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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Version of Record: https://www.sciencedirect.com/science/article/pii/S0923753421011716
Manuscript_2e6f690ee9f8ed1ee2741e7e697371fa

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

Running head: Trabectedin *vs* best supportive care for soft tissue sarcoma

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ABSTRACT

Background: The French Sarcoma Group assessed the efficacy, safety, and quality of life (QoL) of trabectedin *vs* 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 three weeks or BSC, stratified into L-STS (lipo/leiomyosarcoma) and non-L-STS groups (other histotypes). Patients from 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 Jan 26, 2015, and Nov 5, 2015, 103 heavily pretreated 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% CI: 1.8-5.9) in the trabectedin arm *vs* 1.5 months (0.9-2.6) 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 *vs* 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 transaminases increase (32.7%). Health-related EORTC QLQ-C30 QoL questionnaires 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.

ClinicalTrials.gov Identifier: NCT02672527; EudraCT N°: 2014-003176-23

Keywords: Soft tissue sarcoma, randomized trial, trabectedin

HIGHLIGHTS

- In adults with soft tissue sarcoma, trabectedin significantly prolonged PFS as compared to best supportive care (BSC)
- Overall, 13.7% achieved a partial response in the trabectedin arm, while no objective response was observed in the BSC arm
- Benefits were observed across most of analyzed subgroups, but particularly in patients with lipo/leiomyosarcoma
- Quality of life (QoL) questionnaire evidenced no statistical difference between the arms for any domain or time point
- Trabectedin has superior disease control to BSC in patients with recurrent STS of multiple histologies

INTRODUCTION

Trabectedin (Yondelis®) is the first anticancer marine-derived drug, approved in the European Union in 2007 and currently 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 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 U.S. Food and Drug Administration.[2] Trabectedin has a pleiotropic mechanism of action that, in addition to induce 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 performed 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 best supportive care (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 a 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 7th October2014) and the French Drug Agency (approval by the Agence Nationale de Sécurité des Médicaments on 22nd October 2014). Signed informed consents were obtained from all study participants before registration.

Patients

Eligible patients were adults (≥18 years old) with histologically proven ASTS; unresectable and/or metastatic relapse or progressive disease (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 Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[10] an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, and adequate hematologic, renal and hepatic function (neutrophil count ≥1,500/mm^3, hemoglobin ≥9 g/dl, platelets counts ≥100,000/mm^3, creatinine clearance ≥30 ml/min, creatine phosphokinase ≤2.5 X upper limit of normal [ULN], bilirubin ≤ULN, alanine aminotransferase [ALT]/aspartate aminotransferase [AST] ≤2.5 X ULN, alkaline phosphatase ≤2.5 X ULN), albumin ≥25 g/l), and normal left ventricular ejection fraction.

Treatments and study procedures

Trabectedin was administered at the recommended dose of 1.5 mg/m² body surface area through a central venous line as a 24-hour continuous infusion every three weeks. Prophylaxis with corticosteroids (e.g., dexamethasone 20 mg intravenously 30 minutes before trabectedin) and an antiemetic 5-HT3 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 x ULN, grade 4 thrombocytopenia, increase of ALT/AST >2.5 ULN not reversed to baseline values by day 21, and any other ≥grade 3 adverse reaction. At first occurrence of toxicity, the dose was reduced to 1.2 mg/m² in the following cycles, and in case of re-appearance of any toxicity, the dose was further reduced to 1.0 mg/m², then to 0.8 mg/m² 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 progressive disease (PD) according to

RECIST v. 1.1[10], severe toxicity, consent withdrawal, or patient death. In the BSC arm, patients could not receive anti-tumor 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 performed by computerized tomography scans, every three weeks during the first two cycles and then every six 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 performed closest to the follow-up period and prior to 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 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 term 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 treatment start 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 (NCI-CTC), 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 performed when 87 progression or death events were observed in about 100 patients. The primary efficacy analyses were performed 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 evaluable for efficacy if they had at least one assessment of tumor response. We carried out two analyses: first, the analysis of the primary efficacy endpoint (i.e. PFS) was performed 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 performed after a median follow-up of 26 months (range: 0.46-31.1) and concerned all the other endpoints 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 Chi2 test, while Fisher's exact test was used if non-validity of the conditions for applying Chi2 test. A multivariate Cox proportional hazard model, stratified by the histological subtype of sarcoma (L-STS *vs* 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, gender 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) and R software (v. 3.1.2, for the survival curves).

Role of the funding source

The T-SAR was a 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 January 26, 2015, to November 05, 2015, a total of 103 patients with pretreated ASTS were enrolled by 16 FSG centers and allocated to receive either trabectedin (*N*=52) or BSC (*N*=51). All patients were analyzed in an ITT basis for the assessment of PFS and OS (Figure 1). Two patients discontinued the study right after their randomization in 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 3^{rd}-4^{th} line *vs*. 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% *vs* 58.8%, respectively) *vs* non-L-STS (38.5% *vs* 41.2%) and the proportion of patients with metastatic disease (92.3% *vs* 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) over a median treatment duration of 10.1 weeks (range: 3-77.9; IQR: 4.4-31.6), 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% 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 1st 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% 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; IQR: 0.35-05) over a median treatment duration of 12.0 weeks (range: 3-152.0; IQR: 6-26.9), which corresponded to 81.0% of the planned dose intensity. Similar to what 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 prior to 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% *vs* 0%) and erythropoietin (10.2% *vs* 0%) as compared with BSC , while more patients from the BSC arm received antidepressants (25.2% *vs* 7.7%) and hypnotics (15.1% *vs* 4.0%) as compared with trabectedin arm (Supplementary Table S1).

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 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) (HR=0.39, 95% 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 median PFS in the trabectedin arm of 5.1 months 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 observed in patients with non-L-STS (1.8 *vs* 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).

There were no CRs in either treatment group. Among 51 patients evaluable for response from the trabectedin arm, seven patients achieved a PR reaching an ORR of 13.7%, while no objective responses were observed in 49 evaluable 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 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 trabectedin arm *vs* 10.8 months for 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 neutropenia (*N*=23, 44.2%), including four episodes of febrile neutropenia (7.7%), leukopenia (*N*=18, 34.6%), and transaminases 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 transaminases 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 eight months decreased to 59% in the trabectedin

arm and 63% in the BSC arm, respectively. 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).

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 pre-treated 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) 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 arm: 5.1 *vs* 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 those reported in a registration phase II trial[1] and a pivotal, dacarbazine-controlled, phase III U.S. trial,[2] which in patients with L-STS reported a median PFS of 3.3 months and 4.2 months, respectively. Herein 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]

In the present study, the number of patients who received >6 cycles (28.8% *vs* 10.2%), >9 (23.1% *vs* 2.0%) or >12 (9.6% *vs* 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] Those 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 term 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 improve in disease control, numbers of studies performed 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 transaminases elevation were the most frequently reported grade 3/4 AEs in this study. Those 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 preplanned PFS analysis showed a significant improvement in median PFS with trabectedin over BSC in heavily pre-treated patients with advanced STS. The largest impact on PFS was been observed in the L-STS cohort, in whom trabectedin historically has reached the highest range of activity.

ACKNOWLEDGMENTS

This study was funded by PharmaMar, S.A. Medical writing support and editorial assistance was provided by Adnan Tanović and Agnès Laplanche for providing statistical assistance.

FUNDING

This work was supported by PharmaMar, S.A., which provided trabectedin for the randomized part of the trial (no grant number is applicable).

DISCLOSURE

ALC has received honoraria from Deciphera, Bayer, and PharmaMar. JYB has received research support and honoraria from PharmaMar, Bayer, and Eisai. IRC reports research support and honoraria from PharmaMar, Roche, Astra Zeneca, Clovis, GSK, Mersana, Deciphera, Genentech, Advaxis, MSD, and BMS. OM has served as consultant for Amgen, Astra-Zeneca, 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 remaining 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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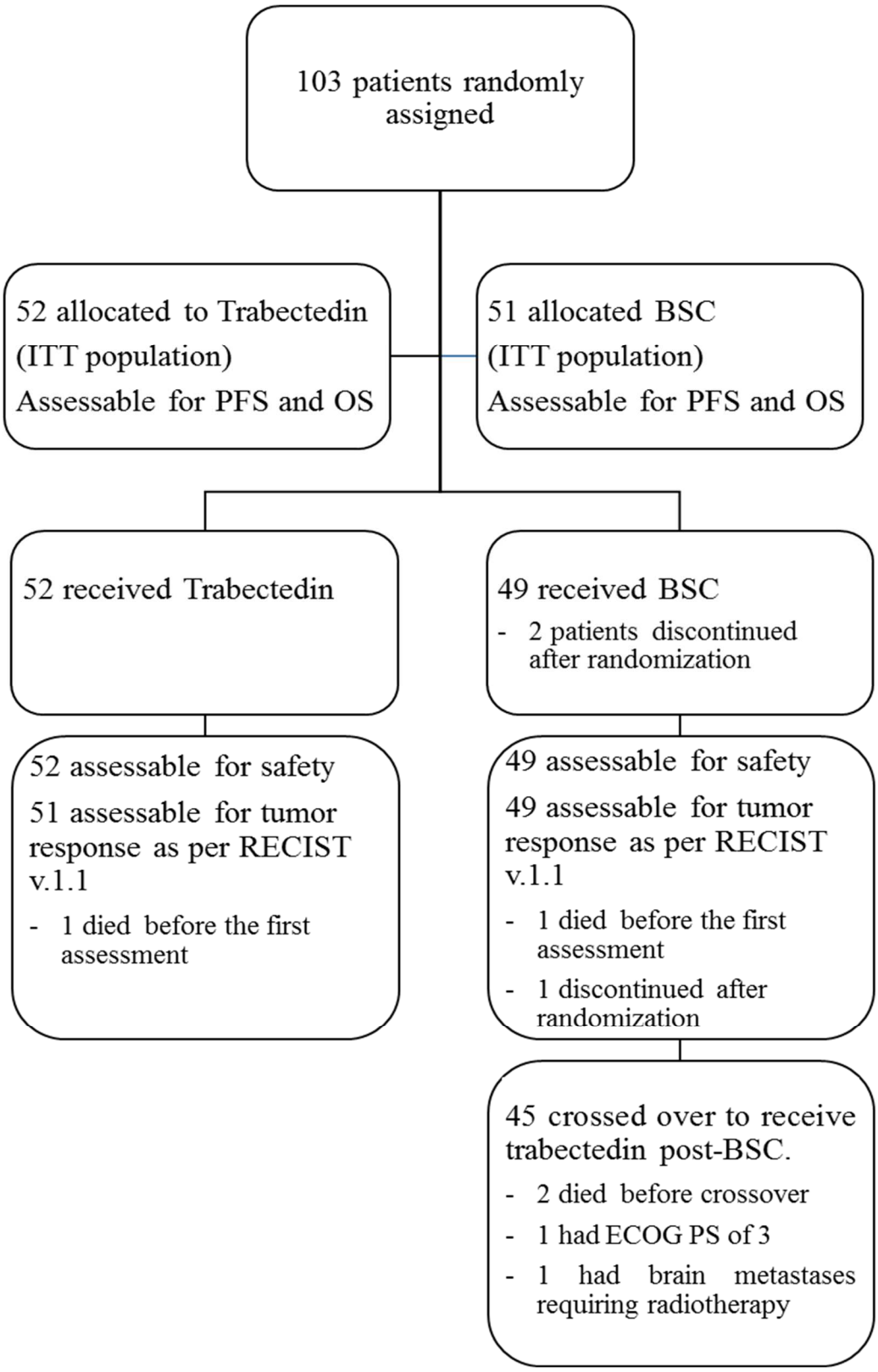
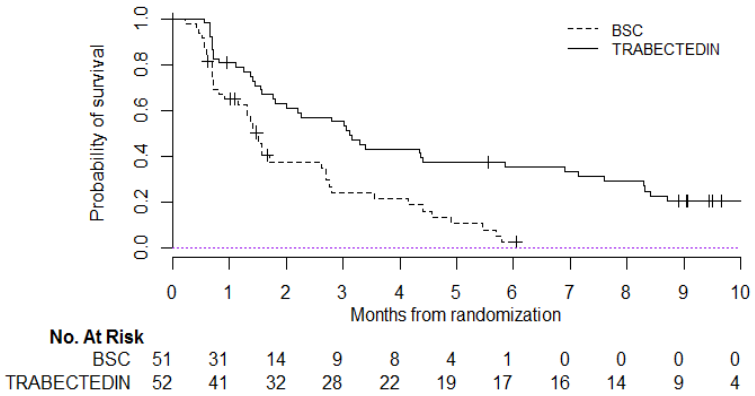
Figure 1. Description of included patients



ECOG PS, Eastern Cooperative Oncology Group performance status; BSC, best supportive care; ITT, intention to treat; OS, Overall survival; PFS, progression-free survival; RECIST v.1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 2. Kaplan-Meier plots of progression-free survival by central radiology review

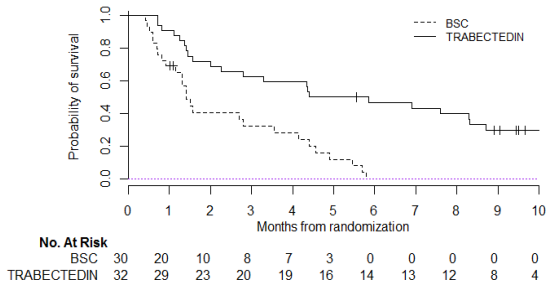
Progression-free survival (PFS); ITT population



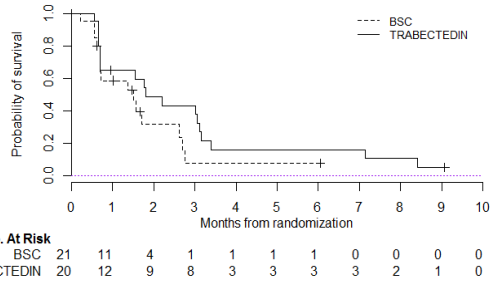
Parameter; *N* (%)	Patients with events	Censored	Median PFS (months) (95% CI)	PFS at 3 months (95% CI)	PFS at 6 months (95% CI)	*P*-value [a]	HR (95% IC)	*P*-value [b]
Evaluable patients, *N*=103	83 (80.6%)	20 (19.4%)	2.2 (1.5-3.0)	41% (32-51)	21% (14-31)	-	-	-
Therapeutic arm						<0.0001		0.0001
Trabectedin (*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	

PFS as per type of sarcoma histology; ITT population

L-STS



non-L-STS

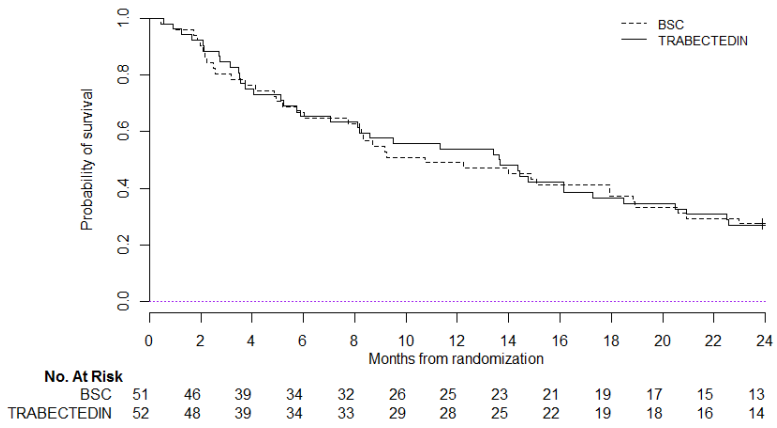


Parameter; *N* (%) Evaluable patients, *N*=103	Patients with events	Censored	Median PFS (months) (95% CI)	PFS at 3 months (95% CI)	PFS at 6 months (95% CI)	*P*-value [a]	HR (95% IC)	*P*-value [b]
L-STS								
Therapeutic arm						<0.0001		0.0001
Trabectedin (*N*=32)	24 (75.0%)	8 (25.0%)	5.1 (2.0-8.3)	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	

BSC, best supportive care; CI, confidence interval; HR, hazard ratio, ITT, intention to treat; L-STS, leiomyosarcoma and liposarcoma.
[a] Log-rank test stratified by the "histological subtype" stratification factor (L-STS *vs* non-L-STS). [b] The Hazard Ratio for trabectedin *vs* BSC was estimated with a Cox model, stratified by the "histological subtype" stratification factor (L-STS *vs* non-L-STS).

Figure 3. Kaplan-Meier plots of overall survival

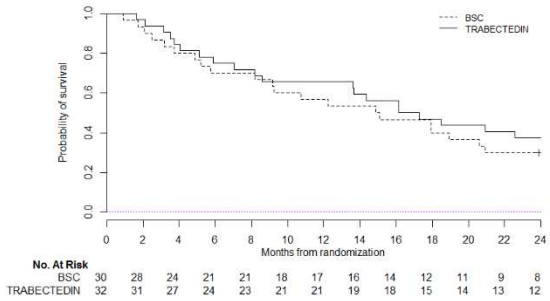
Overall survival (OS); ITT population



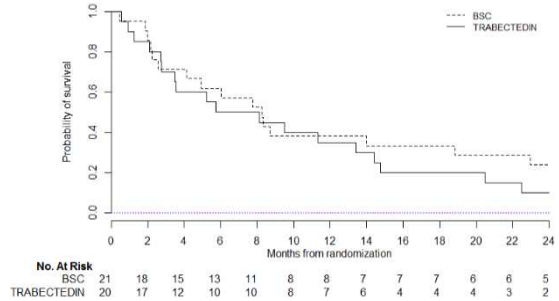
Parameter; *N* (%)	Death events	Censored	Median OS (months) (95% CI)	*P*-value [a]	HR (95% IC)	*P*-value [b]
Evaluable patients, *N*=103	81 (78.6%)	22 (21.4%)	13.4 (8.3-16.1)	-	-	-
Therapeutic arm				0.87		0.87
Trabectedin (*N*=52)	41 (78.8%)	11 (21.2%)	13.6 (7.1-17.3)		1.04 (0.67-1.61)	
BSC (*N*=51)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

OS as per type of sarcoma histology; ITT population

L-STS



non-L-STS



Parameter; *N* (%) Evaluable patients, *N*=103	Death events	Censored	Median OS (months) (95% CI)	*P*-value [a]	HR (95% IC)	*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	

BSC, best supportive care; CI, confidence interval; HR, hazard ratio, ITT, intention to treat; L-STS, leiomyosarcoma and liposarcoma, NR, not reached.

[a] Log-rank test stratified by the "histological subtype" stratification factor (L-STS *vs* non-L-STS). [b] The Hazard Ratio for trabectedin *vs* BSC was estimated with a Cox model, stratified by the "histological subtype" stratification factor (L-STS *vs* non-L-STS).

Table 1. Patient and disease characteristics at baseline

Patients		Trabectedin *N*=52	Best supportive care *N*=51	Total *N*=103
Gender	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	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	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	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	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	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 (-1.4-174.7)	17.3 (-0.6-124.8)	13.9 (-1.4-74.7)
Prior chemotherapy	Neoadjuvant / adjuvant	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	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	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 value 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. [d] One patient from the trabectedin arm was considered missing for prior ifosfamide, gemcitabine ± docetaxel, dacarbazine or pazopanib.

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	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 (%)	<80%	18 (34.6%)	-	-	21 (46.7%)
	≥80%	34 (65.4%)	-	-	24 (53.3%)
Total cycles	Nº of cycles	274	139	413	285
Dose modification and cycles delayed (per cycle)	Nº of 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	Yes	52 (100%)	49 (100%)	101 (100%)	-
Reason for end of treatment of the randomized part	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 1st 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 1st trabectedin cycle, whereas two deaths occurred in the BSC during the 1st cycle due to disease progression. [e] One treatment discontinuation for delay of >6 weeks in administering trabectedin and another owing to reduction of the ventricular ejection fraction.

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]
Partial response (PR); *N* (%)	7 (13.7)	0	7 (7)	
Stable disease (SD); *N* (%)	34 (66.7)	30 (61.2)	64 (64)	
Progressive disease (PD); *N* (%)	10 (19.6)	19 (38.8)	29 (29)	
Objective response rate (% ORR); [95% CI]	13.7 [5.7-26.3]	0	7.0 [2.8-13.9]	0.013 [a]
Disease control rate (% 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]
Partial response (PR); *N* (%)	7 (21.9)	0	7 (11.7)	
Stable disease (SD); *N* (%)	21 (65.6)	18 (64.3)	39 (65)	
Progressive disease (PD); *N* (%)	4 (12.5)	10 (35.7)	14 (23.3)	
Objective response rate (% ORR); [95% CI]	21.9 [9.3-40.0]	0	11.7 [4.8-22.6]	0.012 [a]
Disease control rate (% 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]
Stable disease (SD); *N* (%)	13 (68.4)	12 (57.1)	25 (62.5)	
Progressive disease (PD); *N* (%)	6 (31.6)	9 (42.9)	15 (37.5)	
Disease control rate (% 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.
[a] Fisher exact test [b] Chi Square test. [c] Log-rank