Clinical trial results:
A Randomized Controlled Study of Yondelis (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma

Summary

EudraCT number	2016-000929-40
Trial protocol	Outside EU/EEA
Global end of trial date	05 January 2015

Results information

Result version number	v1 (current)
This version publication date	03 November 2016
First version publication date	03 November 2016

Trial information

Trial identification

Sponsor protocol code	ET743-SAR-3007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01343277
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	05 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of study was to evaluate whether overall survival (OS) for the trabectedin group was superior to the dacarbazine group for subjects with advanced liposarcoma or leiomyosarcoma (L-sarcoma) who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Adverse events of clinical interest (eg, thrombocytopenia and bleeding, neutropenia and infections [including sepsis or septic shock], creatine phosphokinase (CPK) elevations or rhabdomyolysis, catheter-related complications, liver injury, multi-organ failures, cardiac disorders, and renal disorders were reported throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 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	Australia: 23
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	United States: 539
Worldwide total number of subjects	577
EEA total number of subjects	0

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	445
From 65 to 84 years	131
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 577 subjects were planned (380 subjects in the trabectedin group and 190 subjects in the dacarbazine group). Out of them 534 subjects completed the study (367 subjects in the trabectedin group and 167 subjects in the dacarbazine group).

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	Trabectedin

Arm description:

Subjects received trabectedin 1.5 milligram per meter square (mg/m^2) as a 24-hour intravenous (i.v.) infusion once every 3 weeks (q3wk 24-h).

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

Dosage and administration details:

Subjects received trabectedin 1.5 milligram per meter square per meter square (mg/m^2) as a 24-hour intravenous (i.v.) infusion once every 3 weeks (q3wk 24-h).

Arm title	Dacarbazine

Arm description:

Subjects received dacarbazine 1 gram per meter square (g/m^2) as a 20- 120 minutes intravenous (i.v.) infusion once every 3 weeks (q3wk).

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

Dosage and administration details:

Subjects received dacarbazine 1 gram per meter square (g/m^2) as a 20- 120 minutes intravenous (i.v.) infusion once every 3 weeks (q3wk).

Number of subjects in period 1	Trabectedin	Dacarbazine
Started	384	193
Completed	367	167
Not completed	17	26
Withdraw consent for follow-up	12	23
Lost to follow-up	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Trabectedin
Reporting group description:	
Subjects received trabectedin 1.5 milligram per meter square (mg/m^2) as a 24-hour intravenous (i.v.) infusion once every 3 weeks (q3wk 24-h).	
Reporting group title	Dacarbazine
Reporting group description:	
Subjects received dacarbazine 1 gram per meter square (g/m^2) as a 20- 120 minutes intravenous (i.v.) infusion once every 3 weeks (q3wk).	

Reporting group values	Trabectedin	Dacarbazine	Total
Number of subjects	384	193	577
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	1	1
Adults (18-64 years)	290	155	445
From 65 to 84 years	94	37	131
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	56.5	54.1	
standard deviation	± 11.04	± 11.92	-
Title for Gender Units: subjects			
Female	262	140	402
Male	122	53	175

End points

End points reporting groups

Reporting group title	Trabectedin
Reporting group description:	
Subjects received trabectedin 1.5 milligram per meter square (mg/m^2) as a 24-hour intravenous (i.v.) infusion once every 3 weeks (q3wk 24-h).	
Reporting group title	Dacarbazine
Reporting group description:	
Subjects received dacarbazine 1 gram per meter square (g/m^2) as a 20- 120 minutes intravenous (i.v.) infusion once every 3 weeks (q3wk).	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
The OS is defined as the time from the date of first dose of study drug to date of death from any cause. If the subject is alive or the vital status is unknown, the participant will be censored at the date the subject will be last known to be alive. Analysis population included all the randomized subjects up to final analysis cut-off date (05 January 2015).	
End point type	Primary
End point timeframe:	
Approximately 3 years 8 months (From Study start date [27 May 2011] up to final analysis data cut-off [05 January 2015]	

End point values	Trabectedin	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	193		
Units: Months				
median (confidence interval 95%)	13.73 (12.16 to 16)	13.14 (9.1 to 16.23)		

Statistical analyses

Statistical analysis title	Overall Survival Analysis
Comparison groups	Trabectedin v Dacarbazine
Number of subjects included in analysis	577
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.492
Method	Unstratified log rank test
Parameter estimate	Log hazard ratio
Point estimate	0.927

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.748
upper limit	1.15

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

The Progression-Free Survival (PFS) was assessed as median number of months from baseline until the first documented sign of disease progression (increase in disease; radiographic, clinical, or both) or death due to any cause, whichever occurred earlier. Independent Data Monitoring Committee performed ongoing safety monitoring and conducted the interim analysis after 189 death events and 329 PFS events were observed. Analysis population included all the randomized subjects evaluated up to interim analysis cut-off date (16 September 2013).

End point type	Secondary

End point timeframe:

Approximately 2 years 4 months (From Study start date [27 May 2011] up to interim analysis data cut-off [16 September 2013])

End point values	Trabectedin	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	173		
Units: Months				
median (confidence interval 95%)	4.21 (2.99 to 4.83)	1.54 (1.48 to 2.6)		

Statistical analyses

Statistical analysis title	Progression-Free Survival Analysis
Comparison groups	Trabectedin v Dacarbazine
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Unstratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.436
upper limit	0.696

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time interval in months between the date of randomization and the date of disease progression or death due to progression, whichever occurred first. Independent Data Monitoring Committee performed ongoing safety monitoring and conducted the interim analysis after 189 death events and 329 PFS events were observed. Analysis population included all the randomized subjects up to interim analysis cut-off date (16 September 2013).

End point type	Secondary

End point timeframe:

Approximately 2 years 4 months (From Study start date [27 May 2011] up to interim analysis data cut-off [16 September 2013])

End point values	Trabectedin	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	173		
Units: Months				
median (confidence interval 95%)	4.24 (3.22 to 4.93)	1.54 (1.48 to 2.6)		

Statistical analyses

Statistical analysis title	Time to Progression Analysis
Comparison groups	Trabectedin v Dacarbazine
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Unstratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.522
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.412
upper limit	0.661

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

The objective response rate (ORR) is defined as the percentage of subjects who achieved a Complete response (CR) or partial response (PR) as best responses. according to Response Evaluation Criteria in

Solid Tumors, Version 1.1 (RECIST). CR defined as disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to less than 10 millimeter (mm). PR defined as at least 30 percent (%) decrease in sum of the diameters of the target lesions taking as reference the Baseline sum diameters. Confirmed responses are those that persist on repeat imaging study for at least 4 weeks after initial documentation of response. Independent Data Monitoring Committee performed ongoing safety monitoring and conducted the interim analysis after 189 death events and 329 PFS events were observed. Analysis population included all the randomized subjects up to interim analysis cut-off date (16 September 2013).

End point type	Secondary

End point timeframe:

Approximately 2 years 4 months (From Study start date [27 May 2011] up to interim analysis data cut-off [16 September 2013])

End point values	Trabectedin	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	173		
Units: Percentage of subjects				
median (confidence interval 95%)	9.9 (6.9 to 13.5)	6.9 (3.6 to 11.8)		

Statistical analyses

Statistical analysis title	Objective Response Rate Analysis
Comparison groups	Trabectedin v Dacarbazine
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3269
Method	Fisher’s exact test.
Parameter estimate	Odds ratio (OR)
Point estimate	1.467
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.717
upper limit	3.197

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response is defined as the time from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. Independent Data Monitoring Committee performed ongoing safety monitoring and conducted the interim analysis after 189 death events and 329 PFS events were observed. Analysis population included all the randomized subjects up to interim analysis cut-off date (16 September 2013). The value 999 indicated the not estimable data value.

End point type	Secondary

End point timeframe:

Approximately 2 years 4 months (From Study start date [27 May 2011] up to interim analysis data cut-off [16 September 2013])

End point values	Trabectedin	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	12		
Units: Months				
median (confidence interval 95%)	6.47 (3.58 to 7.62)	4.17 (2.14 to 999)		

Statistical analyses

Statistical analysis title	Duration of Response Analysis
Comparison groups	Trabectedin v Dacarbazine
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1415
Method	Unstratified log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.471
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.168
upper limit	1.318

Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all the treated subjects.

End point type	Secondary

End point timeframe:

Approximately 3 years 8 months (From Study start date [27 May 2011] up to final analysis data cut-off [05 January 2015])

End point values	Trabectedin	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378	172		
Units: Subjects				
Serious Adverse Events (SAEs)	155	52		
Adverse Events (AEs)	375	166		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 3 years 8 months (From Study start date [27 May 2011] up to final analysis data cut-off [05 January 2015])

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Dacarbazine

Reporting group description:

Subjects received dacarbazine 1 gram per meter square (g/m^2) as a 20- 120 minutes intravenous (i.v.)
infusion once every 3 weeks (q3wk).

Reporting group title	Trabectedin

Reporting group description:

Subjects received trabectedin 1.5 milligram per meter square (mg/m^2) as a 24-hour intravenous (i.v.) infusion once every 3 weeks (q3wk 24-h).

Serious adverse events	Dacarbazine	Trabectedin	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 172 (30.23%)	155 / 378 (41.01%)	
number of deaths (all causes)	5	25	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	1 / 172 (0.58%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Ascites			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Pain			
subjects affected / exposed	3 / 172 (1.74%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Circulatory Collapse			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep Vein Thrombosis			
subjects affected / exposed	1 / 172 (0.58%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism Venous			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 172 (0.58%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jugular Vein Thrombosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal Arteritis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Hip Surgery			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 172 (0.00%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Inflammation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Discomfort			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 172 (1.74%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 5	
Device Breakage			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Failure			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	1 / 172 (0.58%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait Disturbance			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised Oedema			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Site Extravasation			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ Failure			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Necrosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			

subjects affected / exposed	1 / 172 (0.58%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 172 (0.58%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 172 (1.16%)	12 / 378 (3.17%)	
occurrences causally related to treatment / all	0 / 2	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in Device			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal Fistula			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Haemorrhage			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial Obstruction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 172 (1.16%)	13 / 378 (3.44%)	
occurrences causally related to treatment / all	0 / 2	4 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea Exertional			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	3 / 172 (1.74%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleuritic Pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 172 (0.58%)	6 / 378 (1.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Arrest			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory Distress			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory Failure			

subjects affected / exposed	1 / 172 (0.58%)	6 / 378 (1.59%)	
occurrences causally related to treatment / all	0 / 1	2 / 7	
deaths causally related to treatment / all	0 / 1	0 / 4	
Tachypnoea			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Bilirubin Increased			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 172 (0.00%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased			
subjects affected / exposed	0 / 172 (0.00%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Lactic Acid Increased			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection Fraction Decreased			
subjects affected / exposed	0 / 172 (0.00%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
International Normalised Ratio Increased			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Abnormal			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoglobin Blood Increased			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
subjects affected / exposed	1 / 172 (0.58%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			

subjects affected / exposed	2 / 172 (1.16%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases Increased			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I Increased			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Access Complication			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			

subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
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 / 172 (0.58%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 3	
Cardiac Disorder			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	0 / 172 (0.00%)	7 / 378 (1.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			

subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Dysfunction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Dysfunction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Tachycardia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 172 (0.58%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Intracranial			

subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	2 / 172 (1.16%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyramidal Tract Syndrome			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (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	2 / 172 (1.16%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 172 (1.16%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 172 (2.33%)	15 / 378 (3.97%)	
occurrences causally related to treatment / all	0 / 4	11 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	2 / 172 (1.16%)	12 / 378 (3.17%)	
occurrences causally related to treatment / all	0 / 2	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 172 (1.74%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic Haemolytic Anaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 172 (0.58%)	9 / 378 (2.38%)	
occurrences causally related to treatment / all	0 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 172 (1.74%)	7 / 378 (1.85%)	
occurrences causally related to treatment / all	0 / 3	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual Impairment			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal Hernia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	8 / 172 (4.65%)	13 / 378 (3.44%)	
occurrences causally related to treatment / all	0 / 8	2 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Lower			
subjects affected / exposed	1 / 172 (0.58%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 172 (0.58%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 172 (0.00%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Obstruction			

subjects affected / exposed	2 / 172 (1.16%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal Obstruction			
subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Ulcer			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-Abdominal Haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Obstruction			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (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	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Gastrointestinal Haemorrhage			

subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 172 (1.74%)	15 / 378 (3.97%)	
occurrences causally related to treatment / all	0 / 4	14 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction Gastric			
subjects affected / exposed	1 / 172 (0.58%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal Obstruction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 172 (0.00%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	3 / 172 (1.74%)	9 / 378 (2.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			

subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 172 (1.74%)	15 / 378 (3.97%)	
occurrences causally related to treatment / all	0 / 4	14 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal Vein Thrombosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 172 (0.58%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive Uropathy			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			

subjects affected / exposed	1 / 172 (0.58%)	12 / 378 (3.17%)	
occurrences causally related to treatment / all	0 / 1	6 / 14	
deaths causally related to treatment / all	0 / 0	2 / 2	
Renal Tubular Necrosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	2 / 172 (1.16%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Range of Motion Decreased			

subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Swelling			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck Pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in Extremity			
subjects affected / exposed	2 / 172 (1.16%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 172 (0.00%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	2 / 2	
Soft Tissue Necrosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Infection			

subjects affected / exposed	1 / 172 (0.58%)	8 / 378 (2.12%)	
occurrences causally related to treatment / all	0 / 1	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Infection			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Sepsis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Enterococcal Bacteraemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney Infection			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			

subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 172 (0.00%)	6 / 378 (1.59%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 172 (0.00%)	8 / 378 (2.12%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	2 / 2	
Septic Shock			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Staphylococcal Bacteraemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	2 / 172 (1.16%)	7 / 378 (1.85%)	
occurrences causally related to treatment / all	0 / 2	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Staphylococcal			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Infection			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Abscess			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased Appetite			
subjects affected / exposed	1 / 172 (0.58%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 172 (1.74%)	15 / 378 (3.97%)	
occurrences causally related to treatment / all	0 / 3	12 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to Thrive			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid Overload			

subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid Retention			
subjects affected / exposed	1 / 172 (0.58%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 172 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperlipasaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 172 (0.58%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 172 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dacarbazine	Trabectedin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	166 / 172 (96.51%)	375 / 378 (99.21%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	12 / 172 (6.98%)	186 / 378 (49.21%)	
occurrences (all)	16	529	
Aspartate Aminotransferase Increased			
subjects affected / exposed	10 / 172 (5.81%)	141 / 378 (37.30%)	
occurrences (all)	11	343	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	16 / 172 (9.30%)	87 / 378 (23.02%)	
occurrences (all)	21	194	
Blood Bilirubin Increased			
subjects affected / exposed	5 / 172 (2.91%)	34 / 378 (8.99%)	
occurrences (all)	6	58	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	2 / 172 (1.16%)	54 / 378 (14.29%)	
occurrences (all)	2	134	
Blood Creatinine Increased			
subjects affected / exposed	3 / 172 (1.74%)	47 / 378 (12.43%)	
occurrences (all)	4	103	
Lymphocyte Count Decreased			
subjects affected / exposed	4 / 172 (2.33%)	21 / 378 (5.56%)	
occurrences (all)	5	92	
Neutrophil Count Decreased			
subjects affected / exposed	24 / 172 (13.95%)	93 / 378 (24.60%)	
occurrences (all)	64	306	
Platelet Count Decreased			
subjects affected / exposed	29 / 172 (16.86%)	61 / 378 (16.14%)	
occurrences (all)	117	267	
Weight Decreased			

subjects affected / exposed	5 / 172 (2.91%)	27 / 378 (7.14%)	
occurrences (all)	6	34	
White Blood Cell Count Decreased			
subjects affected / exposed	20 / 172 (11.63%)	96 / 378 (25.40%)	
occurrences (all)	51	371	
Vascular disorders			
Flushing			
subjects affected / exposed	9 / 172 (5.23%)	19 / 378 (5.03%)	
occurrences (all)	10	32	
Hot Flush			
subjects affected / exposed	10 / 172 (5.81%)	13 / 378 (3.44%)	
occurrences (all)	10	18	
Hypertension			
subjects affected / exposed	2 / 172 (1.16%)	22 / 378 (5.82%)	
occurrences (all)	2	61	
Hypotension			
subjects affected / exposed	7 / 172 (4.07%)	19 / 378 (5.03%)	
occurrences (all)	7	23	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 172 (12.21%)	46 / 378 (12.17%)	
occurrences (all)	26	55	
Dysgeusia			
subjects affected / exposed	11 / 172 (6.40%)	34 / 378 (8.99%)	
occurrences (all)	12	38	
Headache			
subjects affected / exposed	33 / 172 (19.19%)	94 / 378 (24.87%)	
occurrences (all)	42	143	
Hypoaesthesia			
subjects affected / exposed	3 / 172 (1.74%)	22 / 378 (5.82%)	
occurrences (all)	4	33	
Paraesthesia			
subjects affected / exposed	9 / 172 (5.23%)	22 / 378 (5.82%)	
occurrences (all)	10	28	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	48 / 172 (27.91%)	149 / 378 (39.42%)	
occurrences (all)	106	416	
Leukopenia			
subjects affected / exposed	11 / 172 (6.40%)	43 / 378 (11.38%)	
occurrences (all)	16	119	
Neutropenia			
subjects affected / exposed	31 / 172 (18.02%)	111 / 378 (29.37%)	
occurrences (all)	65	361	
Thrombocytopenia			
subjects affected / exposed	33 / 172 (19.19%)	70 / 378 (18.52%)	
occurrences (all)	90	311	
General disorders and administration site conditions			
Catheter Site Pain			
subjects affected / exposed	1 / 172 (0.58%)	19 / 378 (5.03%)	
occurrences (all)	1	30	
Chest Pain			
subjects affected / exposed	6 / 172 (3.49%)	19 / 378 (5.03%)	
occurrences (all)	6	25	
Chills			
subjects affected / exposed	11 / 172 (6.40%)	34 / 378 (8.99%)	
occurrences (all)	15	41	
Fatigue			
subjects affected / exposed	90 / 172 (52.33%)	260 / 378 (68.78%)	
occurrences (all)	156	553	
Influenza Like Illness			
subjects affected / exposed	6 / 172 (3.49%)	19 / 378 (5.03%)	
occurrences (all)	6	22	
Oedema Peripheral			
subjects affected / exposed	21 / 172 (12.21%)	107 / 378 (28.31%)	
occurrences (all)	25	143	
Pain			
subjects affected / exposed	9 / 172 (5.23%)	18 / 378 (4.76%)	
occurrences (all)	10	21	
Pyrexia			

subjects affected / exposed	27 / 172 (15.70%)	64 / 378 (16.93%)	
occurrences (all)	35	91	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	16 / 172 (9.30%)	30 / 378 (7.94%)	
occurrences (all)	19	35	
Abdominal Pain			
subjects affected / exposed	29 / 172 (16.86%)	58 / 378 (15.34%)	
occurrences (all)	34	76	
Abdominal Pain Upper			
subjects affected / exposed	8 / 172 (4.65%)	19 / 378 (5.03%)	
occurrences (all)	11	22	
Constipation			
subjects affected / exposed	52 / 172 (30.23%)	140 / 378 (37.04%)	
occurrences (all)	73	199	
Diarrhoea			
subjects affected / exposed	40 / 172 (23.26%)	130 / 378 (34.39%)	
occurrences (all)	50	213	
Dry Mouth			
subjects affected / exposed	13 / 172 (7.56%)	22 / 378 (5.82%)	
occurrences (all)	14	28	
Dyspepsia			
subjects affected / exposed	12 / 172 (6.98%)	30 / 378 (7.94%)	
occurrences (all)	15	31	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	11 / 172 (6.40%)	12 / 378 (3.17%)	
occurrences (all)	11	13	
Nausea			
subjects affected / exposed	85 / 172 (49.42%)	282 / 378 (74.60%)	
occurrences (all)	142	571	
Stomatitis			
subjects affected / exposed	6 / 172 (3.49%)	21 / 378 (5.56%)	
occurrences (all)	6	28	
Vomiting			
subjects affected / exposed	35 / 172 (20.35%)	167 / 378 (44.18%)	
occurrences (all)	48	303	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 172 (20.93%)	85 / 378 (22.49%)	
occurrences (all)	42	104	
Dyspnoea			
subjects affected / exposed	33 / 172 (19.19%)	91 / 378 (24.07%)	
occurrences (all)	42	133	
Dyspnoea Exertional			
subjects affected / exposed	4 / 172 (2.33%)	26 / 378 (6.88%)	
occurrences (all)	5	28	
Nasal Congestion			
subjects affected / exposed	6 / 172 (3.49%)	23 / 378 (6.08%)	
occurrences (all)	9	27	
Oropharyngeal Pain			
subjects affected / exposed	4 / 172 (2.33%)	19 / 378 (5.03%)	
occurrences (all)	4	24	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 172 (5.23%)	13 / 378 (3.44%)	
occurrences (all)	9	14	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	13 / 172 (7.56%)	40 / 378 (10.58%)	
occurrences (all)	16	45	
Depression			
subjects affected / exposed	7 / 172 (4.07%)	30 / 378 (7.94%)	
occurrences (all)	9	31	
Insomnia			
subjects affected / exposed	16 / 172 (9.30%)	55 / 378 (14.55%)	
occurrences (all)	17	75	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 172 (8.72%)	57 / 378 (15.08%)	
occurrences (all)	15	73	
Back Pain			

subjects affected / exposed	28 / 172 (16.28%)	65 / 378 (17.20%)	
occurrences (all)	35	84	
Bone Pain			
subjects affected / exposed	12 / 172 (6.98%)	20 / 378 (5.29%)	
occurrences (all)	12	22	
Muscular Weakness			
subjects affected / exposed	4 / 172 (2.33%)	25 / 378 (6.61%)	
occurrences (all)	5	36	
Musculoskeletal Pain			
subjects affected / exposed	14 / 172 (8.14%)	29 / 378 (7.67%)	
occurrences (all)	14	31	
Myalgia			
subjects affected / exposed	11 / 172 (6.40%)	47 / 378 (12.43%)	
occurrences (all)	13	56	
Pain in Extremity			
subjects affected / exposed	15 / 172 (8.72%)	47 / 378 (12.43%)	
occurrences (all)	21	74	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	10 / 172 (5.81%)	24 / 378 (6.35%)	
occurrences (all)	12	28	
Urinary Tract Infection			
subjects affected / exposed	8 / 172 (4.65%)	29 / 378 (7.67%)	
occurrences (all)	9	34	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	36 / 172 (20.93%)	138 / 378 (36.51%)	
occurrences (all)	43	182	
Dehydration			
subjects affected / exposed	17 / 172 (9.88%)	43 / 378 (11.38%)	
occurrences (all)	17	50	
Hyperglycaemia			
subjects affected / exposed	5 / 172 (2.91%)	30 / 378 (7.94%)	
occurrences (all)	21	75	
Hypoalbuminaemia			

subjects affected / exposed	7 / 172 (4.07%)	32 / 378 (8.47%)	
occurrences (all)	8	70	
Hypocalcaemia			
subjects affected / exposed	3 / 172 (1.74%)	27 / 378 (7.14%)	
occurrences (all)	3	55	
Hypokalaemia			
subjects affected / exposed	22 / 172 (12.79%)	53 / 378 (14.02%)	
occurrences (all)	34	104	
Hyponatraemia			
subjects affected / exposed	7 / 172 (4.07%)	26 / 378 (6.88%)	
occurrences (all)	8	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2010	The amendment includes the inclusion of subjects 15 years of age or older; the prohibition of subject crossover from the dacarbazine group to the trabectedin group; proactive reviews of cases of sepsis; and minor editorial changes and clarifications. No subjects had been enrolled at the time of the first amendment.
24 June 2011	The amendment includes the clarification that assessments for disease status were to be conducted consistently and on schedule; additional dosing instructions for subjects with abnormal liver function tests; treatment windows for the placement of the central venous catheter and dosing; clarification to allow administration of colony stimulating factors (CSFs) during Cycle 1, specification that alkaline phosphatase (ALP) liver fraction or 5’ nucleotidase was to be measured when ALP was more than (>) 2.5 x upper limit of normal (ULN); the option to use echocardiograms if multigated acquisition (MUGA) was not available; and minor editorial changes and clarifications. One subject was enrolled at the time of the second amendment; however, both the first and second amendments were adopted before any study-related procedures had begun.
12 June 2012	The protocol changes in the third amendment included: a change to allow anthracycline and ifosfamide containing regimens or an anthracycline containing regimen and 1 additional cytotoxic chemotherapy (in any order); the provision for de-bulking surgery and the criteria to be met for such surgery; an update to the definition of progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1); an update to the most recent version of the M.D. Anderson Symptom Inventory (MDASI) questionnaire, and minor editorial changes and clarifications. There were 58 subjects enrolled at the time of the third amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No notable study limitations were identified by the Sponsor.

Notes: