsia			
subjects affected / exposed	18 / 228 (7.89%)	7 / 224 (3.13%)	
occurrences (all)	21	8	
Abdominal distension			
subjects affected / exposed	16 / 228 (7.02%)	12 / 224 (5.36%)	
occurrences (all)	19	16	
Dry mouth			
subjects affected / exposed	12 / 228 (5.26%)	4 / 224 (1.79%)	
occurrences (all)	12	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	79 / 228 (34.65%)	6 / 224 (2.68%)	
occurrences (all)	106	6	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	33 / 228 (14.47%)	31 / 224 (13.84%)	
occurrences (all)	37	37	
Myalgia			
subjects affected / exposed	23 / 228 (10.09%)	17 / 224 (7.59%)	
occurrences (all)	29	19	
Pain in extremity			

subjects affected / exposed	20 / 228 (8.77%)	18 / 224 (8.04%)	
occurrences (all)	27	24	
Arthralgia			
subjects affected / exposed	19 / 228 (8.33%)	13 / 224 (5.80%)	
occurrences (all)	23	14	
Muscle spasms			
subjects affected / exposed	13 / 228 (5.70%)	7 / 224 (3.13%)	
occurrences (all)	19	8	
Musculoskeletal pain			
subjects affected / exposed	12 / 228 (5.26%)	11 / 224 (4.91%)	
occurrences (all)	13	11	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	23 / 228 (10.09%)	11 / 224 (4.91%)	
occurrences (all)	28	14	
Upper respiratory tract infection			
subjects affected / exposed	20 / 228 (8.77%)	9 / 224 (4.02%)	
occurrences (all)	25	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 228 (18.86%)	43 / 224 (19.20%)	
occurrences (all)	56	52	
Hypokalaemia			
subjects affected / exposed	23 / 228 (10.09%)	9 / 224 (4.02%)	
occurrences (all)	35	11	
Hyperglycaemia			
subjects affected / exposed	17 / 228 (7.46%)	6 / 224 (2.68%)	
occurrences (all)	38	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2012	Amendment 01: The protocol was amended to update that 1. Subjects should have received at least two standard systemic regimens for advanced STS one of which must have included an anthracycline (unless contraindicated) in inclusion criterion #3. 2. Addition of exclusion of temozolomide from prior therapy in exclusion criterion #3. 3. Removal of exclusion criterion #4, 4. Clarified that only serious and potentially life-threating cardiac arrhythmia would require exclusion from the protocol in exclusion criterion #6. 5. Excluding subjects with a high probability for Long QT Syndrome (LQTS) added in exclusion criterion #7. 6. Exclude serious concomitant illness or infectious disease requiring treatment to exclude infectious disease not requiring treatment but with significant risks for myelosuppressive complications associated with chemotherapy added in exclusion criterion #9. 7. Histologically confirmed complete excision of carcinoma in situ exempted from exclusion criterion #10. 8. Study treatment administration on Day 1 of Cycle 1 and each cycle thereafter. 9. Allowed for dacarbazine dilution up to 500 milliliter (mL) and infusion rate up to 60 minutes. 10. Included instructions for temporary discontinuation of treatment, dose reduction, or resumption of treatment in tabulated form. 11. Permanent discontinuation of study treatment required if unable to administer a scheduled dose of study treatment for more than 21 days due to treatment-related toxicity. 12. Criteria for both arms added for eribulin mesilate and dacarbazine and amendment of serious adverse event (SAE) reporting timeframe to require SAEs to be reported to the Sponsor within 24 hours (and not within 1 business day).
08 August 2012	Amendment 02 Subjects in Arm A (eribulin) who had a Grade 3 or Grade 4 QTc interval prolongation were to have study drug permanently discontinued.
01 December 2015	Amendment 03: The protocol was amended to update in the Extension Phase of the study, following the database lock for the primary analysis, ongoing subjects on study treatment in the dacarbazine arm are allowed to cross over to the eribulin arm at the discretion of the investigator decision, frequency of tumor assessments will be permitted to change from every 9 weeks to a frequency at the investigator’s discretion. For subjects who have discontinued study treatment without disease progression, tumor assessments will no longer be required, Sponsor may decide to terminate survival follow-up of all subjects during the Extension Phase after the completion of the primary analysis and when the sponsor considers the data from the primary analysis to be sufficiently mature to no longer require further collection of survival data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported