Clinical trial results:
A Randomized, Multicenter, Phase III Trial of Trabectedin (Yondelis) versus Doxorubicin-based Chemotherapy as First-Line Therapy in Patients with Translocation-Related Sarcomas (TRS)

Summary

EudraCT number	2008-002326-11
Trial protocol	FR DE ES GB IT
Global end of trial date	20 August 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	ET-C-002-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00796120
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar, S.A.
Sponsor organisation address	Av de los Reyes 1, Poligono Industrial La Mina , Colmenar Viejo, Madrid, Spain, 28770
Public contact	Clinical Development Department of PharmaMar´s Oncology, Business Unit., Pharma Mar, S.A., +34 918466000, clinicaltrials@pharmamar.com
Scientific contact	Clinical Development Department of PharmaMar´s Oncology, Business Unit., Pharma Mar, S.A., +34 918466000, clinicaltrials@pharmamar.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	20 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 August 2014
Global end of trial reached?	Yes
Global end of trial date	20 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of trabectedin compared to standard doxorubicin in participants with advanced translocation-related sarcomas (cancer of connective tissue cells) (TRS).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and was consistent with the Good Clinical Practice (GCP) and applicable regulatory requirements. Safety was evaluated by clinical examination, including vital signs, assessment of Adverse Events (AEs), changes in laboratory parameters (blood counts, clinical chemistry including liver function tests), and other tests that could be necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	121
EEA total number of subjects	68

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)	103
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 121 patients were randomized; out of them, 88 were evaluable for the primary efficacy analysis (51 in Arm A, trabectedin, and 37 in Arm B, DXCT). Efficacy population included all participants randomly assigned to either treatment arm with externally confirmed pathological and molecular diagnosis of translocation-related sarcomas (TRS).

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:

Trabectedin 1.5 milligram per square meter (mg/m^2) given as 24-hour continuous intravenous infusion every 3 weeks until disease progression.

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	YONDELIS
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin 1.5 milligram per square meter (mg/m^2) given as 24-hour continuous intravenous infusion every 3 weeks until disease progression.

Arm title	DXCT

Arm description:

DXCT = Doxorubicin based chemotherapy
Doxorubicin (as a monotherapy) 75 mg per m^2 will be given intravenously every 3 weeks or
Doxorubicin 60 mg per m^2 will be given intravenously every 3 weeks along with ifosfamide 6 to 9 gram (g)/m^2 every 3 weeks until disease progression.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin/Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Doxorubicin (as a monotherapy) 75 or 60 mg per m^2 will be given intravenously every 3 weeks.

Number of subjects in period 1	Trabectedin	DXCT
Started	61	60
Treated	61	57
Completed	0	0
Not completed	61	60
Physician decision	16	17
Consent withdrawn by subject	3	4
death	3	-
Randomized but not treated	-	3
Treatment-related AEs	11	6
Other causes	6	17
Progressive disease	22	13

Baseline characteristics

Reporting groups	
Reporting group title	Trabectedin
Reporting group description:	
Trabectedin 1.5 milligram per square meter (mg/m^2) given as 24-hour continuous intravenous infusion every 3 weeks until disease progression.	
Reporting group title	DXCT
Reporting group description:	
DXCT = Doxorubicin based chemotherapy Doxorubicin (as a monotherapy) 75 mg per m^2 will be given intravenously every 3 weeks or Doxorubicin 60 mg per m^2 will be given intravenously every 3 weeks along with ifosfamide 6 to 9 gram (g)/m^2 every 3 weeks until disease progression.	

Reporting group values	Trabectedin	DXCT	Total
Number of subjects	61	60	121
Age, Customized Units: participants			
>=18 to <=49 years	33	30	63
>=50 to <=65 years	19	21	40
>=65 years	9	9	18
Age continuous Units: years			
median	47	49	
full range (min-max)	19 to 78	19 to 78	-
Gender, Male/Female Units: participants			
Female	25	22	47
Male	36	38	74
Race Units: Subjects			
Caucasian	53	54	107
Black	3	4	7
Asian/oriental	2	0	2
Other	2	2	4
Unk	1	0	1
ECOG PS			
Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	28	29	57
PS 1	32	30	62
PS 2	1	1	2
Tumor diagnosis (investigator)			
A comparison of tumor diagnosis per central pathology review compared to per investigators' classification			
Units: Subjects			
MRCL	28	28	56
Other TRS	33	32	65
Tumor diagnosis (external pathology review)			

A comparison of tumor diagnosis per central pathology review compared to per investigators' classification			
Units: Subjects			
MRCL	23	17	40
Other TRS	28	20	48
Not confirmed	10	23	33
Primary tumor site Units: Subjects			
Lower extremity	39	37	76
Trunk/abdominal wall	2	10	12
Upper extremity	8	1	9
Face and neck	2	1	3
Other	10	11	21
Disease at study entry Units: Subjects			
Locally advanced	18	13	31
Metastatic	43	47	90
Tumor stage at diagnosis Units: Subjects			
Stage I	3	4	7
Stage II	9	10	19
Stage III	13	14	27
Stage IV	21	18	39
Unknown	15	14	29
Signs and symptoms Units: Subjects			
0 signs and symptoms	19	20	39
1 signs and symptoms	12	10	22
2 signs and symptoms	11	9	20
>=3 signs and symptoms	19	21	40
Time from diagnosis to randomization Units: months			
median	10.3	8.2	
full range (min-max)	0.5 to 186.8	0.1 to 309.7	-
Time from unresectable locally advanced disease to randomization Units: months			
median	0.7	0.8	
full range (min-max)	0 to 6.4	0 to 2.3	-
Time from metastatic disease to randomization Units: months			
median	2.2	1.6	
full range (min-max)	0 to 50.7	0.1 to 249.6	-
Time from last progression date before study to randomization Units: months			
median	0.7	0.6	
full range (min-max)	0 to 3.2	0 to 3.1	-
Sites of disease Units: No. of sites			
median	2	2	
full range (min-max)	1 to 8	1 to 5	-

Signs and symptoms			
Units: Number			
median	1	2	
full range (min-max)	0 to 7	0 to 29	-
WBC			
white blood cells			
Units: x10^9/l			
median	6.7	7.2	
full range (min-max)	4 to 17.5	2.8 to 14	-
Hemoglobin			
Units: g/dl			
median	13.7	13.3	
full range (min-max)	9.2 to 17.7	9 to 15.7	-
Hematocrit			
Units: percentage			
median	40.8	39	
full range (min-max)	29.7 to 51	27.5 to 50.3	-
Neutrophils			
Units: x10^9/l			
median	4.2	4.8	
full range (min-max)	2.2 to 13.5	2 to 11.9	-
Lymphocytes			
Units: x10^9/l			
median	1.7	1.7	
full range (min-max)	0.4 to 3	0.3 to 3.9	-
Platelets			
Units: x10^9/l			
median	254	275.5	
full range (min-max)	113 to 597	140 to 836	-
ALT			
Units: ULN			
median	0.5	0.5	
full range (min-max)	0.1 to 2.5	0.2 to 1.7	-
AP			
Units: ULN			
median	0.7	0.7	
full range (min-max)	0.3 to 1.4	0.4 to 1.6	-
AST			
Units: ULN			
median	0.6	0.6	
full range (min-max)	0.2 to 1.5	0.3 to 1.7	-
CPK			
Units: ULN			
median	0.5	0.4	
full range (min-max)	0.1 to 2.3	0.1 to 2	-
Creatinine			
Units: ULN			
median	0.6	0.6	
full range (min-max)	0.3 to 1	0.4 to 1.1	-
Total bilirubin			
Units: ULN			
median	0.4	0.4	

full range (min-max)	0.1 to 1.2	0.2 to 1.3	-
Albumin			
Units: g/dl			
median	4.2	4.2	
full range (min-max)	2.6 to 5	2.5 to 4.8	-
Glucose			
Units: mmol/l			
median	5.5	5.3	
full range (min-max)	3.6 to 17.9	2.4 to 11.9	-

End points

End points reporting groups

Reporting group title	Trabectedin
Reporting group description:	
Trabectedin 1.5 milligram per square meter (mg/m^2) given as 24-hour continuous intravenous infusion every 3 weeks until disease progression.	
Reporting group title	DXCT
Reporting group description:	
DXCT = Doxorubicin based chemotherapy Doxorubicin (as a monotherapy) 75 mg per m^2 will be given intravenously every 3 weeks or Doxorubicin 60 mg per m^2 will be given intravenously every 3 weeks along with ifosfamide 6 to 9 gram (g)/m^2 every 3 weeks until disease progression.	

Primary: Progression - Free Survival (PFS)

End point title	Progression - Free Survival (PFS)
End point description:	
Progression-free survival (PFS) is defined as the time from the date of randomization to the date of documented progressive disease (PD) or death (regardless of the cause of death)	
End point type	Primary
End point timeframe:	
Every 6 weeks from randomization during the first 9 months and thereafter, every 9 weeks	

End point values	Trabectedin	DXCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	37		
Units: months				
median (confidence interval 95%)	19.6 (5.7 to 32.3)	8.3 (7.1 to 25)		

Attachments (see zip file)	Progression-free survival/Kaplan-Meier plot of PFS.bmp

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	Trabectedin v DXCT
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8391 [1]
Method	Log-rank test stratified
Parameter estimate	Hazard ratio (HR)
Point estimate	0.879

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.425
upper limit	1.817

Notes:

[1] - HR: Arm A (trabectedin) compared to Arm B (DXCT). HR and p-value determined by Log-rank test stratified.

Secondary: 6-month Progression - Free Survival

End point title	6-month Progression - Free Survival

End point description:

Percentage of participants survived for 6 months from the start of study treatment without progression of disease. Progression of the disease was associated with increasing symptoms, including pain from new or progressing lesions. Delay in disease progression generally represents a clinical benefit to the participant.

End point type	Secondary

End point timeframe:

6 months

End point values	Trabectedin	DXCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	37		
Units: percentage of participants				
number (confidence interval 95%)	66.7 (50.6 to 82.8)	78.3 (64 to 92.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Objective Response

End point title	Percentage of participants with Objective Response

End point description:

Tumor response was assessed according to RECIST criteria: Partial Response (PR)=at least 30% reduction in the sum of the longest dimensions (LD) of all target lesions in reference to the baseline sum LD, Complete Response (CR) =Disappearance of all non-target lesions. Percentage of participants with objective tumor response was determined by the number of participants with PR or CR divided by the total number of response-evaluable participants.

End point type	Secondary

End point timeframe:

Every 6 weeks during first 9 months of the study and thereafter every 9 weeks

End point values	Trabectedin	DXCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	37		
Units: percentage of participants				
number (confidence interval 95%)	5.9 (1.2 to 16.2)	27 (13.8 to 44.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival defined as time from the date of randomization to the date of death. For participants who were alive at the time of analysis, overall survival was censored at the last contact date. Upper limit of confirdence interval value '99999' signifies that Upper limit of confidence interval was not reached because of high censorship rate that is smaller number of events.

End point type	Secondary

End point timeframe:

Baseline up to End of Study (2008 to 2014)

End point values	Trabectedin	DXCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	37		
Units: months				
median (confidence interval 95%)	46.6 (27.5 to 99999)	33.5 (21.6 to 99999)		

Attachments (see zip file)	Overall survival/Overall survival.bmp

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Trabectedin v DXCT
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4348 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.785

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.427
upper limit	1.441

Notes:

[2] - Arm A (trabectedin) compared to Arm B (DXCT). HR and p-value determined by Cox regression

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time frame for AE	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Trabectedin
Reporting group description:	
Trabectedin 1.5 milligram per square meter (mg/m^2) given as 24-hour continuous intravenous infusion every 3 weeks until disease progression.	
Reporting group title	DXCT
Reporting group description:	
DXCT = Doxorubicin based chemotherapy Doxorubicin (as a monotherapy) 75 mg per m^2 will be given intravenously every 3 weeks or Doxorubicin 60 mg per m^2 will be given intravenously every 3 weeks along with ifosfamide 6 to 9 gram (g)/m^2 every 3 weeks until disease progression.	

Serious adverse events	Trabectedin	DXCT	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 61 (40.98%)	16 / 57 (28.07%)	
number of deaths (all causes)	33	33	
number of deaths resulting from adverse events	4	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 61 (3.28%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	2 / 61 (3.28%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site extravasation			
subjects affected / exposed	3 / 61 (4.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	4 / 61 (6.56%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 61 (1.64%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 61 (1.64%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood CPK increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			

subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dyspraxia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope vasovagal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 61 (3.28%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 61 (1.64%)	7 / 57 (12.28%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 61 (3.28%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 61 (3.28%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 61 (1.64%)	3 / 57 (5.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 61 (3.28%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	4 / 61 (6.56%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	3 / 61 (4.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site infection			

subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal bacteremia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 61 (1.64%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycemia			

subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
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	Trabectedin	DXCT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 61 (100.00%)	57 / 57 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	34 / 61 (55.74%)	32 / 57 (56.14%)	
occurrences (all)	170	107	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	4 / 61 (6.56%)	0 / 57 (0.00%)	
occurrences (all)	16	0	
Hypertension			
subjects affected / exposed	7 / 61 (11.48%)	0 / 57 (0.00%)	
occurrences (all)	23	0	
Hypotension			
subjects affected / exposed	2 / 61 (3.28%)	3 / 57 (5.26%)	
occurrences (all)	2	6	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 61 (4.92%)	3 / 57 (5.26%)	
occurrences (all)	8	3	
Mass			
subjects affected / exposed	11 / 61 (18.03%)	5 / 57 (8.77%)	
occurrences (all)	93	24	
Fatigue			
subjects affected / exposed	45 / 61 (73.77%)	43 / 57 (75.44%)	
occurrences (all)	322	140	
Oedema peripheral			

subjects affected / exposed	18 / 61 (29.51%)	6 / 57 (10.53%)	
occurrences (all)	98	24	
Mucosal inflammation			
subjects affected / exposed	4 / 61 (6.56%)	15 / 57 (26.32%)	
occurrences (all)	6	41	
Pyrexia			
subjects affected / exposed	10 / 61 (16.39%)	11 / 57 (19.30%)	
occurrences (all)	12	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 61 (16.39%)	10 / 57 (17.54%)	
occurrences (all)	31	21	
Dyspnoea			
subjects affected / exposed	12 / 61 (19.67%)	6 / 57 (10.53%)	
occurrences (all)	72	17	
Hiccups			
subjects affected / exposed	0 / 61 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	4	
Pharyngolaryngeal pain			
subjects affected / exposed	5 / 61 (8.20%)	2 / 57 (3.51%)	
occurrences (all)	6	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 61 (9.84%)	4 / 57 (7.02%)	
occurrences (all)	27	11	
Insomnia			
subjects affected / exposed	13 / 61 (21.31%)	6 / 57 (10.53%)	
occurrences (all)	52	9	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 61 (31.15%)	1 / 57 (1.75%)	
occurrences (all)	50	2	
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 61 (14.75%)	0 / 57 (0.00%)	
occurrences (all)	15	0	
Blood alkaline phosphatase increased			

subjects affected / exposed	6 / 61 (9.84%)	0 / 57 (0.00%)	
occurrences (all)	29	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 61 (9.84%)	0 / 57 (0.00%)	
occurrences (all)	36	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 61 (6.56%)	1 / 57 (1.75%)	
occurrences (all)	4	1	
Weight decreased			
subjects affected / exposed	4 / 61 (6.56%)	8 / 57 (14.04%)	
occurrences (all)	19	17	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 61 (4.92%)	4 / 57 (7.02%)	
occurrences (all)	7	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 61 (8.20%)	7 / 57 (12.28%)	
occurrences (all)	9	14	
Headache			
subjects affected / exposed	13 / 61 (21.31%)	14 / 57 (24.56%)	
occurrences (all)	58	30	
Dysgeusia			
subjects affected / exposed	4 / 61 (6.56%)	6 / 57 (10.53%)	
occurrences (all)	21	10	
Neuropathy peripheral			
subjects affected / exposed	4 / 61 (6.56%)	0 / 57 (0.00%)	
occurrences (all)	10	0	
Paraesthesia			
subjects affected / exposed	2 / 61 (3.28%)	3 / 57 (5.26%)	
occurrences (all)	4	5	
Tremor			
subjects affected / exposed	1 / 61 (1.64%)	3 / 57 (5.26%)	
occurrences (all)	1	6	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	29 / 61 (47.54%)	15 / 57 (26.32%)	
occurrences (all)	98	31	
Anaemia			
subjects affected / exposed	11 / 61 (18.03%)	13 / 57 (22.81%)	
occurrences (all)	31	25	
Thrombocytopenia			
subjects affected / exposed	9 / 61 (14.75%)	2 / 57 (3.51%)	
occurrences (all)	29	3	
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 61 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	11	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 61 (6.56%)	2 / 57 (3.51%)	
occurrences (all)	22	5	
Abdominal pain upper			
subjects affected / exposed	8 / 61 (13.11%)	5 / 57 (8.77%)	
occurrences (all)	20	7	
Abdominal pain			
subjects affected / exposed	8 / 61 (13.11%)	7 / 57 (12.28%)	
occurrences (all)	32	11	
Diarrhoea			
subjects affected / exposed	15 / 61 (24.59%)	15 / 57 (26.32%)	
occurrences (all)	26	42	
Constipation			
subjects affected / exposed	27 / 61 (44.26%)	16 / 57 (28.07%)	
occurrences (all)	142	54	
Dry mouth			
subjects affected / exposed	2 / 61 (3.28%)	3 / 57 (5.26%)	
occurrences (all)	10	4	
Dyspepsia			
subjects affected / exposed	8 / 61 (13.11%)	7 / 57 (12.28%)	
occurrences (all)	64	23	
Haemorrhoids			

subjects affected / exposed	1 / 61 (1.64%)	4 / 57 (7.02%)	
occurrences (all)	1	15	
Nausea			
subjects affected / exposed	46 / 61 (75.41%)	39 / 57 (68.42%)	
occurrences (all)	255	146	
Oral pain			
subjects affected / exposed	0 / 61 (0.00%)	10 / 57 (17.54%)	
occurrences (all)	0	16	
Stomatitis			
subjects affected / exposed	1 / 61 (1.64%)	6 / 57 (10.53%)	
occurrences (all)	1	23	
Vomiting			
subjects affected / exposed	29 / 61 (47.54%)	16 / 57 (28.07%)	
occurrences (all)	104	38	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 61 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	5	
Alopecia			
subjects affected / exposed	2 / 61 (3.28%)	25 / 57 (43.86%)	
occurrences (all)	7	129	
Rash			
subjects affected / exposed	4 / 61 (6.56%)	6 / 57 (10.53%)	
occurrences (all)	29	13	
Scar			
subjects affected / exposed	5 / 61 (8.20%)	2 / 57 (3.51%)	
occurrences (all)	24	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 61 (8.20%)	7 / 57 (12.28%)	
occurrences (all)	22	12	
Joint range of motion decreased			
subjects affected / exposed	4 / 61 (6.56%)	1 / 57 (1.75%)	
occurrences (all)	10	6	
Back pain			

subjects affected / exposed	8 / 61 (13.11%)	9 / 57 (15.79%)	
occurrences (all)	30	28	
Muscle spasms			
subjects affected / exposed	2 / 61 (3.28%)	3 / 57 (5.26%)	
occurrences (all)	7	11	
Musculoskeletal pain			
subjects affected / exposed	4 / 61 (6.56%)	1 / 57 (1.75%)	
occurrences (all)	13	4	
Myalgia			
subjects affected / exposed	7 / 61 (11.48%)	2 / 57 (3.51%)	
occurrences (all)	24	4	
Pain in extremity			
subjects affected / exposed	6 / 61 (9.84%)	3 / 57 (5.26%)	
occurrences (all)	28	4	
Infections and infestations			
Catheter related infection			
subjects affected / exposed	4 / 61 (6.56%)	0 / 57 (0.00%)	
occurrences (all)	11	0	
Candidiasis			
subjects affected / exposed	0 / 61 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	5	
Urinary tract infection			
subjects affected / exposed	2 / 61 (3.28%)	3 / 57 (5.26%)	
occurrences (all)	2	5	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	20 / 61 (32.79%)	15 / 57 (26.32%)	
occurrences (all)	60	50	
Dehydration			
subjects affected / exposed	3 / 61 (4.92%)	4 / 57 (7.02%)	
occurrences (all)	3	4	
Hypocalcaemia			
subjects affected / exposed	3 / 61 (4.92%)	4 / 57 (7.02%)	
occurrences (all)	14	6	
Hypokalaemia			

subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 6	4 / 57 (7.02%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2008	This substantial protocol amendment incorporated changes to clarify patient inclusion criteria and to avoid inconsistencies or discrepancies through the document regarding dose adjustment guidance, as follows: 1) potential misinterpretation was avoided by erasing a coma in a sentence describing patient inclusion requirements, and 2) the scheme of ifosfamide consecutive reductions was corrected according to the initial dose range for ifosfamide administration. Additionally, the time of prophylactic dexamethasone before trabectedin administration was adjusted to 30 min, to be in concordance to the Summary of Product Characteristics specifications
30 October 2008	This substantial protocol amendment included changes with respect to: 1) issues affecting the medical management of alveolar rhabdomyosarcoma patients, which led to the exclusion of this subgroup from the study population; 2) a better definition of the study termination (clinical cutoff) period was required; 3) to clarify the reference document for evaluation of AEs in patients under treatment with investigational drugs; 4) to better explain the measures taken for international transfers of personal data, and 5) other changes and additions have been included to disambiguate some unclear statements.
11 March 2009	This substantial protocol amendment included changes with respect to: 1) inclusion criteria: to add progressive disease prior to study entry as well as to allow inclusion of patients with Gilbert's syndrome with total bilirubin > ULN; 2) to modify the frequency of tumor assessments in order to allow close monitoring of disease response to treatment but to decrease the exposure to irradiation of patients; 3) to clarify the times for confirmation of tumor response; 4) some changes in hematology laboratory test schedule in case of neutropenia to make it less restrictive and more practical; 5) to update information on concomitant therapy according to more recent reports of toxicity; 6) to update the study contacts, and 7) minor changes to eliminate grammatical errors and to clarify ambiguous statements in the Time and Events Schedule Table.
29 April 2010	This substantial protocol amendment included changes with respect to: 1) the wording of inclusion criterion No.3 was changed to clarify that recruitment was restricted to only those patients who had any of the tumor subtypes listed in this criterion [in the particular case of endometrial stromal sarcoma, only patients with low grade disease were allowed to enter the study, as translocation t(7;17)(p15;p21) has been found associated with this variant]; 2) a new inclusion criteria (No.5) was added stating that patients had to have measurable disease as defined by RECIST v.1.0; 3) in the case of alveolar soft part sarcoma, due to the absence of available probe to perform FISH, patients with externally confirmed pathological diagnosis of this subtype were also allowed to be included in the efficacy population; 4) some clarifications were added with respect to AEs/SAEs reporting, including guidelines to report laboratory disorders, exclusion of disease progression as an AE, and rewording of sentences about deaths in SAE reporting, and 5) other changes, including update of study contacts, the number of investigational sites, and the planned enrollment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported