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

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For the French Sarcoma Group.

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Running head: first-line chemotherapy for metastatic or advanced leiomyosarcoma.

Study was 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 OS).

Highlights:

Long-term results on PFS and OS of doxorubicin and trabectedin in first line treatment for advanced leiomyosarcoma

Abstract:

Background: uterine leiomyosarcomas (U-LMS) and soft tissue leiomyosarcomas (ST-LMS) are rare tumors 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).

Methods: Patients (pts) received 60 mg/m² intravenous doxorubicin followed by trabectedin 1.1 mg/m² as a 3-hour infusion on Day 1 and pelfilgastrim on day 2, every 3 weeks, up to 6 cycles. Surgery for residual disease was permitted. Patients were stratified into U-LMS and ST-LMS groups.

Results: 108 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% CI: 6.9 - 8.2), the median PFS was 10.1 months (95% CI: 8.5 - 12.6) in the whole population, and 8.3 (95% CI: 7.4 - 10.3) and 12.9 months (95% CI: 9.2 - 14.1) for U-LMS and ST-LMS, respectively. Respective median OS were 34.4 months (95% CI: 26.9 - 42.7), and 27.5 (95% CI: 17.9 - 38.2) and 38.7 months (95% CI: 31.0 - 52.9) for U-LMS and ST-LMS. The median OS of the pts with resected metastases was not reached *versus* 31.6 months in the overall population without surgery (95% IC: 23.9 - 35.4).

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

Keywords: leiomyosarcoma, first line chemotherapy, doxorubicine plus trabectedine

Introduction

Soft tissue sarcomas (STS) 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 (LMS) represent almost a quarter of STS among which uterine location is frequent.^{1,2}

LMS 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 and non-uterine leiomyosarcomas⁵, 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 about 15-17% (i.e., complete or partial responses), with a median of progression-free survival (PFS) of about 5 months, and of overall survival (OS) of about 12 months.^{6,7}

New associations have been tested with and without doxorubicin, but up to date, neither combination with doxorubicin, nor new association are superior to doxorubicin alone in term 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 uterine leiomyosarcoma.¹¹ To our knowledge, no specific study has been conducted in first-line therapy for metastatic/relapsed LMS, except for uterine LMS.¹²

Trabectedin has shown activity in STS, with about 10% of patients achieving an objective response after failure of doxorubicin and ifosfamide; and some studies suggested greater activity in pretreated LMS than in other histological subtypes, with a 6-month PFS of 26–30%.^{13,14}

In uterine LMS, first-line trabectedin is associated with about 10% of patients achieving an objective response, a median progression-free survival of 5-8 months, and a median OS greater than 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-1 studies showed that the combination was feasible when given with granulocyte-colony stimulating factor (G-CSF).^{18,19} Encouraging efficacy was described in patients with STS, particularly in liposarcoma and leiomyosarcoma, with 3-month 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, multicenter, phase-2 study (LMS-02) of doxorubicin combined with trabectedin, as first-line treatment in metastatic or locally advanced uterine or soft-tissue 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 one hundred and seven patients had to be included in the trial, forty-five with uterine LMS (U-LMS) and sixty-two with a soft tissue LMS (ST-LMS). In the two groups, analyses were conducted by intent-to-treat according to the Simon "Optimum Design" multi-stage process.²¹

Our objective was to conclude on the efficacy of this combination if it 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 of this LMS02 trial, about the primary endpoint on response and median PFS (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; with 91 deceased patients (40/47 in the uterine group and 51/61 in the soft tissue group).

METHODS

Statistical analysis

The study was stratified by primary tumor location uterine vs. ST LMS. Each stratum of the study was considered as an independent phase-II study. A two-stage Simons' optimum design has been used for each of the 2 strata, but with different hypotheses for the 2 cohorts.

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

In the uterine study, the assumed baseline response rate was 50%. The study was planned as a two-stage plan. In order to have an alpha risk and a beta risk both at 10%, 45 subjects 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. In order to have an alpha risk at 10% and a beta risk at 5%, 62 subjects were required. Study would be considered positive if at least 29/62 patients

responded or had stable disease.

Analyzed 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 intent to treat. In order to be considered assessable for response, patients had to have received at least one cycle of treatment. Time-to-event variables will be analyzed according to the Kaplan-Meier method.

No information about subsequent lines of therapy was collected.

Between July 28th, 2010, and May 10th, 2013, 109 patients were enrolled and treated, of whom 108 were assessable for response. Most patients had metastatic disease (82.4%), and 20 of the patients (18.5%) had surgical resection of metastases after chemotherapy. The final analysis included 47 patients with U-LMS and 61 with the ST-LMS (Table 1). Thirty-two (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 doxorubicin 60 mg/m² i.v. followed by 3-hour infusion of trabectedin 1.1 mg/m² repeated every 3 weeks, followed by pegfilgrastim 6 mg on Day 2. Surgery for residual disease was permitted. Treatment was performed in outpatient schedule every 3 weeks for a maximum of 6 cycles. Dose modifications or reductions were needed for 76 (14%) of 557 cycles given and in 55 (51%) of 108 patients.

Disease evaluation was performed every two cycles.

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

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

They had to have a physiological age lower than seventy years and a good performance status (PS ECOG \leq 2).

The results published in 2015 were very encouraging: 28 of 47 patients with U-LMS (59.6%, 95% CI 44.3 – 73.6) achieved a partial response, 13 (27.7%, 15.6 – 42.6) a stable disease and 41 (87.2%, 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%, 25.0 – 50.8) a partial response, 32 (52.5%, 40.8 – 67.3) a stable disease; and 56 (91.8%, 81.9 – 97.3) a disease control.²²

Toxicities were predominantly hematological and hepatic ones.

Results

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

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

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

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 primary site alone in 9 cases (2 UT-LMS + 7 ST-LMS), on metastatic sites in 8 cases (4 UT-LMS + 4 ST-LMS), and both in 2 cases (2 UT-LMS) and unknown localization in 1 ST-LMS case. There were clinical complete responses associated with histological complete responses in 6 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) for patients without surgery *versus* 18.2 months (95% CI : 9.5-54.5] when surgery was performed; the impact seemed to be more important for ST-LMS in particular for OS; median OS was 31.6 months (95% CI : 23.9-35.4) for patients without surgery *versus* not reached when surgery was performed (Table 2).

DISCUSSION

In this homogeneous series of 107 patients with advanced/metastatic uterine and soft tissue LMS, efficacy results of trabectedin + 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) and median OS is 34.4 months (95% CI: 26.9 - 42.7).

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

There are a few studies realized at the same period in first-line treatment for STS with LMS cohorts or in specific LMS population: the reported median OS in this setting in the LMS population is 22 to 29 months^{8,10} with doxorubicin alone, and 23 months with the association of doxorubicin plus evofosfamide.⁸

In the GeDDiS study,⁹ the association of gemcitabine and docetaxel was compared to doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic STS in a randomized controlled phase-III trial. For the overall population, the association does not do better than doxorubicin alone in term of OS but with a higher toxicity. Patients were stratified by histological subtype (leiomyosarcoma *versus* synovial sarcoma *versus* pleomorphic sarcoma *versus* other eligible sarcomas) and whatever the subtype, the association of gemcitabine+docetaxel do not better than doxorubicin alone but demonstrated a higher toxicity.

A randomized phase-II trial²³ compared doxorubicin to 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-hour infusion and 24-hour infusion) to doxorubicin in patients with advanced or metastatic untreated STS (TRUSTS trial). The study was stopped due to lack of superiority in both trabectedin treatment arms, as compared to 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 favorable activity of doxorubicin + dacarbazine association in terms of both ORR and PFS, but warrants 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 median OS of 21.9 months (95% CI, 16.7 - 33.4 months) for 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 LMS have poorer prognosis than soft-tissue-LMS (OS is respectively of 27.5 months (95% CI: 17.9 - 38.2) in the uterine group, and 38.7 months (95% CI: 31.0 - 52.9) in the soft tissue group). This result can justify a stratification on this factor for future studies conducted in LMS.

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 with its limitation of 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 non-randomized phase-II study. We performed the LMS04 trial, a randomized phase-III study comparing this doxorubicin plus trabectedin combination followed by trabectedin *versus* doxorubicin alone in first-line therapy in metastatic LMS with a stratification (uterus vs STS LMS).

The strengths are the homogeneity of the population while focussing in a unique soft tissue sarcoma sub-type; the latter seems to be the most sensitive (with liposarcoma) to trabectedin and the more susceptible to benefit from the association with doxorubicin. Other strengths are the analysis of two populations –U-LMS and STS-LMS–, and the design of a “real life” design with the possibility to operate non progressive patients after chemotherapy.

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

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

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Table 1: Patients characteristics

Patients (%)	Uterine (n=47)	Soft tissue (n=61)
Median age [range]	58 [35-73]	59 [32-77]
PS 0	32 (68%)	37 (62%)
PS 1/2	10 (21%) / 2 (4%)	22 (37%) / 1 (1%)
Female	47 (100%)	40 (66%)
Grade 1 /2-3	NA	8 (13%) / 47 (77%)
Site of primary		
- Uterine	47 (100%)	0
- Extremity / RetroP/Pelvis	NA	13 / 16 / 7
- Visceral / Other	NA	15 / 10
Pelvic radiotherapy	17 (36%)	NA
Metastatic disease	37 (79%)	52 (85%)
- Lung / Liver	33 (70%) / 13 (28%)	42 (69%) / 24 (39%)
- Bone / Cutaneous / Other	8 / 2 / 13	6 / 4 / 13

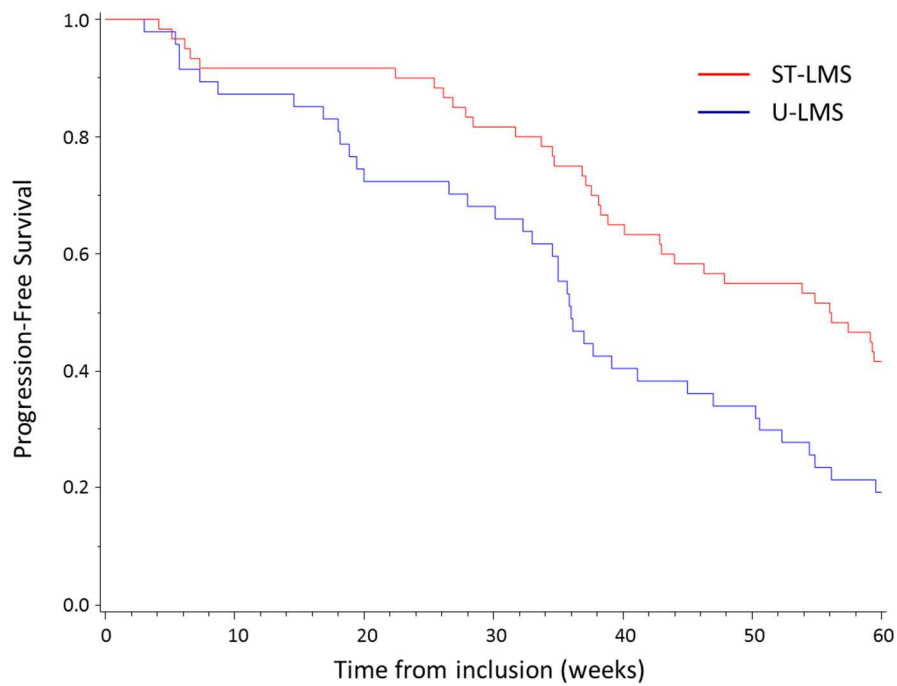
PS: performance status; RetroP: retroperitoneal.

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

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

OS: overall survival; NR: not reached; *unknown for 1 patient.

Figure 1: PFS (weeks) according to localization (uterine and soft tissue LMS)

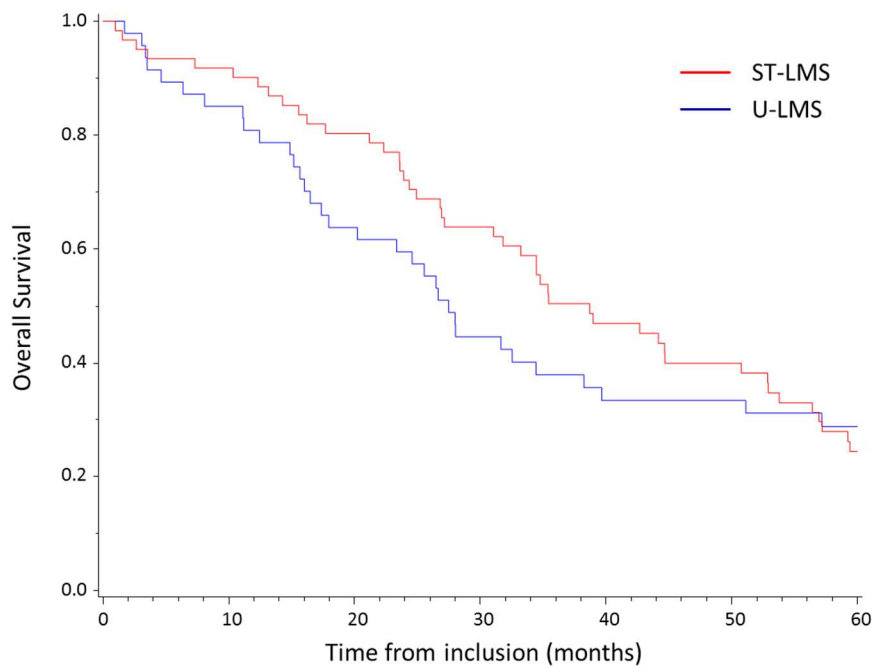


Patients at risk

ST-LMS	61	56	56	49	39	33	25
U-LMS	47	41	35	32	19	16	9

Median PFS: 10.1 months [95% IC: 8.5 - 12.6] in the entire population; 8.3 months [95% CI: 7.4 - 10.3] in the uterine population and 12.9 months [95% CI: 9.2 - 14.1] in the STS population.

Figure 2: OS (months) according to localization (uterine and soft tissue LMS)



Patients at risk

ST-LMS	61	56	49	39	27	23	14
U-LMS	47	40	30	20	15	14	12

Median OS: 34.4 months [95% CI: 26.9 - 42.7] in the overall population (figure 2), 27.5 months [95% CI: 17.9 - 38.2] in the uterine group, and 38.7 months [95% CI: 31.0 - 52.9] in the ST group respectively.