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ORIGINAL ARTICLE

A randomized phase III trial comparing trabectedin to best supportive care in patients with pre-treated soft tissue sarcoma: T-SAR, a French Sarcoma Group trial

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Background: The French Sarcoma Group assessed the efficacy, safety, and quality of life (QoL) of trabectedin versus best supportive care (BSC) in patients with advanced soft tissue sarcoma (STS).

Patients and methods: This randomized, multicenter, open-label, phase III study included adults with STS who progressed after 1-3 prior treatment lines. Patients were randomized (1 : 1) to receive trabectedin 1.5 mg/m^2 every 3 weeks or BSC, stratified into L-STS (liposarcoma/leiomyosarcoma) and non-L-STS groups (other histotypes). Patients from the BSC arm were allowed to cross over to trabectedin at progression. The primary efficacy endpoint was progression-free survival (PFS) confirmed by blinded central review and analyzed in the intention-to-treat population.

Results: Between 26 January 2015 and 5 November 2015, 103 heavily pre-treated patients (60.2% with L-STS) from 16 French centers were allocated to receive trabectedin ($n = 52$) or BSC ($n = 51$). Median PFS was 3.1 months [95% confidence interval (CI) 1.8-5.9 months] in the trabectedin arm versus 1.5 months (0.9-2.6 months) in the BSC arm (hazard ratio = 0.39, 95% CI 0.24-0.64, $P < 0.001$) with benefits observed across almost all analyzed subgroups, but particularly in patients with L-STS (5.1 versus 1.4 months, $P = 0.0001$). Seven patients (13.7%) in the trabectedin arm (all with L-STS) achieved a partial response, while no objective responses were observed in the BSC arm ($P = 0.004$). The most common grade 3/4 adverse events were neutropenia (44.2% of patients), leukopenia (34.6%), and transaminase increase (32.7%). Health-related 30-item core European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire evidenced no statistical differences between the arms for any domain and at any time point. After progression, 91.8% of patients crossed over from BSC to trabectedin.

Conclusion: Trabectedin demonstrates superior disease control to BSC without impairing QoL in patients with recurrent STS of multiple histologies, with greater impact in patients with L-STS.

Key words: soft tissue sarcoma, randomized trial, trabectedin

INTRODUCTION

Trabectedin (Yondelis®; PharmaMar, S.A., Madrid, Spain) is the first anticancer marine-derived drug, approved in the European Union in 2007 and currently in use in nearly 80 countries around the globe for the treatment of adults with advanced soft tissue sarcoma (ASTS) after failure of anthracycline and ifosfamide, or for those patients who are

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unsuited to receive these agents.[1] Since 2015, following the analysis of a pivotal, randomized phase III trial in patients with advanced liposarcoma or leiomyosarcoma after failure of prior anthracycline-containing chemotherapy, trabectedin was also approved by the United States Food and Drug Administration.[2] Trabectedin has a pleiotropic mechanism of action that, in addition to inducing direct growth inhibition and death of malignant cells, also has selective anti-inflammatory, immunomodulatory, and anti-angiogenic properties.[3-5] Trabectedin has an acceptable and manageable safety profile with no evidence of cumulative toxicity or end-organ dysfunction, including those patients who remain on therapy for prolonged periods of time.[6-8]

With the exception of a study in Japanese patients with translocation-related sarcomas,[9] trabectedin has never been compared to best supportive care (BSC) in a clinical trial setting for the treatment of patients with a variety of histologically different sarcoma subtypes. This observation provided the rationale for the French Sarcoma Group (FSG) to perform the randomized phase III T-SAR study, which was also expected by the French health authorities for the reimbursement of this drug by the health system.

PATIENTS AND METHODS

Trial design and study oversight

The T-SAR trial was an open-label, prospective, multicenter, randomized phase III trial carried out at 16 FSG centers across France and coordinated by Gustave Roussy (ClinicalTrials.gov Identifier: NCT02672527; EudraCT N°: 2014-003176-23). Patients who failed at least one anthracycline-containing chemotherapy regimen were randomly assigned on a 1 : 1 basis by the minimization method to receive either trabectedin (trabectedin arm), according to the terms of the marketing authorization, or BSC (BSC arm). The random assignment of patients was done centrally by a computer-generated system using permuted blocks of four patients. The enrolled patients were also stratified by a minimization procedure according to tumor histotypes into an L-STS group, for patients with liposarcoma or leiomyosarcoma, and a non-L-STS group for all other sarcoma histological subtypes. As an open-label study, investigators, patients, and the sponsor were all unmasked to the treatment assignment.

All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the ethics committee (approval by the Comité de Protection des Patients Ile-de-France V on 7 October 2014) and the French Drug Agency (approval by the Agence Nationale de Sécurité des Médicaments on 22 October 2014). Signed informed consents were obtained from all study participants before registration.

Patients

Eligible patients were adults ($\geq$18 years old) with histologically proven ASTS, unresectable and/or metastatic relapse or progressive disease (PD) (confirmed by imaging 14 days before inclusion) after at least one anthracycline-based chemotherapy, and up to three prior treatment lines given in the advanced setting. All eligible patients had to have measurable disease according to RECIST version (v.) 1.1,[10] an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$1, adequate hematologic, renal, and hepatic function [neutrophil count $\geq$1500/mm^3, hemoglobin $\geq$9 g/dl, platelet count $\geq$100 000/mm^3, creatinine clearance $\geq$30 ml/min, creatine phosphokinase $\leq$2.5 $\times$ upper limit of normal (ULN), bilirubin $\leq$ ULN, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) $\leq$2.5 $\times$ ULN, alkaline phosphatase $\leq$2.5 $\times$ ULN, albumin $\geq$25 g/l], and normal left ventricular ejection fraction.

Treatments and study procedures

Trabectedin was administered at the recommended dose of 1.5 mg/m^2 body surface area through a central venous line as a 24-h continuous infusion every 3 weeks. Prophylaxis with corticosteroids (e.g. dexamethasone 20 mg intravenously 30 min before trabectedin) and an antiemetic 5-hidroxitriptamina 3 receptor antagonist was given to all patients randomized in the trabectedin arm. A maximum of three dose reductions was permitted if any of the following events occurred during the previous cycle of therapy: grade 4 neutropenia lasting for >5 days or associated with fever or infection, increase of bilirubin > ULN, increase of alkaline phosphatase >2.5 $\times$ ULN, grade 4 thrombocytopenia, increase of ALT/AST >2.5 ULN not reversed to baseline values by day 21, and any other $\geq$grade 3 adverse reaction. At first occurrence of toxicity, the dose was reduced to 1.2 mg/m^2 in the following cycles, and in case of re-appearance of any toxicity, the dose was further reduced to 1.0 mg/m^2, then to 0.8 mg/m^2, and maintained in subsequent cycles in patients with clinical benefit in terms of objective response or disease stabilization. A cycle was defined as delayed if it was administered >6 days after the scheduled date. There was no predefined limit to the number of administered cycles and the treatment could continue until PD according to RECIST v. 1.1,[10] severe toxicity, consent withdrawal, or patient death. In the BSC arm, patients could not receive antitumor therapy but only treatments to relieve symptoms induced by primary disease and to improve quality of life (QoL). After PD, all patients allocated to the BSC arm were allowed to cross over to trabectedin (post-randomized part). Once trabectedin treatment was discontinued, patients could be treated with subsequent post-protocol anticancer therapies or supportive care as per the clinician's best clinical judgment and at the discretion of patients.

The individual patient's study evaluation began with the first trabectedin dose and continued until patient discontinuation for any reason or death. Tumor response was assessed based on cross-sectional imaging, typically carried out by computerized tomography scans, every 3 weeks during the first two cycles and then every 6 weeks (every

two cycles) thereafter. The progression date corresponded to the date of the objective PD evaluated according to RECIST v. 1.1.[10] During the randomized part of the study, diagnostic imaging studies were validated through an audit by a centralized independent radiologist, blinded to treatment assignment. Therefore, the investigative centers had to await the result of the centralized proofreading before modifying any treatment procedure. The final imaging was the assessment carried out closest to the follow-up period and before initiation of any other chemotherapy treatment. All patients were followed for survival until death from any cause or consent withdrawal.

The health-related QoL was assessed using the 30-item core European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (EORTC QLQ-C30) administered at randomization, every 6 weeks (every two cycles) until the end of follow-up or death. The EORTC QLQ-C30 assesses health-related QoL in cancer patients across nine multi-item scales as described elsewhere.[11]

Endpoints and assessments

The primary endpoint of this study was to compare the treatment with trabectedin with BSC in terms of progression-free survival (PFS) as per blinded independent radiological central review. Secondary endpoints included objective response rate (ORR) measured by RECIST v. 1.1,[10] response duration and the disease control rate (DCR), overall survival (OS), QoL, and safety. The PFS analysis was defined as the time interval from the date of randomization until the earliest date of disease progression or death (regardless of cause), whereas OS was accounted from the date of randomization until death from any cause. Patients considered lost to follow-up, with no reported disease progression, and alive were censored at the day of the last visit. Duration of response was the period from achievement of an objective response until PD or death, whereas duration of stable disease (SD) was the time interval between the date of start of treatment and the date of objective disease progression. The ORR was defined as the percentage of patients who achieved a complete (CR) or partial response (PR), whereas DCR was defined as the percentage of patients with a radiological CR, PR, or SD. Adverse events (AEs) were graded according to the National Cancer Institute-Common Terminology Criteria v. 4.0 and were summarized by the worst grade experienced by patient.

Statistical analysis

According to the data from the EORTC-Soft Tissue and Bone Sarcoma Group[12] in patients not responding to a second-line chemotherapy, we expected a median PFS of 1.75 months in the BSC group. Based on this assumption, to detect a 50% reduction in PFS with type I error of 5% and a power of 90%, the final PFS analysis was carried out when 87 progression or death events were observed in about 100 patients. The primary efficacy analyses were carried out on the intention-to-treat (ITT) analysis set, defined as all the randomized patients into the study. The safety analyses were based on all-treated population, defined as all patients who received at least one dose of treatment, whereas patients were considered assessable for efficacy if they had at least one assessment of tumor response. We carried out two analyses: firstly, the analysis of the primary efficacy endpoint (i.e. PFS) was carried out after observing the fulfilled number of progressions and/or deaths as per protocol after a median follow-up of 11.0 months, whereas the second analysis was carried out after a median follow-up of 26 months (range: 0.46-31.1 months) and concerned all the other endpoint criteria, including OS evaluation.

The demographic and baseline characteristics of patients are depicted by the descriptive statistics. All *P* values were descriptive in nature, except that of the primary endpoint, which is confirmatory. Time-to-event endpoints and their fixed-time estimations were estimated according to the Kaplan—Meier method and were compared using a log-rank test stratified by the tumor histological subtype. Categorical variables were presented as absolute and relative frequencies and numerical variables as median [range or interquartile range (IQR)]. The qualitative criteria were compared by the chi-square test, while Fisher's exact test was used if the conditions were non-valid for applying the chi-square test. A multivariate Cox proportional hazards model, stratified by the histological subtype of sarcoma (L-STS versus non-L-STS group), was used to quantify the treatment effect. The assumption of proportional hazards was graphically checked using the Schoenfeld residuals.[13] To analyze the effect of trabectedin on QoL, a linear mixed-effects model for longitudinal analysis of QoL domains was used. The model included treatment, period, period—treatment interactions, histological subtype, sex and age as fixed effects, and a patient-specific random effect. All tests were two-sided and significance was accepted at the 5% level. All statistical analyses were done with SAS software (v. 9.4, SAS Institute, Inc.; Cary, NC) and R software (v. 3.1.2, R Foundation for Statistical Computing, Vienna, Austria, for the survival curves).

Role of the funding source

The T-SAR was an FSG trial, supported by PharmaMar, S.A., which supplied trabectedin for the randomized portion of the trial. PharmaMar, S.A. did not participate in the design, collection, analysis, interpretation of data, or any other aspect of the trial. All authors had the final responsibility to submit the manuscript for publication.

RESULTS

Patient disposition and characteristics

From 26 January 2015 to 5 November 2015, a total of 103 patients with pre-treated ASTS were enrolled by 16 FSG centers and allocated to receive either trabectedin ($n = 52$) or BSC ($n = 51$). All patients were analyzed on an ITT basis for the assessment of PFS and OS (Figure 1). Two patients discontinued the study right after their randomization in

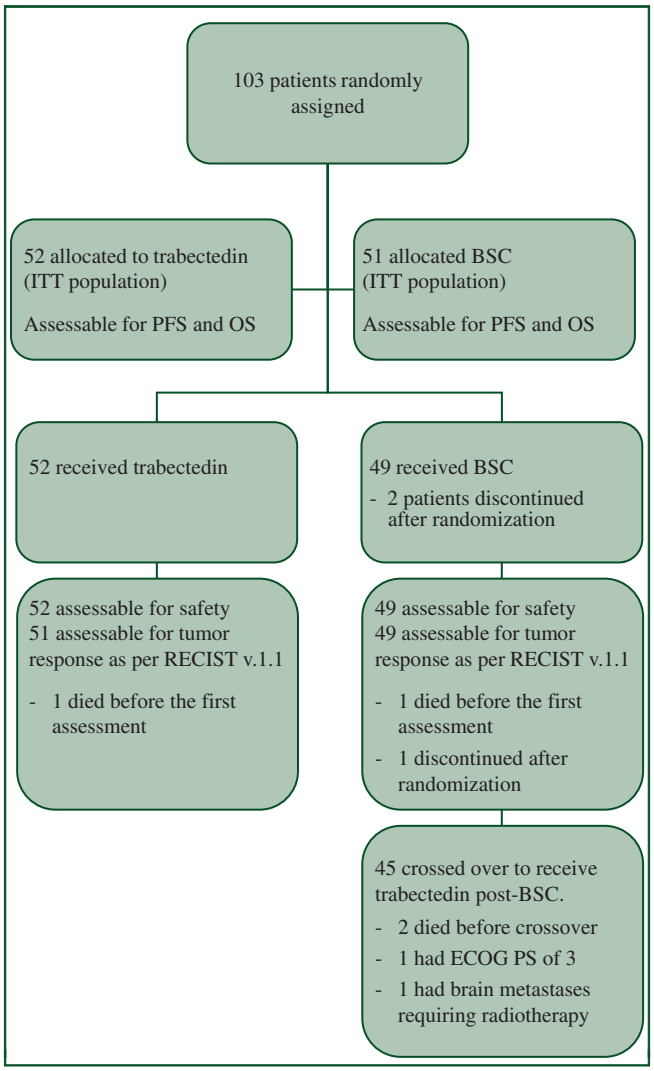


Figure 1. Description of included patients.
BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat; OS, overall survival; PFS, progression-free survival.

the BSC arm and did not receive any treatment in the study. Therefore, 101 patients were evaluated for treatment administration and safety, whereas 100 patients were evaluated for efficacy, according to RECIST v. 1.1, as two patients died before their first assessment for response and one patient discontinued right after randomization in the BSC arm (Figure 1). Patients were heavily pre-treated, with 53.8% of patients in the trabectedin arm receiving trabectedin as third/fourth line versus 37.3% of patients in the BSC arm. Other baseline demographics and disease characteristics of patients were well balanced between arms, particularly regarding the number of patients with L-STS (61.5% versus 58.8%, respectively) versus non-L-STS (38.5% versus 41.2%) and the proportion of patients with metastatic disease (92.3% versus 88.2%) at study entry (Table 1).

Extent of exposure

During the randomized part of the study, patients in the trabectedin arm received a median of 3 cycles (IQR: 1.5-8) with 28.8% patients receiving >6 cycles and up to a maximum of 23 cycles (Table 2). A total of 274 trabectedin cycles were administered with a median dose intensity of 0.43 mg/m^2/week (range: 0.26-0.51 mg/m^2/week) over a median treatment duration of 10.1 weeks (range: 3-77.9 weeks; IQR: 4.4-31.6 weeks), which corresponded to 86.0% of the planned dose intensity. Patients in the BSC arm received 139 cycles with a median of 2 cycles (range: 1-11; IQR: 1-4) with 10.2% of patients receiving >6 cycles. In the trabectedin arm, 59.0% of cycles were given as scheduled with no delay or dose reduction. Overall, 57 out of 222 (25.7%) trabectedin cycles (after excluding the first cycle of treatment) were delayed, while the trabectedin dose was modified in 12 cycles (5.4%), both mostly due to hematological toxicity observed in ∼50% of patients (Table 2). The most common cause for ending the randomized part of the study in both arms was disease progression ($n = 91$, 90.1%).

In the BSC arm, 45 out of 49 patients (91.8%) crossed over to receive trabectedin post-BSC. Four patients did not cross over due to death before the crossover ($n = 2$), ECOG performance status score of 3 ($n = 1$), and brain metastases requiring radiation therapy ($n = 1$). After crossing over from BSC to trabectedin, 285 cycles of trabectedin were administered with a median number of 4 cycles per patient (IQR: 2-7) with 31.1% of patients receiving ≥6 cycles and up to a maximum of 42 cycles (Table 2). Median dose intensity of trabectedin was 0.41 mg/m^2/week (range: 0.22-0.53 mg/m^2/week; IQR: 0.35-0.5 mg/m^2/week) over a median treatment duration of 12.0 weeks (range: 3.0-152.0 weeks; IQR: 6.0-26.9 weeks), which corresponded to 81.0% of the planned dose intensity. Similar to what was observed in the trabectedin arm, 58.0% of cycles were given with no delay or dose reduction, whereas most cycle delays and/or dose modifications (∼40%) were due to hematological toxicity.

Due to mandatory use of prophylactic medication before trabectedin during the randomized part, numerically more patients from the trabectedin arm compared with BSC received antiemetics and corticosteroids. As supportive treatments, more patients from the trabectedin arm received granulocyte colony-stimulating factor (47.1% versus 0%) and erythropoietin (10.2% versus 0%) as compared with BSC, while more patients from the BSC arm received antidepressants (25.2% versus 7.7%) and hypnotics (15.1% versus 4.0%) as compared with the trabectedin arm (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.04.014).

After stopping the treatment with trabectedin in both arms, subsequent chemotherapy was given to 62 patients (61.4%; trabectedin arm: $n = 33$, 63.5%; BSC arm: $n = 29$, 56.9%) who received a median of 1 post-study line (range: 0-5; IQR: 0-2).

Efficacy

At the time of the primary endpoint analysis, 83 PDs confirmed by central review or death events (80.6% of patients) were recorded, whereas 20 patients (19.4%) who

Table 1. Patient and disease characteristics at baseline

Patients	Trabectedin $n = 52$	Best supportive care $n = 51$	Total $N = 103$
Sex, *n* (%)			
Male	24 (46.2)	31 (60.8)	55 (53.4)
Female	28 (53.8)	20 (39.2)	48 (46.6)
Age at randomization (years)			
Median (range)	66.5 (21.5-82.3)	63.7 (24.9-84.2)	65 (21.5-84.2)
Eastern Cooperative Oncology Group performance status, *n* (%)			
0	23 (44.2)	17 (33.3)	40 (38.8)
1	27 (51.9)	33 (64.7)	60 (58.3)
2	2 (3.8)	0	2 (1.9)
Missing	0	1 (2.0)	1 (1.0)
Sarcoma histology, *n* (%)			
L-sarcoma	32 (61.5)	30 (58.8)	62 (60.2)
Liposarcoma	14 (26.9)	16 (31.4)	30 (29.1)
Leiomyosarcoma	18 (34.6)	14 (27.5)	32 (31.1)
Non-L-sarcoma	20 (38.5)	21 (41.2)	41 (39.8)
Synovial sarcoma	2 (3.8)	3 (5.9)	5 (4.9)
Undifferentiated sarcoma	5 (9.6)	6 (11.8)	11 (10.7)
Myxofibrosarcoma	5 (9.6)	3 (5.9)	8 (7.8)
Other histologies	8 (15.4)	9 (17.6)	17 (16.5)
Site of primary tumor, *n* (%)			
Lower limb and/or hip	11 (21.2)	15 (29.4)	26 (25.2)
Trunk	4 (7.7)	5 (9.8)	9 (8.7)
Retroperitoneal	14 (26.9)	13 (25.5)	27 (26.2)
Uterus	12 (23.1)	4 (7.8)	16 (15.5)
Other	6 (11.5)	5 (9.8)	11 (10.7)
Abdominal	5 (9.6)	9 (17.6)	14 (13.6)
Histopronostic grade, *n* (%)			
Grade 1	3 (5.8)	3 (5.9)	6 (5.8)
Grade 2	14 (26.9)	13 (25.5)	27 (26.2)
Grade 3	19 (36.5)	24 (47.1)	43 (41.7)
Missing	16 (30.8)	11 (21.6)	27 (26.2)
Tumor status, *n* (%)			
Metastatic disease	48 (92.3)	45 (88.2)	93 (90.3)
Lung metastases	35 (67.3)	33 (64.7)	68 (66)
Liver metastases	12 (23.1)	10 (19.6)	22 (21.4)
Bone metastases	5 (9.6)	8 (15.7)	13 (12.6)
Time between first diagnosis and randomization (months)			
Median (range)	25.9 (5.3-204.8)	33.4 (3.6-186.7)	28 (3.6-204.8)
Time between first diagnosis and metastatic disease (months)[a]			
Median (range)	9.1 (−1.4 to 174.7)	17.3 (−0.6 to 124.8)	13.9 (−1.4 to 74.7)
Prior chemotherapy			
Neoadjuvant/adjuvant, *n* (%)	17 (32.7)	18 (35.3)	35 (34.0)
Advanced, median lines (range)	2 (0-3)	1 (0-3)	1 (0-3)
Number of lines of advanced chemotherapy, *n* (%)			
0[b]	6 (11.5)	6 (11.8)	12 (11.7)
1	18 (34.6)	26 (51)	44 (42.7)
2	19 (36.5)	14 (27.5)	33 (32.0)
3	9 (17.3)	5 (9.8)	14 (13.6)
Type of prior chemotherapy, *n* (%)			
Anthracyclines	50 (96.2)	50 (98)	100 (97.1)
Ifosfamide[c]	25 (49)	31 (60.8)	56 (54.9)
Gemcitabine ± docetaxel[c]	13 (25.5)	14 (27.5)	27 (26.5)
Dacarbazine[c]	11 (21.6)	13 (25.5)	24 (23.5)
Pazopanib[c]	11 (21.6)	6 (11.8)	17 (16.7)
Cyclophosphamide	7 (13.5)	3 (5.9)	10 (9.7)
Others	9 (17.3)	7 (13.7)	16 (15.5)

[a] Negative values were reported in patients when the first diagnosis was made after the detection of metastases.
[b] Patients who did not receive chemotherapy in advanced setting but had received chemotherapy in neoadjuvant/adjuvant setting.
[c] One patient from the trabectedin arm was considered missing for prior ifosfamide, gemcitabine ± docetaxel, dacarbazine, or pazopanib.

were alive without confirmed PD were censored. Median PFS was significantly longer in the trabectedin arm (3.1 months) compared with BSC (1.5 months) [hazard ratio (HR) = 0.39, 95% confidence interval (CI) 0.24-0.64, $P < 0.001$] (Figure 2). At 3 and 6 months after treatment, 55% and 35% of patients were free from progression in the trabectedin arm compared with 24% and 3% of patients in the BSC arm, respectively. The highest impact of trabectedin was observed in the L-STS cohort, with a median PFS of 5.1 months in the trabectedin arm and 1.4 months in the BSC arm (HR = 0.29, 95% CI 0.15-0.55, $P < 0.0001$), whereas no statistically significant difference in median PFS was

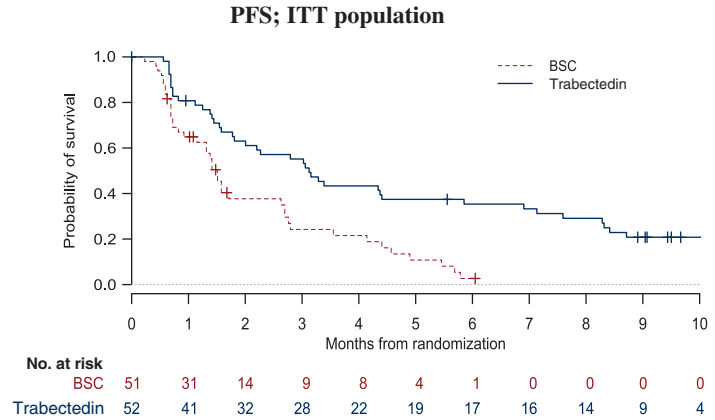
Table 2. Treatment exposure during the randomization part and after crossover

Treatment delivery	Trabectedin $n = 52$	BSC $n = 49$	Total $N = 101$	Trabectedin post-BSC (post crossover) $n = 45$
Time on treatment (weeks)[a]				
Median (range)/(IQR)	10.1 (3-77.9)/(4.4-31.6)	—	—	12 (3-152)/(6-26.9)
Cycles per patient, *n* (%)				
Median (range)/(IQR)	3 (1-23)/(1.5-8)	2 (1-11)/(1-4)		4 (1-42)/(2-7)
1 cycle	13 (25)	19 (38.8)	32 (31.7)	7 (15.6)
2 cycles	8 (15.4)	10 (20.4)	18 (17.8)	10 (22.2)
3 cycles	7 (13.5)	5 (10.2)	12 (11.9)	4 (8.9)
4 cycles	4 (7.7)	6 (12.2)	10 (9.9)	6 (13.3)
5 cycles	3 (5.8)	4 (8.2)	7 (6.9)	—
6 cycles	2 (3.8)	0	2 (2)	4 (8.9)
>6 cycles	15 (28.8)	5 (10.2)	20 (19.8)	14 (31.1)
>9 cycles	12 (23.1)	1 (2)	13 (12.9)	8 (17.8)
>12 cycles	5 (9.6)	0	5 (5)	5 (11.1)
Dose intensity (mg/m^2/week)				
Median (range)/(IQR)	0.43 (0.26-0.51)/(0.37-0.5)	—	—	0.41 (0.22-0.53)/(0.35-0.5)
Relative dose intensity, *n* (%)				
<80%	18 (34.6)	—	—	21 (46.7)
≥80%	34 (65.4)	—	—	24 (53.3)
Total cycles				
N	274	139	413	285
Dose modification and cycles delayed (per cycle), *n* (%)				
Cycles susceptible to have dose modification or delay[b]	222	—	—	240
No dose modification or cycle delay	131 (59.0)	—	—	139 (57.9)
Dose modification and cycle delay	22 (9.9)	—	—	14 (5.8)
Cycle delay only	57 (25.7)	—	—	67 (27.9)
Dose modification only	12 (5.4)	—	—	20 (8.3)
Main reasons for cycle delay per cycle; susceptible cycles[b]	79	—	—	81
Hematological toxicity	42 (53.2)	—	—	23 (28.4)
Unknown	20 (25.3)	—	—	34 (42)
Other reasons	12 (15.2)	—	—	7 (11)
Patient wish	4 (5.1)	—	—	15 (20.5)
Hepatic toxicity	1 (1.3)	—	—	2 (2.5)
Main reasons for dose reduction per cycle; susceptible cycles[b]	34	—	—	34
Hematological toxicity	16 (47.1)	—	—	14 (41.2)
Hepatic toxicity	10 (29.4)	—	–	11 (32.4)
Other reasons	6 (17.6)	—	—	6 (17.6)
Unknown	2 (5.9)	—	—	3 (8.8)
End of treatment of the randomized part, *n* (%)				
Yes	52 (100)	49 (100)	101 (100)	—
Reason for end of treatment of the randomized part, *n* (%)				
Progression	44 (84.6)	47 (95.9)	91 (90.1)	—
Toxicity[c]	4 (7.7)	0	4 (4)	—
Death[d]	1 (1.9)	2 (4.1)	3 (3)	—
Other[e]	2 (3.8)	0	2 (2)	—
Investigator decision	1 (1.9)	0	1 (1)	—

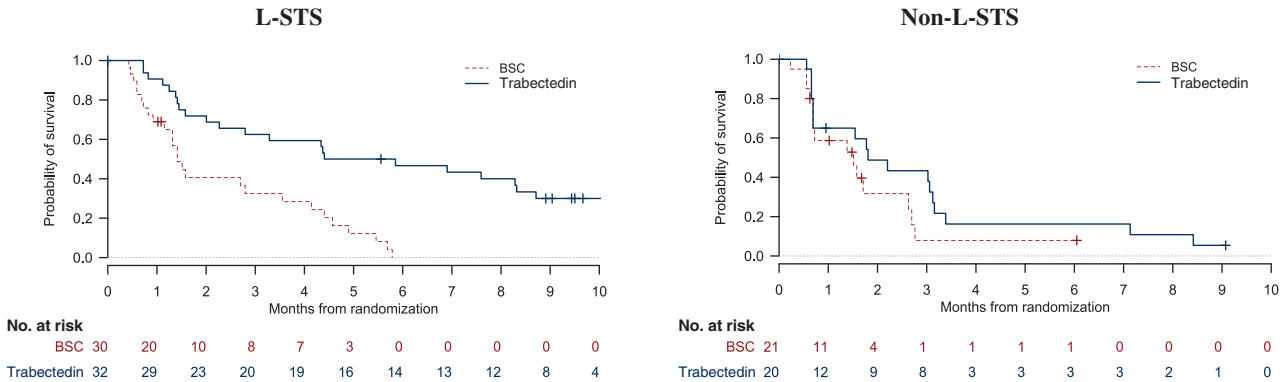
BSC, best supportive care; IQR, interquartile range.
[a] Calculated as (date of last administration − date of first cycle + 21)/7.
[b] Not applicable for the first cycle of treatment: 52 cycles for the randomization part and 45 cycles after crossover.
[c] Two patients ended the treatment due to liver toxicity, one due to thrombocytopenia and another owing to renal failure.
[d] One drug-related death occurred following febrile neutropenia after the first trabectedin cycle, whereas two deaths occurred in the BSC during the first cycle due to disease progression.
[e] One treatment discontinuation due to delay of >6 weeks in administering trabectedin and another owing to reduction of the ventricular ejection fraction.

observed in patients with non-L-STS (1.8 versus 1.5 months; HR = 0.60, 95% CI 0.29-1.26, $P = 0.16$). In addition, the PFS treatment benefit with trabectedin compared with BSC was consistently observed across almost all subgroups examined in sensitivity analyses (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.04.014).

There were no CRs in either treatment group. Among 51 patients assessable for response from the trabectedin arm, 7 patients achieved a PR reaching an ORR of 13.7%, while no objective responses were observed in 49 assessable patients from the BSC arm ($P = 0.013$) (Table 3). All objective responses were observed in patients with L-STS who reached the ORR of 21.9% with a median duration of response of 7.6 months. Additionally, in the trabectedin arm, 34 patients (66.7%) had SD, corresponding to a DCR of 80.4%, with a median duration of



Parameter, *n* (%)	Patients with events	Censored	Median PFS (months) (95% CI)	PFS at 3 months (95% CI)	PFS at 6 months (95% CI)	*P* value[a]	HR (95% CI)	*P* value[b]
Assessable patients, *N* = 103	83 (80.6%)	20 (19.4%)	2.2 (1.5-3.0)	41% (32-51)	21% (14-31)	—	—	—
Therapeutic arm						<0.0001		0.0001
Trabectedin (*n* = 52)	42 (80.8%)	10 (19.2%)	3.1 (1.8-5.9)	55% (42-68)	35% (24-49)		0.39 (0.24-0.64)	
BSC (*n* = 51)	41 (80.4%)	10 (19.6%)	1.5 (0.9-2.6)	24%(14-39)	3% (0.5-14)		1	



Parameter, *n* (%) Assessable patients, *N* = 103	Patients with events	Censored	Median PFS (months) (95% CI)	PFS at 3 months (95% CI)	PFS at 6 months (95% CI)	*P* value[a]	HR (95% CI)	*P* value[b]
L-STS								
Therapeutic arm						<0.0001		0.0001
Trabectedin (*n* = 32)	24 (75.0%)	8 (25.0%)	5.1 (2.0-8.3)	63% (45-77)	47% (31-63)		0.29 (0.15-0.55)	
BSC (*n* = 30)	26 (86.7%)	4 (13.3%)	1.4 (0.9-3.6)	32% (18-52)	0		1	
Non-L-STS								
Therapeutic arm						0.16		0.18
Trabectedin (*n* = 20)	18 (90.0%)	2 (10.0%)	1.8 (0.7-3.1)	43% (24-65)	16% (6-38)		0.60 (0.29-1.26)	
BSC (*n* = 21)	15 (71.4%)	6 (28.6%)	1.5 (0.7-2.6)	8% (1-34)	8% (1-34)		1	

Figure 2. Kaplan–Meier plots of progression-free survival by central radiology review.
BSC, best supportive care; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; L-STS, leiomyosarcoma and liposarcoma; PFS, progression-free survival.
[a] Log-rank test stratified by the 'histological subtype' stratification factor (L-STS versus non-L-STS).
[b] The hazard ratio for trabectedin versus BSC was estimated with a Cox model, stratified by the 'histological subtype' stratification factor (L-STS versus non-L-STS).

3.1 months. In the BSC arm, SD was observed in 30 patients, corresponding to a DCR of 61.2%, with a median duration of 2.6 months.

After 81 death events, median OS was not significantly different between the two arms (13.6 months for the trabectedin arm versus 10.8 months for the BSC arm; HR = 1.04, 95% CI 0.67-1.61, $P = 0.87$) (Figure 3). Similarly, following an analysis of OS according to histological subtype of sarcoma, no statistically significant difference in median OS was observed between arms (L-STS: $P = 0.38$; non-L-STS: $P = 0.22$).

Safety

During the randomized part of the study, the most commonly reported treatment-related grade 3/4 AEs were

Table 3. Response assessment by RECIST v. 1.1

Best response according to RECIST v. 1.1	Trabectedin	Best supportive care	Total	*P* value
Full analysis set	$n = 51$	$n = 49$	$N = 100$	0.004[a]
PR, *n* (%)	7 (13.7)	0	7 (7)	
SD, *n* (%)	34 (66.7)	30 (61.2)	64 (64)	
PD, *n* (%)	10 (19.6)	19 (38.8)	29 (29)	
ORR, % (95% CI)	13.7 (5.7-26.3)	0	7.0 (2.8-13.9)	0.013[a]
DCR, %; PR + SD (95% CI)	80.4 (66.9-90.2)	61.2 (46.2-74.8)	71.0 (61.1-79.6)	0.035[b]
Response duration, median; months (95% CI)	7.6 (1.3-9.9)	—	7.6 (1.3-9.9)	—
SD duration, median; months (95% CI)	3.1 (2.0-4.3)	2.6 (1.6-2.8)	2.8 (2.1-3.4)	0.036[c]
Patients with L-STS	$n = 32$	$n = 28$	$N = 60$	0.006[a]
PR, *n* (%)	7 (21.9)	0	7 (11.7)	
SD, *n* (%)	21 (65.6)	18 (64.3)	39 (65)	
PD, *n* (%)	4 (12.5)	10 (35.7)	14 (23.3)	
ORR, % (95% CI)	21.9 (9.3-40.0)	0	11.7 (4.8-22.6)	0.012[a]
DCR, %; PR + SD (95% CI)	87.5 (71.0-96.5)	64.3 (44.1-81.4)	76.7 (64.0-86.6)	0.034[b]
Response duration, median; months (95% CI)	7.6 (1.3-9.9)	—	7.6 (1.3-9.9)	—
SD duration, median; months (95% CI)	4.3 (1.7-8.2)	2.8 (1.4-4.6)	3.3 (2.0-4.6)	0.063[c]
Patients with non-L-STS	$n = 19$	$n = 21$	$N = 40$	0.46[b]
SD, *n* (%)	13 (68.4)	12 (57.1)	25 (62.5)	
PD, *n* (%)	6 (31.6)	9 (42.9)	15 (37.5)	
DCR, %; PR + SD (95% CI)	68.4 (43.5-87.4)	57.1 (34.0-78.2)	62.5 (45.8-77.3)	0.46[b]
SD duration, median; months (95% CI)	3.1 (1.8-3.4)	2.1 (1.3-2.7)	2.5 (1.7-3.1)	0.11[c]

CI, confidence interval; DCR, disease control rate; ORR, objective response rate; L-STS, liposarcoma/leiomyosarcoma-soft tissue sarcoma; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Fisher's exact test.
[b] Chi-square test.
[c] Log-rank test.

neutropenia ($n = 23$, 44.2%), including four episodes of febrile neutropenia (7.7%), leukopenia ($n = 18$, 34.6%), and transaminase increase ($n = 17$, 32.7%). One patient (1.9%) died due to trabectedin-related febrile neutropenia. Fatigue and digestive symptoms were also more frequently reported in the trabectedin arm than in the BSC arm.

After crossing over from BSC to trabectedin, patients experienced similar pattern of grade 3/4 AEs, with transaminase increase ($n = 24$, 53.3%), leukopenia ($n = 16$, 35.6%), and neutropenia ($n = 23$, 51.1%), with two episodes of febrile neutropenia (4.4%), as the most frequently observed serious AEs. In addition, during the crossover part of the study, two patients died due to treatment-related AEs: a combination of general physical health deterioration, with acute kidney failure, septic shock, and aplasia in one patient, and tumor hemorrhage and thrombocytopenia in another. Regarding the latter patient, according to the investigator, the tumor hemorrhage leading to death was linked to the course of the disease but might have been aggravated by trabectedin-related thrombocytopenia.

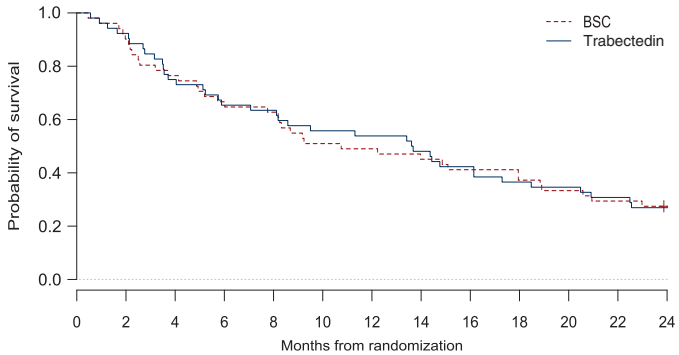
Quality of life

Compliance to EORTC QLQ-C30 was good in both arms at baseline (96% in trabectedin and 88% in BSC) and after 8 months decreased to 59% in the trabectedin arm and 63% in the BSC arm. There was no statistical difference between the two arms for any QoL domain. The mean global health status scores were stable and linear over time in both arms (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2021.04.014).

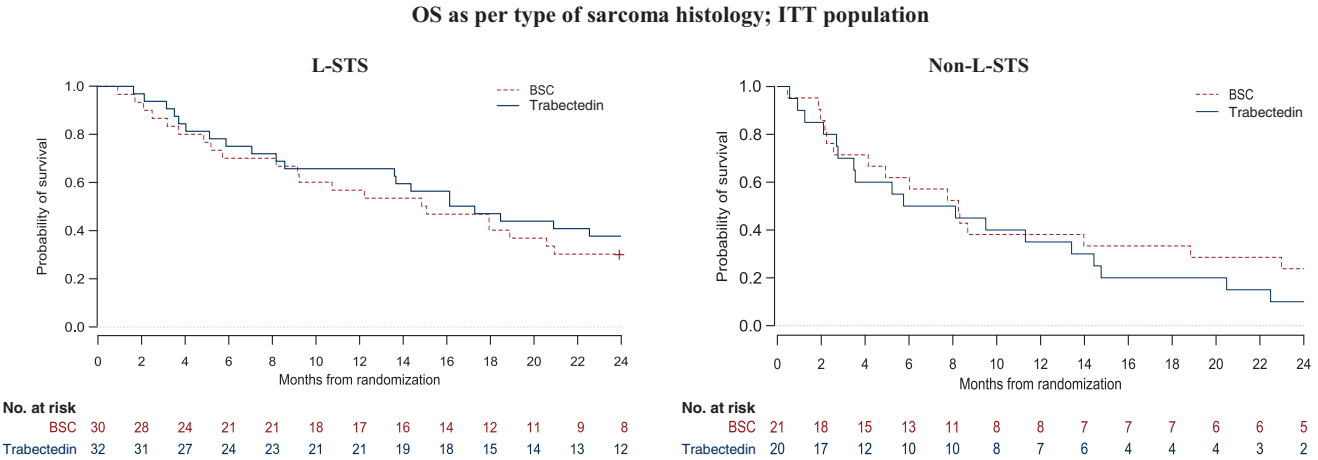
DISCUSSION

The T-SAR study met its primary endpoint confirming that trabectedin reduces the risk of progression or death (regardless of cause) compared with BSC and without impairing QoL of patients with ASTS who relapsed after at least one anthracycline-based chemotherapy and received up to three prior chemotherapy lines. T-SAR was the first randomized phase III study that prospectively evaluated trabectedin's outcomes compared to BSC in heavily pretreated patients with ASTS of multiple histologies.

In the present study, trabectedin administration resulted in a median PFS of 3.1 months (95% CI 1.8-5.9 months) with 3- and 6-month PFS rates of 55% and 35%, respectively. Indeed, a major impact of trabectedin was observed in the L-STS cohort of patients (median PFS in the trabectedin and BSC arms: 5.1 versus 1.4 months, respectively; $P < 0.0001$) (Figure 2), which is consistent with the results of prior reports of these especially sensitive STS subtypes.[1,2,14] The benefit in PFS among patients with L-STS was comparable to that reported in a registration phase II trial[1] and a pivotal, dacarbazine-controlled, phase III US trial,[2] which in patients with L-STS reported a median PFS of 3.3 and 4.2 months, respectively. In this study, the benefit of trabectedin in PFS was also supported by other secondary endpoints, with improvements in the overall population in both the ORR (13.7%) and DCR (80.4%). Furthermore, patients with L-STS yielded even higher ORR (21.9%) and DCR (87.5%), which favorably compare with those from randomized phase II/III studies in patients with L-STS (ORR range: 5.6%-9.9%; DCR range: 58.4%-61.2%).[1,2]



Parameter, *n* (%)	Death events	Censored	Median OS (months) (95% CI)	*P* value[a]	HR (95% CI)	*P* value[b]
Assessable patients, *N* = 103	81 (78.6%)	22 (21.4%)	13.4 (8.3-16.1)	—	—	—
Therapeutic arm				0.87		0.87
Trabectedin (*n* = 52)	41 (78.8%)	11 (21.2%)	13.6 (7.1-17.3)		1.04 (0.67-1.61)	
BSC (*n* = 51)	40 (78.4%)	11 (21.6%)	10.8 (6.0-18.8)		1	



Parameter, *n* (%) Assessable patients, *N* = 103	Death events	Censored	Median OS (months) (95% CI)	*P* value[a]	HR (95% CI)	*P* value[b]
L-STS						
Therapeutic arm				0.38		0.38
Trabectedin (*n* = 32)	21 (65.6%)	11 (34.4%)	16.7 (8.2-NR)		0.77 (0.42-1.39)	
BSC (*n* = 30)	23 (76.7%)	7 (23.3%)	15.0 (8.2-20.9)		1	
Non-L-STS						
Therapeutic arm				0.22		0.22
Trabectedin (*n* = 20)	20 (100.0%)	0	6.9 (2.7-14.4)		1.50 (0.78-2.89)	
BSC (*n* = 21)	17 (81.0%)	4 (19.0%)	8.3 (2.6-18.8)		1	

Figure 3. Kaplan–Meier plots of overall survival.
BSC, best supportive care; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; L-STS, leiomyosarcoma and liposarcoma, NR, not reached; OS, overall survival.
[a] Log-rank test stratified by the 'histological subtype' stratification factor (L-STS versus non-L-STS).
[b] The hazard ratio for trabectedin versus BSC was estimated with a Cox model, stratified by the 'histological subtype' stratification factor (L-STS versus non-L-STS).

In the present study, the number of patients who received >6 (28.8% versus 10.2%), >9 (23.1% versus 2.0%), or >12 (9.6% versus 0%) cycles of trabectedin was much higher than in the BSC arm (Table 2). This allowed patients to benefit from a long-term treatment with trabectedin and to get longer disease control with an acceptable safety profile. Moreover, the rates of patients achieving long-term tumor control after the six initial cycles in the trabectedin (28.8%) and trabectedin post-BSC after crossover (31.1%) arms were in the same range and similar to those reported in the previous studies (range: 25.1%-34.4%).[7,15] These data draw attention to the role of treatment duration, as an important factor for long-term benefits, and emphasize that trabectedin should be given until intolerance or progression, as an early discontinuation of trabectedin may result in a rapid disease progression.[16,17]

In the current study, no difference in terms of OS between the two arms was observed, neither in the overall

population nor in an analysis as per sarcoma histotype. Indeed, our study was underpowered to assess OS and the study protocol allowed crossing over from the BSC to trabectedin arm at progression. Consistently, despite a robust improvement in disease control, a number of studies carried out in patients with STS reported no improvement in OS, even when the control arm involved a placebo.[18-20] Thus, because of the historical difficulty in revealing OS improvement, the clinical documentation of disease control, measured as PFS and DCR, has been proposed as a proper measure of clinically relevant efficacy in advanced sarcomas.[21]

The present study also illustrates the favorable safety profile of trabectedin, being consistent with extensive prior experience and reports observed throughout the development program of trabectedin, and, subsequently, in real-life settings after approval.[1,2,7,8] Laboratory abnormalities such as neutropenia and asymptomatic transaminase elevation were the most frequently reported grade 3/4 AEs in this study. These abnormalities were generally transient and non-cumulative, were managed by dose delays, reductions or supportive care, and showed no evidence of end-organ cumulative toxicity, including those patients who remained on therapy for prolonged periods of time (i.e. until 42 cycles in the trabectedin post-BSC arm). These findings can be indirectly corroborated by the health-related QoL results from our trial, particularly considering that regardless of treatment the patients reported comparable QoL with a stable global health status over the whole study period.

In conclusion, this trial met its first endpoint, as a pre-planned PFS analysis showed a significant improvement in median PFS with trabectedin over BSC in heavily pre-treated patients with ASTS. The largest impact on PFS was observed in the L-STS cohort, in whom trabectedin historically has reached the highest range of activity.

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DISCLOSURE

ALC has received honoraria from Deciphera, Bayer, and PharmaMar. J-YB has received research support and honoraria from PharmaMar, Bayer, and Eisai. IR-C reports research support and honoraria from PharmaMar, Roche, AstraZeneca, Clovis, GSK, Mersana, Deciphera, Genentech, Advaxis, MSD, and BMS. OM has served as consultant for Amgen, AstraZeneca, Bayer, Bristol Myers-Squibb, Eli-Lilly, Ipsen, Lundbeck, MSD, Novartis, Pfizer, Roche, Servier, and Vifor Pharma, and is a shareholder of Amplitude surgical, Ipsen, and Transgene. All other authors have declared no conflicts of interest.

DATA SHARING

De-identified individual data might be made available following publication by reasonable request and on a case-by-case basis to the corresponding author, including the clinical study results and statistical analysis plan. A research proposal should be included, which will be evaluated by the French Sarcoma Group and the ethics committee for clinical investigation.

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