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Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas

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Abstract ***Aim:*** This randomised phase III trial evaluated first-line trabectedin versus doxorubicin-based chemotherapy (DXCT) in patients with advanced/metastatic translocation-related sarcomas (TRS).
Methods: Patients were randomly assigned (1:1) to receive trabectedin 1.5 mg/m^2 24-h intravenous (i.v.) infusion every 3 weeks (q3wk) (*Arm A*), or doxorubicin 75 mg/m^2 i.v. q3wk, or doxorubicin 60 mg/m^2 i.v. plus ifosfamide (range, 6–9 g/m^2) i.v. q3wk (*Arm B*). Progression-free survival (PFS) by independent review was the primary efficacy end-point.
Results: One hundred and twenty-one patients were randomised; 88 of them had TRS confirmed by central pathology review (efficacy population). Twenty-nine PFS events were

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assessed by independent review (16 with trabectedin; 13 with DXCT). PFS showed non-significant difference between arms (stratified log rank test, $p = 0.9573$; hazard ratio = 0.86, $p = 0.6992$). At the time of this analysis, 63.9% and 58.3% of patients were alive in trabectedin and DXCT arms, respectively. There was no statistically significant difference in survival curves. Response rate according to Response Evaluation Criteria in Solid Tumours (RECIST) v.1.0 was significantly higher in DXCT arm (27.0% versus 5.9%), but response according to Choi criteria showed fewer differences between treatment arms (45.9% versus 37.3%). Safety profile was as expected for both arms, with higher incidence of severe neutropenia, alopecia and mucositis in the DXCT arm.

Conclusion: Neither trabectedin nor doxorubicin-based chemotherapy showed significant superiority in the first-line treatment of patients with advanced translocation-related sarcoma.

1. Introduction

Trabectedin is a marine-derived antineoplastic agent active against advanced soft tissue sarcoma (STS) [1–4] which has shown relevant antitumor activity in prospective and retrospective series of patients with myxoid/round cell liposarcoma (MRCL) resistant or relapsed to conventional chemotherapy [5–7]. The genetic hallmark of MRCL is translocation t(12:16)(q13;p11) [8], which produces the chimeric fusion protein FUS-CHOP that binds to specific DNA promoters, leading to deregulated expression of downstream proteins which eventually cause neoplastic transformation [9]. *In vitro*, trabectedin interferes with the binding of this fusion protein to DNA promoters [10]. Based on structural and functional similarities of chimeric fusion proteins that generate new transcription factors, it was hypothesised that trabectedin could induce in other translocation-related sarcomas (TRS) effects similar to those described in MRCL. Indeed, trabectedin was efficacious in some patients with prevalent TRS: synovial sarcoma, alveolar soft part sarcoma and endometrial stromal sarcoma [7,11–13].

As preclinical and preliminary clinical data pointed to a potentially increased efficacy of trabectedin in MRCL and other TRS, this randomised trial compared trabectedin with standard first-line treatment (doxorubicin-based chemotherapy, DXCT) in patients with confirmed locally advanced unresectable or metastatic TRS. This is the first randomised trial performed in this subtype of STS.

2. Patients and methods

This study was conducted at 22 investigational sites from United States of America (USA) ($n = 8$), France ($n = 5$), United Kingdom (UK) ($n = 4$), Germany ($n = 2$), Italy ($n = 2$) and Spain ($n = 1$) according to the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations on clinical trials, and was approved by respective independent ethics committees. Signed informed consent was obtained from all patients. An Independent Data Monitoring Committee (IDMC) reviewed the study conduct.

Trial codes were Eudra CT: 2008-002326-11; ClinicalTrials.gov Identifier: NCT00796120.

2.1. Selection of patients

Eligibility criteria included patients $\geqslant 18$ year-olds with initial pathological diagnosis of TRS of following subtypes: alveolar soft part sarcoma, angiomatoid fibrous histiocytoma, clear cell sarcoma, desmoplastic small round cell tumour, low grade endometrial stromal sarcoma, low grade fibromyxoid sarcoma, myxoid chondrosarcoma, MRCL and synovial sarcoma. Ewing's sarcoma and dermatofibrosarcoma protuberans were excluded. Evidence of translocation by fluorescence *in situ* hybridisation was not required for patient enrolment into the trial, but only patients with confirmed translocation were included in the primary study analysis. Patients had to have unresectable locally advanced or metastatic progressive disease; measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST v.1.0); Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score 0–2; adequate cardiac function [left ventricular ejection function (LVEF) within normal limits], and adequate haematological (haemoglobin $\geqslant 9$ g/dl; absolute neutrophil count $\geqslant 1.5 \times 10^9$/l; platelets $\geqslant 100 \times 10^9$/l), renal (serum creatinine $\leqslant 1.5$ mg/dl) and hepatic function [bilirubin $\leqslant$ upper limit of normal (ULN); aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leqslant 2.5 \times$ ULN; alkaline phosphatase (AP)$\leqslant 2.5 \times$ ULN (if total AP $>2.5 \times$ ULN, AP liver fraction and/or gamma glutamyltransferase and/or 5′-nucleotidase had to be $\leqslant$ULN) and albumin >25 g/l].

Patients were excluded if they had received prior chemotherapy; prior lesion irradiation (if administered to a single target lesion); if they had any malignancy within the previous 5 years (except for basal cell carcinoma or treated cervical carcinoma *in situ*), or other relevant clinical conditions (active infection, active viral hepatitis or chronic liver disease, brain and/or leptomeningeal metastasis, congestive heart failure or angina pectoris,

myocardial infarction within the previous year, uncontrolled arterial hypertension, arrhythmias or abnormal LVEF). Pregnant or breast-feeding women or patients not using appropriate contraceptive measures were excluded.

2.2. Randomisation and treatments

Eligible patients were randomly assigned on a 1:1 basis to receive trabectedin or DXCT. Since single-agent doxorubicin is the standard treatment for advanced STS, but some oncologists prefer combination treatment with ifosfamide, especially for certain tumour types, the choice of doxorubicin single agent or in combination was left to the investigators.

Trabectedin was administered at a dose of 1.5 mg/m^2 24-h intravenous (i.v.) infusion every 3 weeks (q3wk), with antiemetic and liver-protecting prophylaxis (dexamethasone 20 mg i.v.) 30 min before (*Arm A*), Doxorubicin was administered at 75 mg/m^2 i.v. q3wk, single agent, or at 60 mg/m^2 i.v. plus ifosfamide (range, 6–9 g/m^2) i.v. q3wk, with proper hydration and mesna administration (*Arm B*). Permuted-block randomisation method was used, with stratification by baseline ECOG PS score (0 versus 1–2) and pathological subtype (MRCL versus other TRS). In Arm A, treatment could continue until disease progression or discontinuation for other reasons (e.g. unacceptable toxicity or consent withdrawal). In Arm B, treatment was stopped if maximum doxorubicin cumulative dose was reached or if LVEF was abnormally reduced. In both treatment arms, a maximum of two dose reductions were allowed in the event of febrile neutropenia; grade 4 neutropenia >5 days; grade 4 thrombocytopenia; 3-week delay for recovery from grade 3/4 ALT or AST; AP or bilirubin increases of any grade; grade 3/4 nausea/vomiting (except if reversible with adequate supportive/symptomatic therapy), or any other grade 3/4 toxicity.

2.3. Efficacy end-points and tumour assessment

Primary efficacy end-point was progression-free survival (PFS) evaluated in the efficacy population (i.e. patients randomised with confirmed pathological diagnosis of TRS and evidence of translocation by fluorescence *in situ* hybridisation). PFS and objective tumour response were assessed by an Independent External Review Committee (IERC) according to RECIST v.1.0 [14]. Disease assessments were done symmetrically across treatment arms; within 4 weeks before randomisation, every 6 weeks during the first 9 months and every 9 weeks thereafter. Exploratory evaluations according to Choi criteria [15] were predefined per protocol and they were also performed by the IERC. Secondary analysis of efficacy was based on the population of all randomised patients according to the investigators' assessment, as an intent-to-treat evaluation.

2.4. Safety assessment

Safety was evaluated in all patients receiving at least one dose of study drug, by assessment of adverse events (AEs), laboratory test results, physical examinations and vital signs. AEs and laboratory values were graded according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events, v.3.0.

2.5. Statistical methods

A flexible adaptive design with sample size reassessment, if necessary, was used. *A priori* assumptions were a two-sided 5% significance level with 80% power, expected median PFS with DXCT = 11 months and 55% reduction in relative risk of progression or death [hazard ratio (HR) = 0.45].

At first stage, a minimum of 80 evaluable patients was required [at least 50% (i.e. 40 patients) with MRCL]. An interim analysis of primary end-point (PFS) to reject H0 (HR = 1) was planned in the first stage of the trial, with approximately 45 PFS events assessed by independent review; the adjusted Pocock boundary *p*-value to reject H0 with 45 events should be <0.0432. Comparison between treatment arms was done by a stratified log-rank test and significance level determined by actual observed number of events. After interim analysis, sample size could be increased if the desired power was not achieved with the observed HR but was still clinically meaningful.

Response rates were compared by Fisher's exact test. Unstratified log rank test and Cox regression were also used to evaluate secondary time-to-event end-points, such as overall survival (OS).

EAST v.4 and SAS v.9.2 were used to calculate sample size and for all statistical analysis outputs, respectively.

Patients will be followed for overall survival until August 2014.

3. Results

3.1. Patient disposition

The first patient was enrolled on 18th November 2008. As of 20th February 2012, a total of 121 patients had been randomised (trabectedin, $n = 61$; DXCT $n = 60$) (Fig. 1); 88 patients were evaluable for the primary efficacy end-point (trabectedin, $n = 51$; DXCT, $n = 37$) and 40 of them had MCRL. Therefore, accrual was put on hold. At the time of interim analysis (August 2012), 26 PFS events assessed by independent review were reached (trabectedin, $n = 16$; DXCT, $n = 10$). Because

