Clinical trial results:
An Open-Label, Multicenter, Randomized Phase Ib/II Study of Eribulin Mesylate Administered in Combination with Pemetrexed Versus Pemetrexed Alone as Second Line Therapy in Patients with Advanced Non-Small Cell Lung Cancer

Summary

EudraCT number	2009-016047-19
Trial protocol	CZ DE
Global end of trial date	18 March 2015

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	E7389-701

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01126736
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard Woodcliff Lake, New Jersey, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., 01 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 01 888-274-2378, 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	18 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Phase 1b was to define the maximum tolerated dose (MTD)/dose recommended for Phase II of eribulin mesylate, administered in combination with pemetrexed in subjects with nonsquamous, non-small cell lung cancer (NSCLC), previously treated with 1 cytotoxic chemotherapy regimen for stage IIIB or IV disease. The primary objective of Phase 2 was to evaluate the safety and tolerability of multiple doses of eribulin administered in combination with pemetrexed, compared with pemetrexed alone as second-line therapy in subjects with advanced nonsquamous NSCLC.

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 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Czechia: 25
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	98
EEA total number of subjects	43

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)	69
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 23 investigative sites in the United States, Germany, Italy, Ukraine, and the Czech Republic from 10 June 2010 to 18 March 2015.

Pre-assignment

Screening details:

A total of 15 subjects were enrolled and treated in Phase 1b portion of the study and 83 subjects were randomized of which 80 subjects received study treatment in Phase 2 portion of the study.

Period 1

Period 1 title	Phase 1b and Phase 2 (overall) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Arm 1 - Cohort 1 (Eribulin+Pemetrexed)

Arm description:

Subject received intravenous (IV) bolus of eribulin 0.9 milligram per square meter (mg/m^2) in combination with IV infused pemetrexed 500 mg/m^2 on Day 1 of each 21-day treatment cycle. Subject within the same cohort received the same dose of eribulin. Subject also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was escalated to 1.4 mg/m^2 in Cohort 2 of Arm 1.

Arm type	Experimental
Investigational medicinal product name	Eribulin Mesilate
Investigational medicinal product code	E7389
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 0.9 mg/m^2, IV infusion in combination with pemetrexed (500 mg/m^2) on Day 1 of a 21 day treatment cycle.

Arm title	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)

Arm description:

Subjects received IV bolus of eribulin 1.4 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.

Arm type	Experimental
Investigational medicinal product name	Eribulin Mesilate
Investigational medicinal product code	E7389
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 1.4 mg/m^2, IV infusion in combination with pemetrexed (500 mg/m^2) on Day 1 of a 21 day treatment cycle.

Arm title	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)

Arm description:

Subjects received IV bolus of eribulin 0.7 mg/m^2 on Days 1 and 8 of each 21-day treatment cycle. On Day 1 only of each 21-day treatment cycle, subjects also received IV infused pemetrexed (500

mg/m^2). Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.

Arm type	Experimental
Investigational medicinal product name	Eribulin Mesilate
Investigational medicinal product code	E7389
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 0.7 mg/m^2, IV infusion in combination with pemetrexed (500 mg/m^2) on Days 1 and 8 of a 21 day treatment cycle.

Arm title	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)

Arm description:

Subjects received IV bolus of eribulin 0.9 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.

Arm type	Experimental
Investigational medicinal product name	Eribulin Mesilate
Investigational medicinal product code	E7389
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 0.9 mg/m^2, IV infusion in combination with pemetrexed (500 mg/m^2) on Day 1 of a 21 day treatment cycle.

Arm title	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)

Arm description:

Subjects received IV infused pemetrexed (500 mg/m^2) alone on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.

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

Dosage and administration details:

Subjects received pemetrexed 500 mg/m^2 IV infusion on Day 1 of a 21 day treatment cycle.

Number of subjects in period 1	Phase 1b: Arm 1 - Cohort 1 (Eribulin+Pemetrexed)	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)
Started	4	6	5
Completed	0	0	0
Not completed	4	6	5
Consent withdrawn by subject	-	-	-
Study terminated by Sponsor	-	-	-
Death	2	2	1

Not specified	2	4	4
Completed 1 Year Follow-Up Per Protocol	-	-	-
Progressive disease	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)
Started	42	41
Completed	0	0
Not completed	42	41
Consent withdrawn by subject	1	1
Study terminated by Sponsor	-	1
Death	19	19
Not specified	16	15
Completed 1 Year Follow-Up Per Protocol	3	3
Progressive disease	2	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1b: Arm 1 - Cohort 1 (Eribulin+Pemetrexed)
Reporting group description:	
Subject received intravenous (IV) bolus of eribulin 0.9 milligram per square meter (mg/m^2) in combination with IV infused pemetrexed 500 mg/m^2 on Day 1 of each 21-day treatment cycle. Subject within the same cohort received the same dose of eribulin. Subject also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was escalated to 1.4 mg/m^2 in Cohort 2 of Arm 1.	
Reporting group title	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)
Reporting group description:	
Subjects received IV bolus of eribulin 1.4 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.	
Reporting group title	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)
Reporting group description:	
Subjects received IV bolus of eribulin 0.7 mg/m^2 on Days 1 and 8 of each 21-day treatment cycle. On Day 1 only of each 21-day treatment cycle, subjects also received IV infused pemetrexed (500 mg/m^2). Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.	
Reporting group title	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)
Reporting group description:	
Subjects received IV bolus of eribulin 0.9 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.	
Reporting group title	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)
Reporting group description:	
Subjects received IV infused pemetrexed (500 mg/m^2) alone on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.	

Reporting group values	Phase 1b: Arm 1 - Cohort 1 (Eribulin+Pemetrexed)	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)
Number of subjects	4	6	5
Age categorical Units: subjects			
Adults (18-64 years)	2	6	5
From 65-84 years	2	0	0
Age continuous Units: years			
arithmetic mean	61.8	57.2	50.0
standard deviation	± 10.75	± 6.62	± 7.48
Gender categorical Units: subjects			
Female	2	1	1
Male	2	5	4

Race Units: Subjects			
White	4	6	5
Ethnicity Units: Subjects			
Hispanic Or Latino	0	1	0
Not Hispanic Or Latino	4	5	5
Not Reported/Unknown	0	0	0

Reporting group values	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)	Total
Number of subjects	42	41	98
Age categorical Units: subjects			
Adults (18-64 years)	29	27	69
From 65-84 years	13	14	29
Age continuous Units: years			
arithmetic mean	59.1	60.4	
standard deviation	± 10.63	± 8.91	-
Gender categorical Units: subjects			
Female	16	14	34
Male	26	27	64
Race Units: Subjects			
White	42	41	98
Ethnicity Units: Subjects			
Hispanic Or Latino	3	1	5
Not Hispanic Or Latino	39	40	93
Not Reported/Unknown	0	0	0

End points

End points reporting groups

Reporting group title	Phase 1b: Arm 1 - Cohort 1 (Eribulin+Pemetrexed)

Reporting group description:

Subject received intravenous (IV) bolus of eribulin 0.9 milligram per square meter (mg/m^2) in combination with IV infused pemetrexed 500 mg/m^2 on Day 1 of each 21-day treatment cycle. Subject within the same cohort received the same dose of eribulin. Subject also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was escalated to 1.4 mg/m^2 in Cohort 2 of Arm 1.

Reporting group title	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)

Reporting group description:

Subjects received IV bolus of eribulin 1.4 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.

Reporting group title	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)

Reporting group description:

Subjects received IV bolus of eribulin 0.7 mg/m^2 on Days 1 and 8 of each 21-day treatment cycle. On Day 1 only of each 21-day treatment cycle, subjects also received IV infused pemetrexed (500 mg/m^2). Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.

Reporting group title	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)

Reporting group description:

Subjects received IV bolus of eribulin 0.9 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.

Reporting group title	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)

Reporting group description:

Subjects received IV infused pemetrexed (500 mg/m^2) alone on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.

Primary: Phase 1b: Number of Subjects With Dose-Limiting Toxicity (DLTs)

End point title	Phase 1b: Number of Subjects With Dose-Limiting Toxicity (DLTs)[1][2]

End point description:

DLT were defined as clinically significant adverse events (AE) occurring less than or equal to(<=)21 days after treatment.Events as: Non-hematological: 1)Grade greater than or equal to(>=)3 peripheral neuropathy; 2)Grade >=3 nausea,vomiting despite optimal antiemetic treatment; 3)Any nonhematologic toxicity of Grade >=3, with exceptions as alopecia,single laboratory values out of normal range,hypersensitivity reaction. Hematological:1)Grade 4 neutropenia lasting >7 days; 2)Febrile neutropenia as fever >=38.5 degree celsius with absolute neutrophil count less than(<)1.0*10^9 per liter(/L); 3)Grade 3 thrombocytopenia with nontraumatic bleeding requiring platelet transfusion; 4)Grade 4 thrombocytopenia with/without nontraumatic bleeding. Other 1)Study drug related death; 2)Toxicity that dose escalation committee believed to be DLT that was not covered by above DLT criteria. Phase 1b safety analysis set was defined as all subjects enrolled into the Phase 1b portion of

End point type	Primary

End point timeframe:

Cycle 1 (each cycle length = 21 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Planned analyses for these data was descriptive only.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only data for Phase 1b are reported in this end point.

End point values	Phase 1b: Arm 1 - Cohort 1 (Eribulin+Pemetrexed)	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	5	
Units: subjects				
Alanine transaminase (ALT) increased (grade 3)	0	1	1	
Aspartate transaminase (AST) increased (grade 3)	0	1	0	
Febrile neutropenia (grade 4)	0	1	0	
Neutropenia (grade 4)	0	1	0	
Pneumonia (grade 4)	0	0	1	
Thrombocytopenia (grade 4)	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Percentage of Subjects With Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs)

End point title	Phase 1b: Percentage of Subjects With Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs)[3][4]

End point description:

Safety assessment included monitoring and recording all AE including all Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grades (for both increasing and decreasing severity), and serious adverse events (SAE); regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and electrocardiograms (ECGs); and performance of physical examinations. A TEAE was defined as an AE that had on onset date, or a worsening in severity from Baseline (pretreatment), on or after the first dose of study drug up to the end of the study. Phase 1b safety analysis set was defined as all subjects enrolled into the Phase 1b portion of this study. As per CTCAE, Grade 1 scales as Mild; Grade 2 scales as Moderate; Grade 3 scales as severe or medically significant but not immediately life threatening; Grade 4 scales as life-threatening consequences; and Grade 5 scales as death related to AE.

End point type	Primary

End point timeframe:

From date of first dose up to 30 days after the last dose of study drug, up to approximately 1 year 2 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Planned analyses for these data was descriptive only.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only data for Phase 1b are reported in this end point.

End point values	Phase 1b: Arm 1 - Cohort 1 (Eribulin+Pemetrexed)	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	5	
Units: percentage of subjects				
number (not applicable)	100.0	83.3	100.0	

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Subjects Who Experienced Treatment Emergent Adverse Events (TEAEs)

End point title	Phase 2: Percentage of Subjects Who Experienced Treatment Emergent Adverse Events (TEAEs)[5][6]

End point description:

Safety assessments consisted of monitoring and recording all AEs, including CTCAE version 4.0 grades (for both increasing and decreasing severity), and SAEs, regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs, and performance of physical examinations. Phase 2 safety population included all subjects enrolled and randomized to treatment in the Phase 2 portion of the study, except for those who (I) dropped out prior to receiving any study drug, (ii) were without any safety assessment following the first dose of study drug.

End point type	Primary

End point timeframe:

From date of first dose up to 30 days after the last dose of study drug, up to approximately 3 years 6 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Planned analyses for these data was descriptive only.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only data for Phase 2 are reported in this end point.

End point values	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: percentage of subjects				
number (not applicable)	95.1	94.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival (PFS) in Subjects Receiving Eribulin in Combination With Pemetrexed or Pemetrexed Alone

End point title	Phase 2: Progression-free Survival (PFS) in Subjects Receiving Eribulin in Combination With Pemetrexed or Pemetrexed Alone[7]

End point description:

PFS was defined as the time from the date of randomization until the earlier of the following two events: the date of PD or the date of death based on response evaluation criteria in solid tumor (RECIST) version 1.1. Progressive disease (PD) is defined as at least a 20 percent (%) increase or 5 millimeter (mm) increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS was estimated and analyzed using Kaplan Meier method. Modified intent-to-treat population included all randomized subjects who received at least one dose of study drug without major protocol eligibility violations.

End point type	Secondary

End point timeframe:

From the date of randomization until the earlier of the following two events: the date of PD or the date of death (Up to approximately 3 years 5 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only data for Phase 2 are reported in this end point.

End point values	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: weeks				
median (confidence interval 95%)	18.1 (8.43 to 34.14)	22.0 (12.14 to 29.00)		

Statistical analyses

No statistical analyses for this end point

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 drug (up to approximately 3 years 6 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Phase 1b: Arm 1 - Cohort 1 (Eribulin + Pemetrexed)

Reporting group description:

Subject received IV bolus of eribulin 0.9 mg/m^2 in combination with IV infused pemetrexed 500 mg/m^2 on Day 1 of each 21-day treatment cycle. Subject within the same cohort received the same dose of eribulin. Subject also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was escalated to 1.4 mg/m^2 in Cohort 2 of Arm 1.

Reporting group title	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)

Reporting group description:

Subjects received IV bolus of eribulin 1.4 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.

Reporting group title	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)

Reporting group description:

Subjects received IV bolus of eribulin 0.7 mg/m^2 on Days 1 and 8 of each 21-day treatment cycle. On Day 1 only of each 21-day treatment cycle, subjects also received IV infused pemetrexed (500 mg/m^2). Subjects within the same cohort received the same dose of eribulin. Subjects also received dexamethasone and vitamin supplements as recommended in the prescribing information for pemetrexed. The dose of eribulin was not further escalated.

Reporting group title	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)

Reporting group description:

Subjects received IV bolus of eribulin 0.9 mg/m^2 in combination with IV infused pemetrexed (500 mg/m^2) on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.

Reporting group title	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)

Reporting group description:

Subjects received IV infused pemetrexed (500 mg/m^2) alone on Day 1 of each 21-day treatment cycle. Dexamethasone and vitamin supplements were administered as recommended in the prescribing information for pemetrexed.

Serious adverse events	Phase 1b: Arm 1 - Cohort 1 (Eribulin + Pemetrexed)	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 6 (50.00%)	4 / 5 (80.00%)
number of deaths (all causes)	2	2	1
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Malignant Pleural Effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases To Bone			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases To Central Nervous System			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mucosal Inflammation			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-Organ Failure			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pulmonary Embolism			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Spinal Compression Fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiopulmonary Failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Loss Of Consciousness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenic Syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Ischaemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophageal Stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis Syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Hypochloraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 41 (31.71%)	7 / 39 (17.95%)	
number of deaths (all causes)	19	19	
number of deaths resulting from adverse events	3	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Pleural Effusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metastases To Bone			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metastases To Central Nervous System			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Mucosal Inflammation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ Failure			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			

subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory Failure			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
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			
Spinal Compression Fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiopulmonary Failure			

subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic Syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Stenosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis Syndrome			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypochloraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase 1b: Arm 1 - Cohort 1 (Eribulin + Pemetrexed)	Phase 1b: Arm 1 - Cohort 2 (Eribulin + Pemetrexed)	Phase 1b: Arm 2 - Cohort 1 (Eribulin + Pemetrexed)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	6 / 6 (100.00%)	5 / 5 (100.00%)
Vascular disorders			

Aortic Aneurysm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Deep Vein Thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hot Flush			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vasculitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	3	0	1
Chest Discomfort			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	4	1	2
Mucosal Inflammation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Oedema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oedema Peripheral			

subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	0	1	3
Chest Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	3	0	1
Cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	0	1	3
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	2
Hypoxia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	3
Oropharyngeal Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	2
Pleuritic Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pulmonary Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rhonchi			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	5	4
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	3	4
Blood Alkaline Phosphatase Increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Breath Sounds Abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Platelet Count Decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	2	4
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	2
C-Reactive Protein Increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Creatinine Renal Clearance Decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Weight Decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Muscle Strain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rib Fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Poisoning			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Sinus Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hypotonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 6 (33.33%)	3 / 5 (60.00%)
occurrences (all)	13	4	11
Febrile Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	3 / 5 (60.00%)
occurrences (all)	4	0	3
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	3 / 4 (75.00%)	3 / 6 (50.00%)	3 / 5 (60.00%)
occurrences (all)	7	5	5
Thrombocytopenia			

subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	3	3	1
Thrombocytosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis Allergic			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	5	1	0
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	2	0	3
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dry Skin			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	3	1	2
Skin Ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Renal Failure			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Muscular Weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pain In Extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Bacteraemia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Bronchitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Candidiasis			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Cellulitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye Infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Herpes Simplex			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oral Candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Sepsis Syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	3 / 4 (75.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	3	0	1
Dehydration			

subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diabetes Mellitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Malnutrition			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Phase 2: Arm 1 (Eribulin 0.9 mg/m^2 + pemetrexed 500 mg/m^2)	Phase 2: Arm 2 (Pemetrexed 500 mg/m^2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 41 (97.56%)	37 / 39 (94.87%)	
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Deep Vein Thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Hot Flush			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Hypotension			

subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Vasculitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 41 (12.20%)	1 / 39 (2.56%)	
occurrences (all)	7	1	
Chest Discomfort			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	6 / 41 (14.63%)	12 / 39 (30.77%)	
occurrences (all)	12	14	
Mucosal Inflammation			
subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Oedema			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Oedema Peripheral			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	5 / 41 (12.20%)	2 / 39 (5.13%)	
occurrences (all)	6	3	
Chest Pain			

subjects affected / exposed	2 / 41 (4.88%)	4 / 39 (10.26%)	
occurrences (all)	5	4	
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Dysphonia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	4 / 41 (9.76%)	6 / 39 (15.38%)	
occurrences (all)	5	7	
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Haemoptysis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Hypoxia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal Pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Pleuritic Pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Pulmonary Hypertension			

subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Rhonchi			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Wheezing			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	11 / 41 (26.83%)	15 / 39 (38.46%)	
occurrences (all)	50	92	
Aspartate Aminotransferase Increased			
subjects affected / exposed	10 / 41 (24.39%)	14 / 39 (35.90%)	
occurrences (all)	36	60	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Breath Sounds Abnormal			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Platelet Count Decreased			

subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
C-Reactive Protein Increased			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
Creatinine Renal Clearance Decreased			
subjects affected / exposed	1 / 41 (2.44%)	3 / 39 (7.69%)	
occurrences (all)	1	4	
Weight Decreased			
subjects affected / exposed	3 / 41 (7.32%)	4 / 39 (10.26%)	
occurrences (all)	5	4	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Muscle Strain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Rib Fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Poisoning			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Sinus Tachycardia			
subjects affected / exposed	1 / 41 (2.44%)	4 / 39 (10.26%)	
occurrences (all)	1	5	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 41 (4.88%)	4 / 39 (10.26%)	
occurrences (all)	2	4	
Hypotonia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 41 (14.63%)	14 / 39 (35.90%)	
occurrences (all)	13	37	
Febrile Neutropenia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Leukopenia			
subjects affected / exposed	3 / 41 (7.32%)	7 / 39 (17.95%)	
occurrences (all)	6	17	
Lymphadenopathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Lymphopenia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	13 / 41 (31.71%)	11 / 39 (28.21%)	
occurrences (all)	15	21	
Thrombocytopenia			
subjects affected / exposed	2 / 41 (4.88%)	4 / 39 (10.26%)	
occurrences (all)	4	4	
Thrombocytosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 41 (4.88%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Eye disorders			

Conjunctivitis Allergic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 41 (12.20%)	2 / 39 (5.13%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	5 / 41 (12.20%)	2 / 39 (5.13%)	
occurrences (all)	8	2	
Dysphagia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Gastritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	10 / 41 (24.39%)	6 / 39 (15.38%)	
occurrences (all)	20	8	
Vomiting			
subjects affected / exposed	3 / 41 (7.32%)	3 / 39 (7.69%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Dry Skin			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Erythema			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	3 / 41 (7.32%)	3 / 39 (7.69%)	
occurrences (all)	5	5	
Skin Ulcer			

subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Renal Failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Muscular Weakness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Pain In Extremity			
subjects affected / exposed	1 / 41 (2.44%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Musculoskeletal Pain			
subjects affected / exposed	1 / 41 (2.44%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Bronchitis			
subjects affected / exposed	4 / 41 (9.76%)	0 / 39 (0.00%)	
occurrences (all)	4	0	
Candidiasis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Cellulitis			

subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Eye Infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Herpes Simplex			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	3 / 41 (7.32%)	4 / 39 (10.26%)	
occurrences (all)	3	6	
Oral Candidiasis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Sepsis Syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	8 / 41 (19.51%)	5 / 39 (12.82%)	
occurrences (all)	9	7	
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Diabetes Mellitus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 39 (7.69%)	
occurrences (all)	1	4	
Hypocalcaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	

Hypokalaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Malnutrition			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2010	Protocol Amendment 01: Clarified that subjects experiencing clinical benefit following 6 cycles of study treatment could, at the discretion of the Investigator and in consultation with the Medical Monitor, continue pemetrexed with or without eribulin or single-agent eribulin; Clarified that follow-up was to be for up to 1 year after the end of treatment; Clarified that dose reductions were not permitted in Cycle 1 of Phase 1b; Clarified the use of erythroid-stimulating agents; Added lymph nodes to the physical examination; Clarified that electronic case report forms would be used; Clarified that the Medical Monitor would be the contact person for any questions regarding treatment.
25 May 2010	Protocol Amendment 02: For Germany only - clarified that treatment would last no longer than 24 months.
30 March 2011	Protocol Amendment 03: Set the dose for the Phase 2 portion of the study and changes the design from a 3 arm to a 2 arm design; Due to changes in the Tumor Node Metastasis (TNM) staging system, the study title was changed to include subjects with advanced NSCLC; Updated Introduction with information from the Phase 1b portion of the study; Changed inclusion criteria for liver function from ALT/AST of 3*upper limit of normal (ULN) to <= 2*ULN and <= 3*ULN in the case of liver metastases; Added exclusion of subjects with a high probability of Long QT Syndrome; Added stopping criteria for Phase 2; Allowed for standard of care labs to be used for Screening labs if collected within 21 days of the first dose of study treatment; Clarified when other lab assessments were to be collected; Changed frequency of radiological scans from every 2 cycles to every 6 weeks (+/- 7 days); Clarified dose modification guidelines; Clarified the use of granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating to allow prophylactic use after Day 21; Inconsistencies in the text are also clarified/corrected.
04 April 2011	Protocol Amendment 04: For Germany only, was identical to Amendment 3 only with the Germany-specific language from Amendment 2 included.
04 April 2011	Protocol Amendment 05: For Argentina and Brazil only, was identical to Amendment 3 but with the addition of HBV, HCV, and HIV serology at Screening.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported