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ORIGINAL RESEARCH

A single-arm multicentre phase II trial of doxorubicin in combination with trabectedin in the first-line treatment for leiomyosarcoma with long-term follow-up and impact of cytoreductive surgery☆

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Background: Uterine leiomyosarcomas (U-LMSs) and soft tissue leiomyosarcomas (ST-LMSs) are rare tumours with poor prognosis when locally advanced or metastatic, and with moderate chemosensitivity. In 2015 we reported very encouraging results of the LMS-02 study (NCT02131480) with manageable toxicity. Herein, we report the updated and long-term results of progression-free survival (PFS) and overall survival (OS).

Patients and methods: Patients received 60 mg/m^2 intravenous doxorubicin followed by trabectedin 1.1 mg/m^2 as a 3-h infusion on day 1 and pegfilgrastim on day 2, every 3 weeks, up to six cycles. Surgery for residual disease was permitted. Patients were stratified into U-LMS and ST-LMS groups.

Results: One-hundred and eight patients were enrolled, mainly with metastatic disease (85%), and 20 patients (18.5%) had surgical resection of metastases after chemotherapy. With a median follow-up of 7.2 years [95% confidence interval (CI) 6.9-8.2 years], the median PFS was 10.1 months (95% CI 8.5-12.6 months) in the whole population, and 8.3 months (95% CI 7.4-10.3 months) and 12.9 months (95% CI 9.2-14.1 months) for U-LMSs and ST-LMSs, respectively. The median OS was 34.4 months (95% CI 26.9-42.7 months), 27.5 months (95% CI 17.9-38.2 months), and 38.7 months (95% CI 31.0-52.9 months) for the whole population, U-LMSs, and ST-LMSs, respectively. The median OS of the patients with resected metastases was not reached versus 31.6 months in the overall population without surgery (95% CI 23.9-35.4 months).

Conclusions: These updated results confirm the impressive efficiency of the doxorubicin plus trabectedin combination given in first-line therapy for patients with locally advanced/metastatic LMS in terms of PFS and OS. Results of the LMS04 trial (NCT02997358), a randomized phase III study comparing the doxorubicin plus trabectedin combination versus doxorubicin alone in first-line therapy in metastatic LMSs, are pending.

Key words: leiomyosarcoma, first-line chemotherapy, doxorubicin plus trabectedin

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☆ Note: This study was previously presented at:
– the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2013 (oral presentation First results in patients with u-LMS);
– the Annual Meeting of the European Cancer Organization (ECCO) in 2013 (results of the soft tissue group: Poster);
– the Annual Meeting of the Connective Tissue Oncology Society (CTOS) in 2013 (oral presentation of both groups);
– the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2020 (oral update results with overall survival).

INTRODUCTION

Soft tissue sarcomas (STSs) represent a rare and heterogeneous group of tumours which includes different tumour entities with considerable differences in terms of clinical behaviour and genetic variances. Leiomyosarcomas (LMSs) represent almost a quarter of STSs among which uterine location is frequent.[1,2]

LMSs have a poor prognosis when being metastatic or locally advanced. With some exception, systemic chemotherapy for the different STS subtypes is largely similar, with doxorubicin and ifosfamide or dacarbazine being the backbone of treatment.[3,4]

Although gene expression patterns differ between uterine LMSs (U-LMSs) and non-U-LMSs,[5] both are judged to be moderately sensitive to conventional chemotherapy. In metastatic LMS, the first-line treatments with doxorubicin, gemcitabine, or dacarbazine report objective response rates of ∼15%-17% (i.e. complete or partial responses), with a median progression-free survival (PFS) of ∼5 months, and a median overall survival (OS) of ∼12 months.[6,7]

New associations have been tested with and without doxorubicin, but to date, none of these combinations with doxorubicin, nor new associations are superior to doxorubicin alone in terms of OS.[3,4,8-10] A more recent approach is to dedicate a specific study to a specific histology as for alveolar soft part sarcoma, angiosarcoma, clear cell sarcoma, liposarcoma, translocation-related sarcomas, undifferentiated pleomorphic sarcoma, and U-LMS.[11] To our knowledge, no specific study has been conducted in first-line therapy for metastatic/relapsed LMSs, except for uterine LMSs.[12]

Trabectedin has shown activity in STS, with ∼10% of patients achieving an objective response after failure of doxorubicin and ifosfamide, and some studies have suggested greater activity in pretreated LMSs than in other histological subtypes, with a 6-month PFS of 26%-30%.[13,14]

In uterine LMSs, first-line trabectedin is associated with ∼10% of patients achieving an objective response, a median PFS of 5.8 months, and a median OS >26 months.[15]

Preclinical data also suggest that the association of trabectedin and doxorubicin is an effective combination in sarcoma.[16,17] Findings from two phase I studies showed that the combination was feasible when given with granulocyte colony-stimulating factor.[18,19] Encouraging efficacy was described in patients with STSs, particularly in liposarcoma and LMS, with 3- and 6-month PFS rates of 85% and 58%, respectively.

These data therefore provided the rationale for the French Sarcoma Group to perform a single-arm, multicentre, phase II study (LMS-02) of doxorubicin combined with trabectedin as a first-line treatment in metastatic or locally advanced U-LMS or soft tissue LMS (ST-LMS).

As some phase II studies reported that uterine LMS might be more chemosensitive than other LMS sites, we performed a stratification by primary site.[20]

Patients eligible were those with metastatic or unresectable LMS and who had not received any previous chemotherapy for adjuvant or metastatic disease.

A minimum of 107 patients had to be included in the trial, 45 with a U-LMS and 62 with an ST-LMS. In the two groups, analyses were conducted by the intention-to-treat protocol according to the Simon 'optimum design' multistage process.[21]

Our objective was to conclude on the efficacy of this combination, that is, whether this combination led to a disease control rate of at least 70% in the uterine group and 60% in the soft tissue group.

In 2015, we reported the first results in response rate and median PFS (primary endpoint) of this LMS02 trial (ClinicalTrials.gov Identifier: NCT02131480), with very interesting results on response rates, disease control rate, and PFS rate in both groups.[22]

With a median follow-up of 7.2 years, we report here the updated results on PFS and OS of the LMS02 study. A total of 91 patients died during the study period (40/47 in the uterine group and 51/61 in the soft tissue group).

METHODS

Statistical analysis

The study was stratified by primary tumour location: U-LMSs versus ST-LMSs. Each stratum of the study was considered as an independent phase II study. A two-stage Simon optimum design has been used for each of the two strata, but with different hypotheses for the two cohorts.

A minimum of 107 patients had to be included: 45 with a U-LMS and 62 with an ST-LMS. The study was considered positive if the disease control rate was at least 70% for the uterine cohort and 60% for the soft tissue cohort.

In the uterine study, the assumed baseline response rate was 50%. The study was planned as a two-stage plan. To have both α and β risk at 10%, 45 patients were planned to be included. The study would be considered positive if at least 27/45 patients responded or had stable disease.

In the soft tissue study, the assumed baseline response rate was 40%. The study was planned as a two-stage plan. To have an α risk at 10% and a β risk at 5%, 62 patients were required. The study would be considered positive if at least 29/62 patients responded or had stable disease.

Analysed patients

All patients provided written informed consent and the study was performed in accordance with the ethical principles of the Declaration of Helsinki. An analysis was conducted by the intention-to-treat protocol. In order to be considered assessable for response, patients must have received at least one cycle of treatment. Time-to-event variables will be analysed according to the Kaplan—Meier method.

No information about subsequent lines of therapy was collected.

Between 28 July 2010, and 10 May 2013, 109 patients were enrolled and treated, of whom 108 were assessable for response. Most patients had a metastatic disease (82.4%), and 20 patients (18.5%) had surgical resection of metastases after chemotherapy. The final analysis included 47 patients with a U-LMS and 61 with an ST-LMS (Table 1). A total of 32 (68%) patients in the uterine group and 45 (74%) in the soft tissue group received all six cycles of treatment.[22]

Patients were treated on day 1 with an intravenous administration of doxorubicin (60 mg/m^2) followed by a 3-h infusion of trabectedin (1.1 mg/m^2) repeated every 3 weeks, and pegfilgrastim (6 mg) administration on day 2. Surgery for residual disease was permitted. Treatment was performed (outpatient schedule) every 3 weeks for a maximum of six cycles. Dose modifications or reductions were needed for 76 (14%) of 557 cycles given and in 55 (51%) of 108 patients.

Table 1. Characteristics of patients

Patients	Uterine ($n = 47$)	Soft tissue ($n = 61$)
Age (years), median (range)	58 (35-73)	59 (32-77)
Performance status, *n* (%)		
0	32 (68)	37 (62)
1/2	10 (21)/2 (4)	22 (37)/1 (1)
Female, *n* (%)	47 (100)	40 (66)
Grade 1/2-3, *n* (%)	NA	8 (13)/47 (77)
Site of primary		
Uterine, *n* (%)	47 (100)	0 (0)
Extremity/retroperitoneal/pelvis, *n*	NA	13/16/7
Visceral/other, *n*	NA	15/10
Pelvic radiotherapy, *n* (%)	17 (36)	NA
Metastatic disease, *n* (%)	37 (79)	52 (85)
Lung/liver, *n* (%)	33 (70)/13 (28)	42 (69)/24 (39)
Bone/cutaneous/other, *n*	8/2/13	6/4/13

NA, not adapted.

Disease evaluation was performed every two cycles.

The primary endpoint was the proportion of patients who achieved disease control (i.e. disease control rate), defined as those achieving a complete or partial response or stable disease, with stratification by site (i.e. uterine and extrauterine).

Secondary endpoints were OS, defined as the time from inclusion to death from any cause, and PFS, defined as the time from inclusion to disease progression or death from any cause.

Patients had to have a physiological age <70 years and a good performance status (Eastern Cooperative Oncology Group performance status ≤ 2).

The results published in 2015 were very encouraging: 28/47 patients with U-LMS [59.6%; 95% confidence interval (CI) 44.3%-73.695%] achieved a partial response, 13/47 [27.7%; 95% CI 15.6%-42.6%)] a stable disease, and 41/47 (87.2%; 95% CI 74.3%-95.2%) a disease control. Of 61 patients with ST-LMS, 2 (3.3%; 95% CI 0.4%-11.7%) achieved a complete response, 22 (36.1%; 95% CI 25.0%-50.8%) a partial response, 32 (52.5%; 95% CI 40.8%-67.3%) a stable disease, and 56 (91.8%; 95% CI 81.9%-97.3%) a disease control.[22]

Toxicities were predominantly haematological and hepatic.

RESULTS

With a median follow-up of 7.2 years, median PFS was 10.1 months (95% CI 8.5-12.6 months) in the overall population, 8.3 months (95% CI 7.4-10.3 months) in the uterine population, and 12.9 months (95% CI 9.2-14.1 months) in the STS population (Figure 1).

The median OS was 34.4 months (95% CI 26.9-42.7 months) in the overall population, 27.5 months (95% CI 17.9-38.2 months) in the uterine group, and 38.7 months (95% CI 31.0-52.9 months) in the ST group (Figure 2).

We also evaluated the impact of complete surgical resection of metastases at the end of chemotherapy regimen.

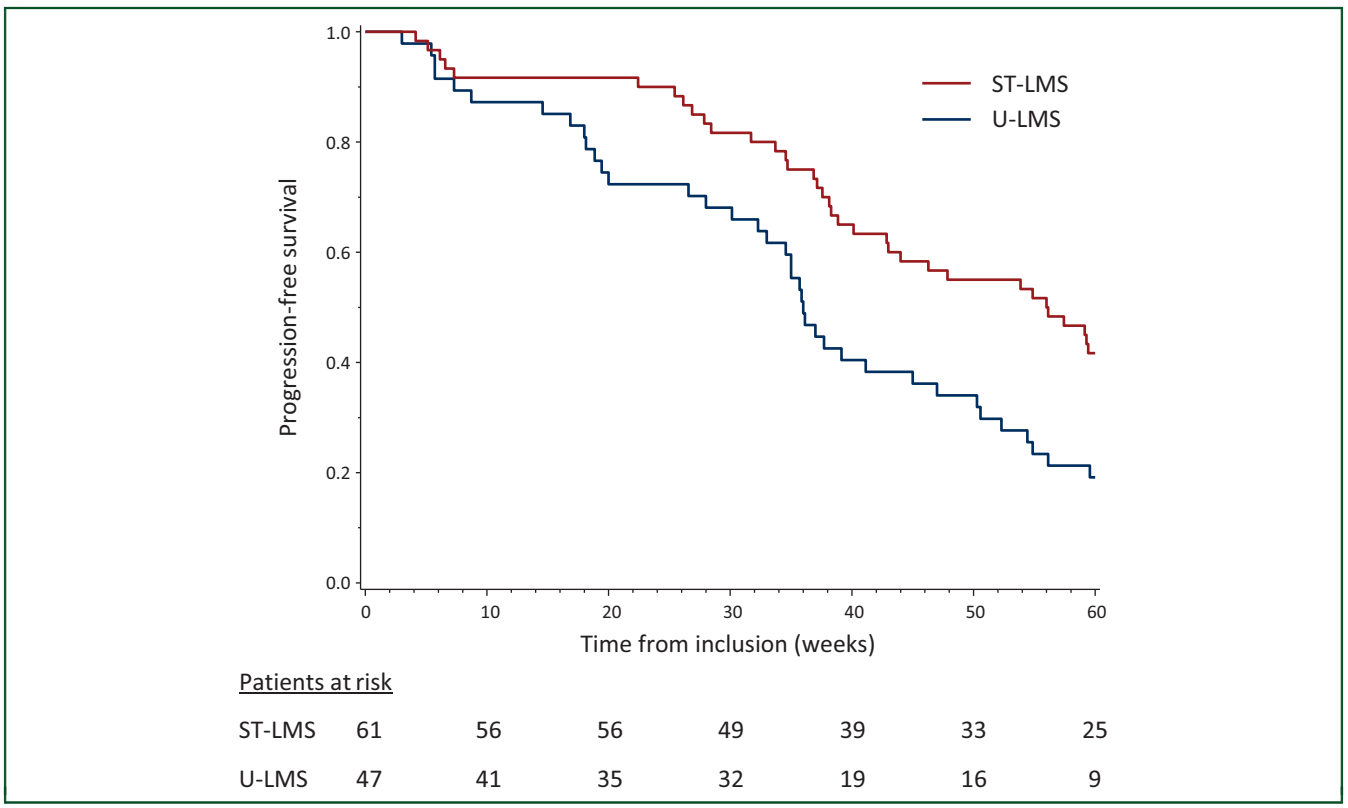

Figure 1. PFS (weeks) according to localization (uterine and soft tissue LMS).
Median PFS was 10.1 months (95% CI 8.5-12.6 months) in the entire population, 8.3 months (95% CI 7.4-10.3 months) in the uterine population, and 12.9 months (95% CI 9.2-14.1 months) in the STS population.
CI, confidence interval; LMS, leiomyosarcoma; STS, soft tissue sarcoma; ST-LMS, soft tissue leiomyosarcoma; PFS, progression-free survival; U-LMS, uterine leiomyosarcoma.

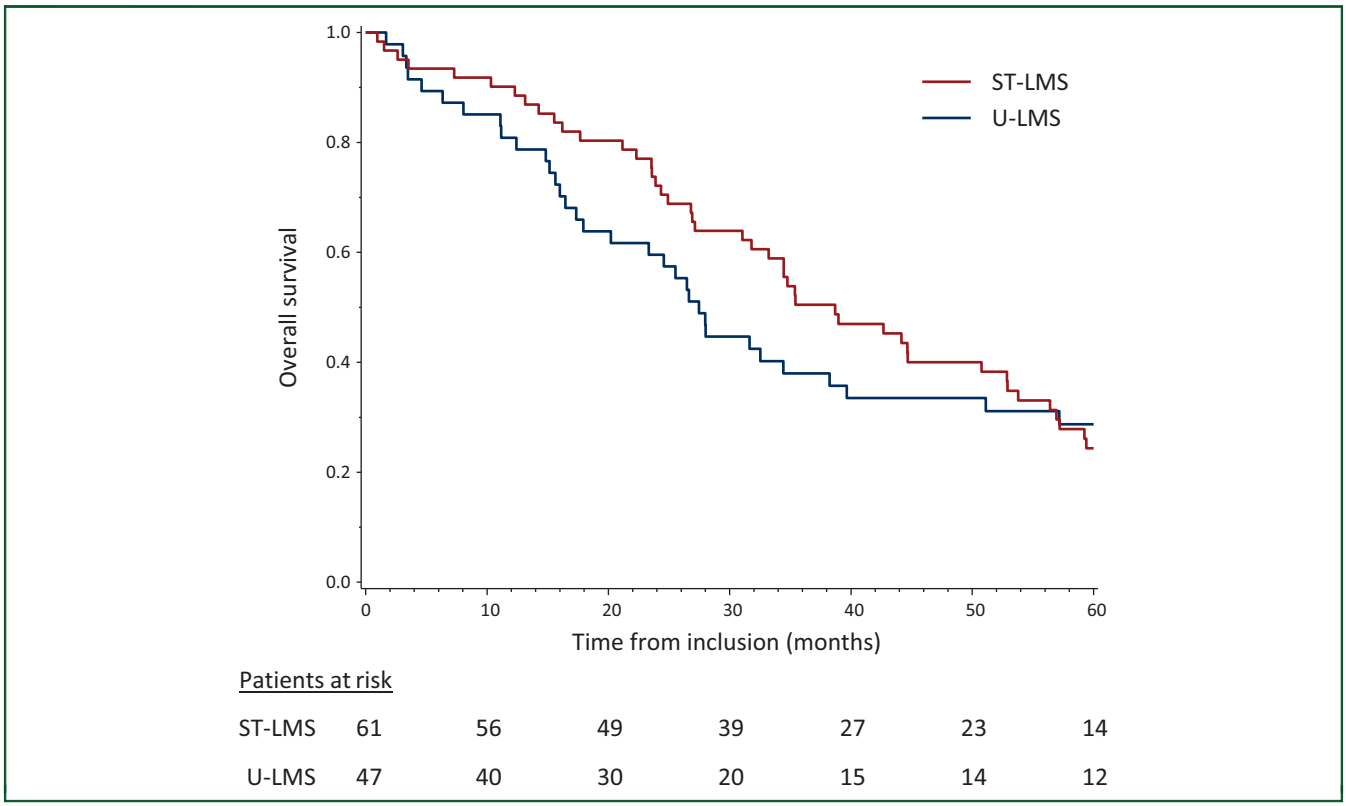

Figure 2. OS (months) according to localization (uterine and soft tissue LMS).
Median OS: 34.4 months (95% CI 26.9-42.7 months] in the overall population, 27.5 months (95% CI 17.9-38.2 months) in the uterine group, and 38.7 months (95% CI 31.0-52.9 months) in the ST group respectively.
CI, confidence interval; LMS, leiomyosarcoma; OS, overall survival ST, soft tissue; ST-LMS, soft tissue leiomyosarcoma; STS, soft tissue sarcoma; U-LMS, uterine leiomyosarcoma.

Table 2. Progression-free survival and overall survival according to surgery

	Uterine LMS *N* = 46[a]		Soft tissue LMS *N* = 61	
PFS (95% CI)	No surgery (*n* = 38)	Surgery (*n* = 8)	No surgery (*n* = 49)	Surgery (*n* = 12)
Median (95% CI)	8.0 months (6.1-8.7 months)	12.9 months (0.7-NR months)	10.6 months (8.8-13.6 months)	24.8 months (7.3-NR)
OS (95% CI)	No surgery (*n* = 38)	Surgery (*n* = 8)	No surgery (*n* = 49)	Surgery (*n* = 12)
At 2 years (95% CI)	55.3% (39.7%-69.9%)	75% (40.9%-92.9%)	65.3% (51.3%-77.1%)	100%
Median (95% CI)	36.6 months (16.5-32.5 months)	NR	34.8 months (24.3-44.2 months)	NR

CI, confidence interval; LMS, leiomyosarcoma; NR, not reached; OS, overall survival; PFS, progression-free survival.
[a] Unknown for one patient.

Surgery was performed at the end of the six chemotherapy cycles in 20% of the patients (8/46 UT-LMS and 12/61 ST-LMS). Surgery was performed on the primary site alone in nine cases (2 UT-LMS + 7 ST-LMS), on metastatic sites in eight cases (4 UT-LMS + 4 ST-LMS), and on both sites in two cases (2 UT-LMS). Surgery was also performed on one ST-LMS case with unknown localization. There were clinical complete responses associated with histological complete responses in six cases (2 UT-LMS + 4 ST-LMS).

Results of PFS and OS were better in patients with oligometastatic disease who could benefit from surgery of all metastases: median PFS was 8.8 months (95% CI 8.0-10.8 months) for patients without surgery versus 18.2 months (95% CI 9.5-54.5 months) when surgery was performed; the impact seemed to be more important for ST-LMS, especially for OS. The median OS was 31.6 months (95% CI 23.9-35.4 months) for patients without surgery versus not reached when surgery was performed (Table 2).

DISCUSSION

In this homogeneous series of 107 patients with advanced/metastatic U-LMSs and ST-LMSs, efficacy results of trabectedin plus doxorubicin in first-line therapy are very

encouraging. After a follow-up of 7.2 years, the median PFS is 10.1 months (95% CI 8.5-12.6 months) and the median OS is 34.4 months (95% CI 26.9-42.7 months).

Until the start of LMS02 trial, there were different published randomized controlled trials in the first-line treatment of STSs (of several histologies); however, none of these showed a survival advantage for any schedule over single-agent doxorubicin treatment.

There are a few studies carried out at the same period in the first-line treatment of STSs with LMS cohorts or in specific LMS population: the reported median OS in this setting in the LMS population was 22-29 months[8,10] with doxorubicin alone, and 23 months using the combination of doxorubicin and evofosfamide.[8]

In the GeDDiS study,[9] the association of gemcitabine and docetaxel was compared with doxorubicin as a first-line treatment in previously untreated advanced unresectable or metastatic STSs in a randomized controlled phase III trial. For the overall population, the association does not show better performance than doxorubicin alone in terms of OS; however, it had a higher toxicity. Patients were stratified by histological subtype (LMS versus synovial sarcoma versus pleomorphic sarcoma versus other eligible sarcomas) and irrespective of the subtype, the combination of gemcitabine and docetaxel did not do better than doxorubicin alone but demonstrated a higher toxicity.

A randomized phase II trial[23] compared doxorubicin with doxorubicin and trabectedin in different histologic STS subtypes, but without published data on OS.

A phase IIb multicentre study compared the efficacy of trabectedin alone (2 arms: 3-h infusion and 24-h infusion) with doxorubicin in patients with advanced or metastatic untreated STS (TRUSTS trial). However, the study was terminated due to lack of superiority in both trabectedin treatment arms, as compared with the doxorubicin control arm.

A recent propensity score matching analysis of the EORTC STBSG group compared the retrospective results of different doxorubicin-based regimens given as first-line treatment for advanced LMS.[6] Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone showed favourable activity of the doxorubicin plus dacarbazine combination in terms of both objective response rate and PFS, but these warrant further evaluation in prospective trials. Indeed, with the limitations of a retrospective analysis, doxorubicin plus dacarbazine was associated with a median OS of 36.8 months (95% CI 27.9-47.2 months) in comparison with a median OS of 21.9 months (95% CI 16.7-33.4 months) for the doxorubicin plus ifosfamide combination and a median OS of 30.3 months (95% CI 21.0-36.3 months) for doxorubicin alone.

Our study also confirms that, as described by some authors,[20] despite a higher response rate, metastatic uterine LMSs have poorer prognosis than ST-LMS [OS of 27.5 months (95% CI 17.9-38.2 months) in the uterine group and 38.7 months (95% CI 31.0-52.9 months) in the soft tissue group]. This result can justify a stratification on this factor for future studies conducted in LMSs.

The impact of surgery after response or stability seems to be positive according to the good results on PFS, but the analysis regarding the impact of surgery should be critically discussed owing to its limitation of a small number of patients and also because patients with oligometastatic disease might have in general a better prognosis.

The weakness of the study is that it is a nonrandomized phase II study. We performed the LMS04 trial, a randomized phase III study comparing the doxorubicin plus trabectedin combination followed by trabectedin with doxorubicin alone as first-line therapy in metastatic LMSs with a stratification (U-LMS versus ST-LMS).

The strengths are the homogeneity of the population while focussing on a unique STS subtype; the latter seems to be the most sensitive (with liposarcoma) to trabectedin and the most susceptible to benefit from the association with doxorubicin. Other strengths are the analysis of two populations (i.e. U-LMS and ST-LMS), and the 'real-life' design with the possibility to operate nonprogressive patients after chemotherapy.

In conclusion, the LMS02 study is a new association tested in first-line ST-LMSs with interesting results in terms of response rate, PFS, and OS.

The results of the randomised phase III study in the same population are pending (NCT02997358), and could possibly change the standard of care of first-line therapy in metastatic LMSs.

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DISCLOSURE

The authors have declared no conflicts of interest.

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