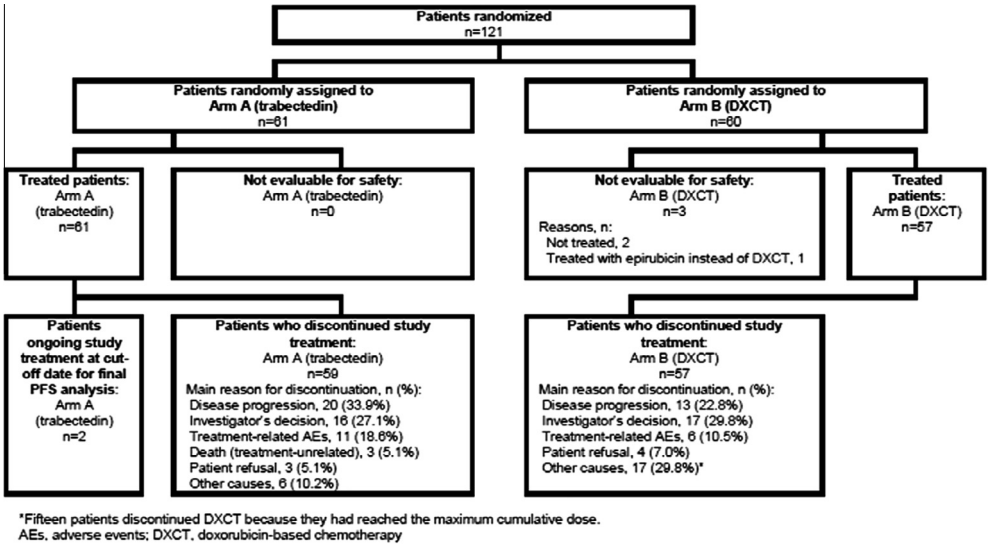

Fig. 1. Disposition of patients (study flow chart, CONSORT diagram).

recalculation of the patient population needed to achieve a significant difference in PFS of either treatment arm yielded a too large sample size to be practical (>500 patients), the IDMC advised to end the study in its first stage. Figures shown here (29 PFS events assessed by independent review: trabectedin, $n = 16$; DXCT, $n = 13$) correspond to last data available in May 2013.

3.2. Patient characteristics

External pathological review did not confirm TRS diagnosis and/or translocation in 33 of 121 randomised patients (Table 1). Therefore, primary efficacy population consisted of 88 patients: 40 (33.1%) with MRCL and 48 (39.7%) with other TRS. Patients and disease characteristics were well balanced between treatment arms.

3.3. Treatment and dosing

Of 121 randomised patients, 61 were treated with trabectedin, 57 with DXCT (36 with doxorubicin as single-agent, and 21 with doxorubicin and ifosfamide in combination), one patient received epirubicin instead of DXCT and two were not treated (Fig. 1). At cut-off date, two patients in the trabectedin arm (3.3%) continued therapy. A total of 454 cycles of trabectedin (median = 5 cycles per patient; range, 1–31) and 264 cycles of DXCT (median = 6 cycles per patient; range, 1–8) were administered.

3.4. Progression-free survival

Primary end-point, PFS in efficacy population ($n = 88$), was non-statistically different between treatment arms (stratified log rank test $p = 0.9573$) (Fig. 2a). Hazard ratio was HR = 0.86 (95% confidence interval (CI), 0.4–1.8) ($p = 0.6992$) (Table 2). Secondary efficacy analysis ($n = 121$) was also non-statistically significant: unstratified log rank test $p = 0.5533$ (Fig. 2b) and HR = 0.85 (95% CI, 0.5–1.5) ($p = 0.5551$) (Table 2). Multivariate stepwise Cox regression showed MRCL subtype as the most favourable prognostic factor, along with a low number of sites involved and no prior surgery, for patients treated with both trabectedin and DXCT. Importantly, a high percentage of patients were censored in both treatment arms rendering the analyses underpowered (Table 3). Main censoring reason in primary efficacy population ($n = 88$) was surgical lesion removal (curative or palliative) before disease progression: 23.5% (trabectedin arm) and 16.2% (DXCT arm). Other frequent censoring reason was the administration of new anticancer therapy before disease progression: 17.6% (trabectedin arm: chemotherapy in 11.8% and radiotherapy in 5.9%) and 24.3% (DXCT arm: chemotherapy in 18.9% and radiotherapy in 5.4%). Administration of other therapies without disease progression was not addressed in the protocol, but it was assumed that treating Investigators would manage the patients in their best benefit.

3.5. Response rate

In efficacy population, RECIST v.1.0 response rate was significantly higher in DXCT arm (Table 4); disease control rate was similar: 82.4% (trabectedin arm) versus 86.5% (DXCT arm). Choi response criteria showed no significant difference between treatment arms: 37.3% (trabectedin arm) versus 45.9% (DXCT arm).

3.6. Overall survival

Median follow-up for survival was 17.6 months. Of 121 randomised patients, 39 (63.9%, trabectedin) and

Table 1
Demographic and baseline characteristics (all randomised patients).

Characteristic	Arm A (trabectedin) ($n = 61$)		Arm B (DXCT) ($n = 60$)	
	n	%	*n*	%
Race				
Caucasian	53	86.9	54	90.0
Black	3	4.9	4	6.7
Asian/Oriental	2	3.3		
Other[a]	3	4.9	2	3.3
Gender				
Male	36	59.0	38	63.3
Female	25	41.0	22	36.7
Age (years)				
Median (range)	47 (19–78)		49 (19–78)	
ECOG PS				
0	28	45.9	29	48.3
1	32	52.5	30	50.0
2	1	1.6	1	1.7
Tumour diagnosis (external pathology review)				
MRCL	23	37.7	17	28.3
Other TRS[b]	28	45.9	20	33.3
Not confirmed[c]	10	16.4	23	38.3
Primary tumour site				
Lower extremity	39	63.9	37	61.7
Trunk/abdominal wall	2	3.3	10	16.7
Upper extremity	8	13.1	1	1.7
Face and neck	2	3.3	1	1.7
Other	10	16.4	11	18.3
Extent of disease				
Metastatic	43	70.5	47	78.3
Locally advanced	18	29.5	13	21.7
No. of sites				
Median (range)	2 (1–8)		2 (1–5)	
Most common sites of disease				
Soft tissue	33	54.1	33	55.0
Lung	29	47.5	29	48.3
Lymph node	17	27.9	11	18.3
Previous therapy				
Radiotherapy	24	39.3	21	35.0
Surgery				
Radical	32	52.5	36	60.0
Palliative	5	8.2	12	20.0
Anticancer therapy	1[d]	1.6	5[e]	8.3

Data shown are n of patients (%) except for median and range.
ECOG PS, Eastern Cooperative Oncology Group performance status; DXCT, doxorubicin-based chemotherapy; MRCL, myxoid/round cell liposarcoma; TRS, translocation-related sarcomas.
[a] Hispanic ($n = 3$), North African and unknown.
[b] Synovial sarcoma ($n = 24$), extraskeletal myxoid chondrosarcoma ($n = 7$), clear cell sarcoma ($n = 7$), alveolar soft part sarcoma ($n = 4$), low grade endometrial stromal sarcoma ($n = 4$) and desmoplastic small round cell tumour ($n = 2$).
[c] No confirmation of diagnosis by the central laboratory was due to wrong diagnosis in 4 (7%) and 9 patients (15%) in trabectedin and DXCT arms; no evidence of translocation in 3 (5%) and 2 patients (3%) and lack of available material for central review in 3 (5%) and 12 patients (20%), respectively.
[d] Patients with endometrial stromal sarcoma who had previously received hormonal therapy.
[e] Three patients were previously treated with chemotherapy; these three cases were considered protocol deviations. The other two cases consisted of one patient with endometrial stromal sarcoma who had previously received hormonal therapy, and one patient with clear cell sarcoma who had previously received melphalan as locoregional therapy.

35 (58.3%, DXCT) were alive at cut-off date. Although these preliminary survival data did not show significant differences between therapies: HR = 0.77 (95% CI, 0.4–1.4) ($p = 0.3672$), survival curves separated in favour of trabectedin after month 20 (Fig. 3).

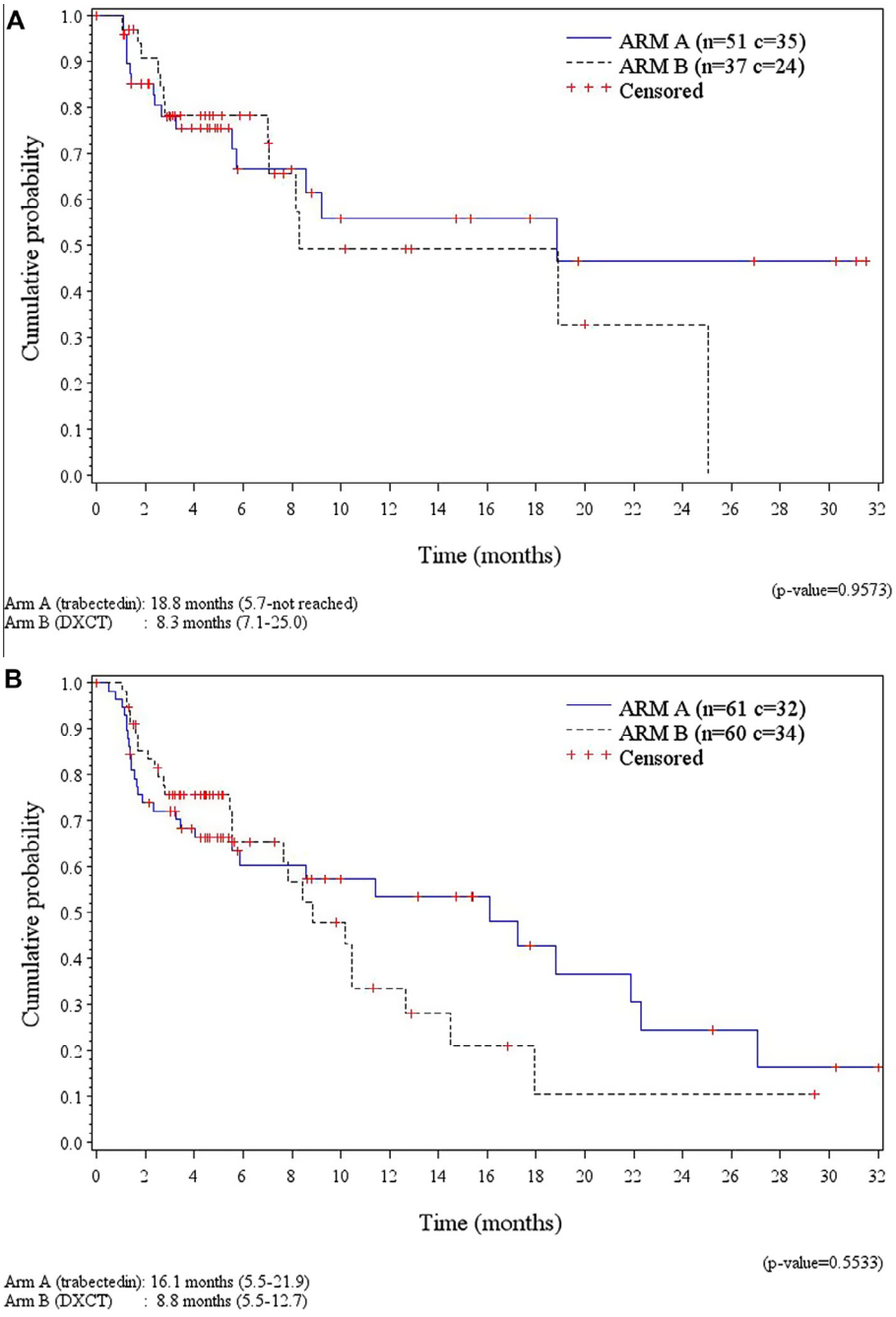

Fig. 2. Kaplan–Meier plot of progression-free survival (PFS). N, number of patients; C, censored patients. Arm A (trabectedin); Arm B (doxorubicin-based chemotherapy (DXCT)). (a) Efficacy population, independent review. (b) All randomised patients, investigators' assessment. Data shown in the bottom of each figure are medians (95% confidence interval (CI)).

3.7. Safety

Most frequent grade $\geqslant 3$ treatment-related AEs were fatigue ($n = 4$; 6.6%) in trabectedin arm, and febrile neutropenia ($n = 7$; 12.3%) and mucositis ($n = 5$; 8.8%) in DXCT arm (Table 5). One death occurred in each arm as outcome of a treatment-related event: rhabdomyolysis (trabectedin) and pneumonia (DXCT).

Neutropenia was a common laboratory abnormality in both treatment arms, and the main reason for administration delays. Incidence of grade 3/4 neutropenia was higher in DXCT arm (75.0% versus 55.0% in trabectedin arm) (Table 5), but was generally well controlled with growth factors (G-CSF), administered to 61.4% of patients, while in the trabectedin arm it was more frequently managed with drug administration delay until neutrophil count recovery (49.2% of patients received G-CSF). Neutropenia associated with trabectedin followed a predictable reversible pattern, and was uncomplicated (rarely associated with fever or

Table 2
Progression-free survival in the efficacy population (independent review) and in all randomised patients (investigators' assessment).

	Arm A (trabectedin)	Arm B (DXCT)	LR (*p*-value) HR (95% CI) (*p*-value)
PFS, months (efficacy population, independent review)			
n of patients	51	37	
Number of events, *n* (%)	16 (31.4%)	13 (35.1%)	
Censored	35 (68.6%)	24 (64.9%)	
Median (95% CI)	18.8 (5.7-nr)	8.3 (7.1–25.0)	$p = 0.9573$ [a]HR [b]: 0.86 95% CI (0.4–1.8) ($p = 0.6992$)
PFS, months (all randomised patients, investigators' assessment)			
n of patients	61	60	
Number of events, *n* (%)	29 (47.5%)	26 (43.3%)	
Censored	32 (52.5%)	34 (56.7%)	
Median (95% CI)	16.1 (5.5–21.9)	8.8 (5.5–12.7)	$p = 0.5533$ [c]HR [b]: 0.85 95% CI (0. 5–1.5) ($p = 0.5551$)

CI, confidence interval; DXCT, doxorubicin-based chemotherapy; HR, hazard ratio; LR, log rank; nr, not reached; PFS, progression-free survival.
[a] Stratified log rank test.
[b] HR: Arm A (trabectedin) compared to Arm B (DXCT). HR and *p*-value determined by Cox regression.
[c] Unstratified log rank test.

Table 3
Censoring reasons.

	Arm A (trabectedin) ($n = 51$)		Arm B (DXCT) ($n = 37$)	
	n	%	*n*	%
Efficacy population, independent review				
Surgery	12	23.5	6	16.2
Chemotherapy	6	11.8	7	18.9
Radiotherapy	3	5.9	2	5.4
Last tumour assessment[a]	12	23.5	5	13.5
Other[b]	2	3.9	4	10.8
Total	35	68.6	24	64.9
	Arm A (trabectedin) ($n = 61$)		Arm B (DXCT) ($n = 60$)	
	n	%	*n*	%
All randomised patients, investigators' assessment				
Surgery	11	18.0	12	20.0
Chemotherapy	5	8.2	4	6.7
Radiotherapy	3	4.9	6	10.0
Last tumour assessment[a]	9	14.8	6	10.0
Other[b]	4	6.6	6	10.0
Total	32	52.5	34	56.7

DXCT, doxorubicin-based chemotherapy.
[a] Patients still on treatment or in follow-up for disease assessments or with event out of study window.
[b] Censored at randomisation (e.g. untreated) or withdrawn due to related/unrelated adverse event or refusal before treatment onset/disease progression or new treatment out of study window.

infection): one patient had febrile neutropenia with trabectedin (1.6%) versus seven patients (12.3%) with DXCT (Table 5). Incidence or severity of neutropenia did not worsen in patients with most prolonged trabectedin treatment.

As expected, most common severe non-haematological laboratory abnormality associated with trabectedin was transaminases elevation, which occurred infrequently with DXCT (53.3% for ALT and 33.3% for AST with trabectedin versus 1.9% for both ALT and AST with DXCT). In agreement with previous trials, severe transaminase increases had a transient pattern, with a peak elevation on Day 8 and return to grade <1 before Day 22 of each cycle, and showed a clear trend to reduction in subsequent cycles of treatment.

4. Discussion

Advanced STS are a heterogeneous group of tumours that require medical treatment tailored according to histological and molecular subtypes. Until now, no clinical trials have investigated a novel treatment option in STS with translocations that produce new or deregulated transcription factors. This clinical trial was designed to evaluate trabectedin versus DXCT as first-line therapy in unresectable locally advanced or metastatic, pathologically confirmed TRS by means of externally assessed PFS. To date, no other phase III randomised trials have been conducted comparing first-line standard doxorubicin or doxorubicin plus ifosfamide versus other therapies in adult STS; only one phase II randomised

Table 4
Response rate in the efficacy population (independent review).

	Arm A (trabectedin) ($n = 51$)		Arm B (DXCT) ($n = 37$)		p-Value [a]
	n	%	n	%	
Best objective response (RECIST)					
PR	3[b]	5.9	10[c]	27.0	
SD	39	76.5	22	59.5	
PD	6	11.8	1	2.7	
NE	3	5.9	4	10.8	
Objective response rate (95% CI)	5.9% (1.2–16.2%)		27.0% (13.8–44.1%)		0.0123
Best response (Choi criteria)					
PR	19	37.3	17	45.9	
SD	5	9.8	2	5.4	
PD	5	9.8	1	2.7	
NE	22	43.1	17	45.9	
Choi response rate (95% CI)	37.3% (24.1–51.9%)		45.9% (29.5–63.1%)		0.5109

CI, confidence interval; DXCT, doxorubicin-based chemotherapy; MRCL, myxoid/round cell liposarcoma; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Fisher's exact test.

[b] PRs were observed in two patients with MRCL and in one patient with synovial sarcoma.

[c] PRs were observed in five patients with MRCL, four patients with synovial sarcoma and one patient with desmoplastic small round cell tumour.

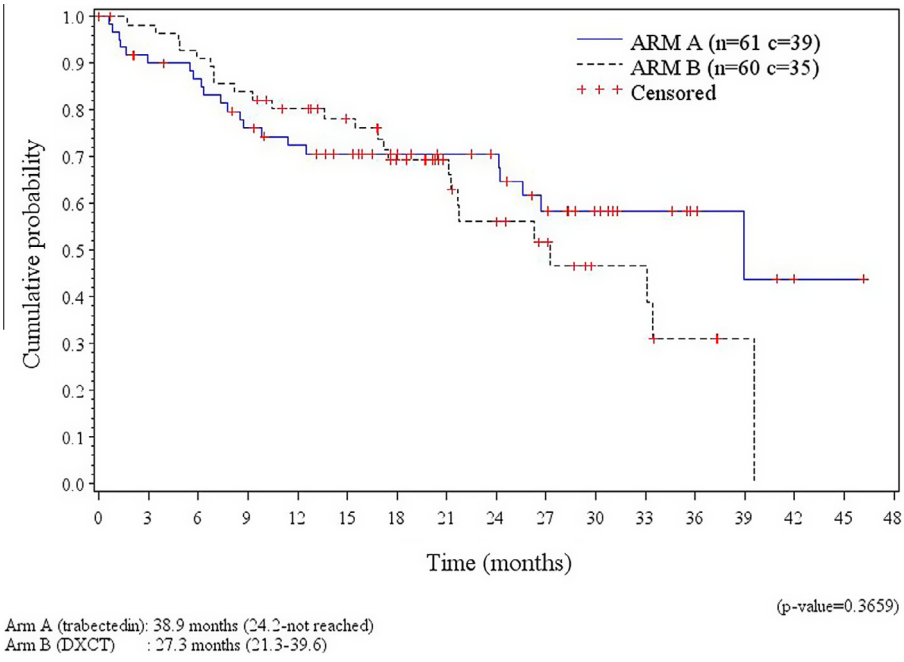

Fig. 3. Kaplan–Meier plot of overall survival (OS) in all randomised patients. N, number of patients; C, censored patients. Arm A (trabectedin); Arm B (doxorubicin-based chemotherapy (DXCT)). Data shown in the bottom of figure are medians (95% confidence interval (CI)).

trial has been previously published [16]. This trial started with the first stage, to be expanded in the second stage, depending on results of interim analysis. For this interim evaluation, target population was 80 evaluable patients, and 45 PFS events were expected. The analysis had to be conducted before reaching this event rate. Finally, 29 independently assessed PFS events were reached from 88 evaluable patients in May 2013 (55 PFS events in all randomised patients). High attrition rate of evaluable patients from all randomised populations (27.3%) due to inaccurate diagnosis and/or lack of specific translocation, together with high censoring rate (67.0% in efficacy population) resulted in fewer PFS events than expected and, therefore, the analysis was underpowered for statistical comparisons. First-line setting largely contributed to high censoring. Patients suitable for surgery after several treatment cycles underwent tumour removal in both arms and, in Arm B, many patients who completed 6–8 DXCT cycles per protocol received a new anticancer therapy. As a consequence, results of this trial do not allow confirming superiority of either treatment arm as first-line chemotherapy in this sarcoma

Table 5
Treatment-related adverse events occurring in ⩾10% of patients in any of treatment arms.

	Arm A (trabectedin) ($n = 61$) NCI-CTCAE grade[a]				Arm B (DXCT) ($n = 57$) NCI-CTCAE grade[a]			
	1/2		3/4		1/2		3/4	
	n	%	n	%	n	%	n	%
Abdominal pain	6	9.8	1	1.6	2	3.5	1	1.8
Alopecia	1	1.6	–	–	25	43.9	–	–
ALT increased	24	40.0	32	53.3	20	37.0	1	1.9
AP increased	34	56.7	3	5.0	21	38.9	–	–
Anaemia	46	75.4	10	16.4	42	75.0	9	16.1
Anorexia	14	23.0	1	1.6	12	21.1	–	–
AST increased	31	51.7	20	33.3	20	37.0	1	1.9
Constipation	12	19.7	–	–	8	14.0	–	–
CPK increased	20	34.5	5	8.6	4	8.2	2	4.1
Creatinine increased	12	19.7	3	4.9	4	7.4	1	1.9
Diarrhoea	10	16.4	–	–	10	17.5	1	1.8
Dysgeusia	4	6.6	–	–	6	10.5	–	–
Fatigue	36	59.0	4	6.6	35	61.4	1	1.8
Febrile neutropenia	–	–	1	1.6	–	–	7	12.3
Headache	8	13.1	–	–	8	14.0	–	–
Leukopaenia	30	49.2	18	29.5	17	30.4	33	58.9
Mucositis	3	4.9	1	1.6	15	26.3	5	8.8
Nausea	42	68.9	1	1.6	37	64.9	–	–
Neutropenia	15	25.0	33	55.0	6	10.7	42	75.0
Oral pain	–	–	–	–	8	14.0	–	–
Pyrexia	4	6.6	–	–	7	12.3	–	–
Thrombocytopenia	16	26.2	10	16.4	21	37.5	8	14.3
Total bilirubin increased	12	20.0	1	1.7	7	13.0	–	–
Vomiting	26	42.6	1	1.6	15	26.3	–	–
Weight decreased	3	4.9	1	1.6	6	10.5	–	–

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; DXCT, doxorubicin-based chemotherapy; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Toxicity Criteria for Adverse Events.

[a] Haematological and biochemical laboratory abnormalities are shown regardless of their relationship to treatment. Denominators in some of these abnormalities could vary because of missing data.

subset. There was no statistically significant difference in PFS between trabectedin and DXCT arms in both primary and secondary efficacy analyses. Current results indicate that design of a trial in this patient population and setting would require a much larger sample size (>500 patients). Recruitment of this population was not feasible in a realistic timeframe and IDMC recommended ending the study in the first stage.

Curative or palliative removal of tumour lesions, which was the most common censoring reason, was performed in a similar proportion of patients from both arms in efficacy population (23.5% in trabectedin arm; 16.2% in DXCT arm) but specially in all randomised population (18.0% in trabectedin arm; 20.0% in DXCT arm) may imply a similar clinical benefit for both treatments. Response rate was significantly higher in the DXCT arm, but did not appear to translate into a long-term clinical benefit. Indeed, 5 of 13 patients who achieved a partial response in DXCT arm (all randomised analysis) relapsed when left untreated. In addition, disease control rate was similar with both therapies: 82.4% (trabectedin) versus 86.5% (DXCT) and Choi response assessment showed no significant differences between treatment arms. In this regard, the method described by Choi has been previously suggested to be more accurate than RECIST to predict outcome in sarcomas [17,18]. Furthermore, preliminary survival curves were overlapping and showed a trend of better outcome for trabectedin after a certain time point (month ⩾20), thus supporting the advantage of prolonged treatment in some TRS.

Safety profile observed in this clinical trial was that expected for both trabectedin and DXCT. Most common side-effects related to trabectedin were gastrointestinal and general disorders (nausea, fatigue, vomiting and anorexia); these findings agree with previous phase II analyses [19]. Most common side-effects related to DXCT were gastrointestinal, general disorders and skin and mucous membranes disorders (nausea, fatigue, alopecia, mucositis, vomiting and anorexia), which was also in line with the well-known safety profile of anthracyclines [20–22]. The number of patients who discontinued therapy because of treatment-related events was slightly higher in the trabectedin arm: 18.6% versus 10.5% in DXCT arm. Nevertheless, a considerable number of patients

receiving trabectedin were treated for prolonged periods of time due to lack of cumulative toxicities: ⩾25% received ⩾ 10 cycles, for a maximum of 31 cycles (maximum of eight cycles with DXCT). This prolonged exposure compares favourably with standard treatments in STS, as administration of anthracyclines and ifosfamide is limited by cumulative cardiac toxicity, and cumulative haematological and renal toxicity [23]. Similar to previous randomised clinical trials [16,24,25], first-line doxorubicin was limited per protocol to 6–8 cycles of therapy. Thus, 26 of 57 patients treated with DXCT (45.6%) stopped therapy due to treatment completion (i.e. maximal cumulative dose reached); and two additional patients stopped treatment before completion because of decreased LVEF. In addition, anthracyclines cannot be administered in subsequent lines once the established threshold of cumulative dose has been reached. Conversely, absence of cardiac toxicity [26] or other cumulative toxicities of trabectedin makes this agent suitable for the maintenance of treatment while patients are obtaining clinical benefit. In this study, 20 of 33 DXCT patients who received post-study chemotherapy were treated with trabectedin.

Grade 3/4 neutropenia was more common in DXCT arm (75.0% versus 55.0% in trabectedin arm). A pooled analysis from trabectedin phase II trials [19] showed a similar rate of severe neutropenia (50.5%), while standard first-line agents in STS, doxorubicin and ifosfamide, induce substantially more severe haematological toxicities. Randomised studies with doxorubicin showed grade 3/4 neutropenia in 77% of patients, with 16–19% febrile neutropenia, and high-dose ifosfamide caused neutropenia and infection in 20% and 4% of patients, respectively [27,28]. Combination regimens cause more severe haematological toxicity despite routine G-CSF support [28,29]. In spite of this, more patients in the trabectedin arm had drug dose adjustments, with a median relative dose intensity of 87.9% versus 100% in DXCT arm, because neutropenia was more frequently controlled with G-CSF in DXCT arm, while it was managed with administration delay in patients receiving trabectedin.

Most common laboratory disorder associated with trabectedin was elevated transaminases, which is uncommon in patients treated with DXCT. Incidence of trabectedin associated grade 3/4 increase (53.3% and 33.3% for ALT and AST, respectively) in this trial was similar to those previously reported (51.2% for ALT and 40.7% for AST) [19]. Transaminase increase was the most frequent reason for dose reductions. However, the occurrence of hepatobiliary adverse events was low, further supporting the observation that the liver dysfunction induced by trabectedin is mostly transient, non-cumulative and mostly without clinical consequences.

In conclusion, this phase III randomised trial performed in a selected subset of TRS showed no significant differences in PFS between the two arms, but was underpowered due to the high rate of censoring. Incidence and type of censure were well balanced between treatment arms, with surgery before disease progression as the most frequent reason. No statistically significant difference was observed in OS. Safety was the expected for trabectedin and DXCT; no new safety signals were reported. Considering the limitations of the current study, trabectedin showed efficacy and a manageable safety profile in this patient population and setting.

Conflict of interest statement

Jean-Yves Blay had a consultant/advisory role with PharmaMar, GSK and Novartis, and received research funding from PharmaMar, Roche and GSK. Michael G. Leahy received honoraria from PharmaMar for attending a conference as well as research funding. Shreyaskumar R. Patel had a consultant/advisory role and received research funding from Johnson and Johnson. Peter Hohenberger and Nicolas Penel had a consultant/advisory role and received honoraria and research funding from PharmaMar. Pilar Lardelli, Vicente Alfaro and Antonio Nieto are employees of PharmaMar. Pilar Lardelli and Antonio Nieto own stock of PharmaMar. Sant P. Chawla had a consultant/advisory role and received research funding from PharmaMar.

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The design of this study was presented at the American Society of Clinical Oncology (ASCO) 2012 Meeting. 'Blay JY, Leahy MG, Nguyen BB, Patel S, Santoro A, Hohenberger P, Demetri GD, Lardelli P, Pérez I, Chawla SP. Randomised multicenter phase III trial of trabectedin (T) versus doxorubicin-based chemotherapy as first-line therapy in patients with translocation-related sarcoma (TRS). J Clin Oncol 30, 2012 (suppl.; abstr. TPS10101).' Preliminary results of this study were presented at the American Society of Clinical Oncology (ASCO) 2013 Meeting. 'Hendifar AE, Chawla SP, Leahy MG, Italiano A, Patel S, Santoro A, Staddon AP, Penel N, Piperno-Neumann S, Demetri GD, Hayward L, White J, Gouw LG, De Miguel B, Lardelli P, Soto A, Nieto A, Blay JY. Results of the randomised phase III trial of trabectedin (T) versus doxorubicin-based chemotherapy (DXCT) as first-line therapy in patients (pts) with translocation-related sarcoma (TRS). J Clin Oncol 31, 2013 (suppl.; abstr. 10517)'.

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