Doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin alone as first-line therapy for metastatic or unresectable leiomyosarcoma (LMS-04): a randomised, multicentre, open-label phase 3 trial.

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LMS-04 study: a randomised, multicenter open-label phase-3 study comparing doxorubicin alone *versus* doxorubicin with trabectedin followed by trabectedin in non-progressive patients as first-line therapy in patients with metastatic or unresectable leiomyosarcoma. A French Sarcoma Group study.

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

Highlights: comparing PFS and assessing ORR of an association of doxorubicin and trabectedin with trabectedin maintenance *versus* doxorubicin in first-line treatment for metastatic or unresectable leiomyosarcoma.

Sponsor: Gustave-Roussy, Villejuif, France

Study was presented at:

-the Annual Meeting of the European Society for Medical Oncology (ESMO) in 2021 (oral presentation in sarcoma session).

ABSTRACT

Background: Doxorubicin alone remains the standard first-line treatment for metastatic (met) leiomyosarcoma (LMS). We reported encouraging results of a doxorubicin + trabectedin (Dox+Trab) combination as first-line therapy.

Methods: LMS-04 was a randomised multicentered, open-label comparative phase 3 trial included patients from 20 centres in France. Eligible patients were aged 18 years or older, had an EGOG performance status of 0-1, and had previously untreated met or unresectable LMS. Patients were randomly assigned 1:1 to receive up to 6 cycles of IV Dox (75 mg/m²) (arm A) *vs* up to 6 cycles of IV Dox (60 mg/m²) + IV Trab (1.1 mg/m²) q 3w followed by maintenance with Trab alone (arm B). Surgery for residual disease was allowed in both arms after 6 cycles. Primary endpoint was progression-free survival (PFS) assessed by blinded central review (according to RECIST 1.1); randomisation was stratified by tumour location (uterine *vs* soft tissue) and locally advanced *vs* metastatic. Efficacy analyses were based on intention-to-treat principle. This trial is registered with ClinicalTrials.gov NCT02131480 and is closed to enrolment.

Findings: Between Jan 18, 2017, and Mar 21, 2019, 150 patients were recruited (67 uterine-LMS; 83 soft tissue-LMS) (76 in arm A and 74 in arm B). Median duration of follow-up was 37 months (IQR [31;44]). Grade 3-4 adverse events were reported in 39/75 patients (52%) of arm A *vs* 71/74 patients (96%) of arm B, mostly hematologic. There was one treatment related death in arm A.

Median PFS was statistically significantly improved with Dox+trab *versus* Dox alone, (12.2 months (95% CI 10.1-15.6) *vs* 6.2 months (95% CI 4.1-7.1, adjusted HR : 0.41 [0.29;0.58], p<.0001)).

Interpretation

Dox+Trab in first-line therapy statistically significantly increases the PFS of metastatic or unresectable LMS compared to Dox alone, and could be considered for first line treatment of metastatic LMS.

Funding: PharmaMar.

Research in context

Evidence before this study:

No combination with doxorubicin, nor other associations without doxorubicin previously explored in randomised clinical trials are superior to doxorubicin alone in terms of OS in STS and more specifically in LMS. Trabectedin is an active drug in second line leiomyosarcoma after doxorubicin failure. Preclinical data and previous LMS02 phase 2 study suggest that the association of trabectedin and doxorubicin is an effective combination in first line treatment of leiomyosarcoma. We searched PubMed for articles published between Jan 1, 2000, and Mar 31, 2022, without language restrictions, using the terms “chemotherapy”, “leiomyosarcoma”, “soft tissue sarcoma”, “uterine sarcoma”, “metastatic disease”, “doxorubicin”, “trabectedin”; The search identified no previous randomized trial data on the combination of doxorubicin and trabectedin compared to doxorubicin in metastatic leiomyosarcoma.

Added value of this study

LMS-04, a randomised phase 3 study, met its primary endpoint, demonstrating a statistically significant improvement in PFS with the doxorubicin + trabectedin combination compared with standard-of-care doxorubicin alone in first-line treatment of metastatic leiomyosarcomas. Improved PFS was observed in both the uterine and the soft tissue populations.

Implications:

Doxorubicin+trabectedin combination followed by trabectedin in non-progressive patients could be considered for first-line treatment of metastatic leiomyosarcomas, in particular for patients requiring tumor shrinkage and possibly for patients requiring neoadjuvant therapy.

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 genomic profile. Leiomyosarcomas (LMSs) represent almost a quarter of STSs

among which uterine location is the most frequent.[1] Locally advanced or metastatic LMSs have a poor prognosis. With some exceptions, systemic chemotherapy for the different STS subtypes is largely similar, with doxorubicin and ifosfamide or dacarbazine being the backbone of treatment.[2,3]

Gene expression patterns differ between uterine LMSs (U-LMSs) and non-U-LMSs,[4] but both are judged to be poorly sensitive to conventional chemotherapy. In metastatic LMS, the first line treatments with doxorubicin, ifosfamide, or dacarbazine reports objective response rates of about 15%-17% (i.e. complete or partial responses), with a median progression-free survival (PFS) of about 5 months, and a median overall survival (OS) of around 12 months in older studies and 24 to 30 months in more recent ones.[5,6] New combinations have been tested with and without doxorubicin. Some of combinations showed a superiority in terms of PFS but never by more than 3 months[2,3]. However, to date, none of these combinations are superior to doxorubicin alone in terms of OS in STS including LMS.[2,3,7,8]

Recently, clinical studies are increasingly dedicated to a specific histological subtype of sarcoma such as alveolar soft part sarcoma, angiosarcoma, clear cell sarcoma, liposarcoma, translocation related sarcomas, undifferentiated pleomorphic sarcoma, and U-LMS.[9]

Trabectedin has shown activity in STS, with 10% of patients achieving an objective response after failure of doxorubicin and ifosfamide, but with greater activity in pretreated LMSs than in other histological subtypes, with a 6-month PFS of 26%-30%.[10,11]

In uterine LMSs, first-line trabectedin is associated with 10% objective response rate, a median PFS of 5.8 months, and a median OS >26 months.[12]

Preclinical data also suggest that the association of trabectedin and doxorubicin is an effective combination in sarcoma.[13,14] Findings from two phase 1 studies showed that the combination was feasible when given with granulocyte colony-stimulating factor.[15,16] Promising 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 2 study (LMS-02) (ClinicalTrials.gov Identifier: NCT02131480) of doxorubicin combined with trabectedin as a first-line treatment in metastatic or locally

advanced U-LMS or non-uterine soft tissue LMS (ST-LMS). As some previous phase 2 studies reported that uterine LMS might be more chemosensitive than other LMS sites, a stratification by primary site was implemented.[17]

LMS-02 trial reported interesting results on PFS (primary endpoint), response rates and disease control rate in both groups.[18] In updated results with a median follow-up of 7.2 years, the median progression-free survival (mPFS) was 10.1 months (95% CI 8.5 - 12.6), and median overall survival (OS) was 34.4 months (95% CI 26.9 - 42.7).[19]

Since the end of the LMS-02 trial, the T-DIS results supported the continuation of trabectedin for patients with non-progressive soft-tissue sarcoma after six cycles.[20]
Given the results of the LMS-02 and T-Dis studies, we conducted a multicenter phase 3 study in patients with metastatic or unresectable leiomyosarcomas as first line therapy.

The primary objective was to determine and compare the PFS of patients with metastatic or unresectable uterine or soft tissue leiomyosarcoma treated in first line with doxorubicin alone, or the combination of doxorubicin and trabectedin followed by trabectedin alone for non-progressive patients.

The secondary objectives were to determine the response rate (Response Evaluation Criteria in Solid Tumors (RECIST) 1.1)[21] after 6 cycles and duration of response, the clinical benefit rate (objective responses and stable disease) after 6 cycles, toxicities (graded with the NCI common terminology criteria for Adverse Events (CTCAE version 4)), the time to second disease progression (PFS2), and the overall survival of patients.

Methods

Study design and participants

LMS04 was a multicentre, open-label, two-arms, randomised phase 3 superiority study comparing efficacy of doxorubicin alone (arm A) *versus* doxorubicin associated with trabectedin followed by trabectedin alone in non-progressive patients (arm B) as first-line therapy in patients with metastatic or unresectable leiomyosarcoma (uterine or soft tissue). All patients were enrolled in 20 centers of the French Sarcoma Group (appendix 1). Ethics committee approval was obtained by Gustave-Roussy Institute. All patients provided written

informed consent before the start of any study-specific procedures. Gustave-Roussy was the sponsor of the study.

The full study protocol is in appendix 2.

Patients included had histologically confirmed diagnosis by experts (within the national RRePS network) of metastatic or relapsed or unresectable uterine or soft tissue leiomyosarcoma previously untreated with chemotherapy, with at least one measurable lesion according to RECIST V 1.1 criteria (for targets in a previously irradiated field progression confirmed radiologically or histologically), ≥ 18 years old, with ECOG performance status <2, with adequate haematological, liver and cardiac functions. Patients with a history of malignancy and who were in complete remission for less than 5 years, or who had CNS metastases, were excluded.

Randomisation

Investigators identified and enrolled the patients into the trial. Patients were randomly assigned (1:1) in arm A or arm B by means of an interactive Web response system. Randomization was stratified by tumour location (uterus *versus* soft tissue) and disease (locally advanced *versus* metastatic). Permuted blocks of different sizes (from two to six) were used to allocate patients to treatment group. The randomisation request was signed by the investigator and sent by fax to the data center. The data manager randomised the patient using the on-line TEN Alea randomisation software (TENAlea version 2.2, TransEuropean Network for Clinical Trial Services, Amsterdam, Netherlands). A report with randomisation number and an arm assignment was then provided to the investigator. Due to the open-label trial design, patients, investigators, and the study sponsor were not masked to the study treatment.

Procedures

Patients in arm A received doxorubicin alone 75 mg/m² once every three weeks for up to 6 cycles *via* central venous route per slow perfusion (VI) over 10 to 15 minutes. An injection of SC lenograstim (granulocyte-colony stimulation factor (G-CSF)) was given every day from day 3 to day 9. In arm B, patients received doxorubicin 60 mg/m² over 10–15 min *via* central

veinous perfusion followed by a 3-hours central venous perfusion of 1.1 mg/m² trabectedin on day 1. Pretreatment with 20 mg dexamethasone was given 30 min before trabectedin. An injection of pegfilgrastim 6 mg (pegylated G-CSF) per subcutaneous route was given on day 2.

Treatment was given every 3 weeks for a maximum of six cycles. No maintenance treatment was allowed in arm A.

For non-progressive patients after 6 cycles of doxorubicin-trabectedin (+/– surgery) in arm B, patients received trabectedin 1.1 mg/m² *per* central venous perfusion over 3 hours (even in case of previous dose reductions of trabectedin in the combined phase with doxorubicin) after a premedication with dexamethasone I.V 20 mg. Maintenance trabectedin was administered every 3 weeks until disease progression or for a maximum time period of 12 months of treatment (maximum 17 cycles in maintenance therapy), whichever occurred first.

Surgery for residual disease (primary tumor and/or metastasis) was allowed in both arms (except for progressive disease) after 6 cycles according to investigator decision; the objective was complete resection.

Treatment with aprepitant —a cytochrome CYP3A4 inhibitor— was not allowed with trabectedin. Other supportive measures, including transfusions and haematopoietic growth factors, were permitted.

Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 4.0. A maximum of two dose reductions for each drug was permitted. The two dose reductions permitted for doxorubicin in arm A were from 75 mg/m² to 60 mg/m², and then to 50 mg/m²; and in arm B from 60 mg/m² to 50 mg/m², and then to 45 mg/m²; for trabectedin, dose reductions were from 1.1 mg/m² to 0.9 mg/m², and then to 0.7 mg/m² (see protocol appendix 2).

A delay upper than 3 weeks for adverse events withdraw the patient from the study.

Pre-treatment assessments consisted of medical history, physical examination, laboratory tests, electrocardiogram, and measurement of LVEF by ultrasound or isotopic ventriculography within 28 days before study entry and after the sixth cycle. During

induction treatment in both arms, a weekly follow-up of haematological and liver function tests was performed. Tumour imaging (CT scan of chest, abdomen, and pelvis or MRI) was done at baseline, and then every 6 weeks, and 3 weeks after the last cycle. Then, imaging was performed every 9 weeks, for 2 years, and, in non-progressive patients, every 3 months for one additional year and then every 6 months.

At time of progression, data on second-line management was collected.
After first progression, the patient was monitored every 6 months for date of second progression and survival evaluation.
There was no external monitoring committee, since there was sufficient experience with the previous phase 2 LMS-02 study performed on the same population of patients.
Since maintenance with trabectedin after 6 cycles of association was a new option, toxicity have been monitored for the first 10 patients on maintenance in arm B and been discussed with the internal data safety monitoring board. No particular signal of toxicity have been seen and no amendment to the protocol was needed. Consent withdrawal was the only criteria for a patient to be removed from the study.

Outcomes

The primary endpoint was progression-free survival validated by blinded independent central review. Progression-free survival was defined as the time from randomisation until date of progression based on RECIST criteria or date of death from any cause, whichever occurred first. Tumour response was assessed by the investigator per RECIST 1.1. For the primary endpoint analysis (PFS), a blinded radiographic central review (BICR), based on imaging only was performed at Gustave-Roussy before database lock to confirm progression. In case of no event, follow-up of patient was censored at date of last news. Secondary endpoints were disease control rate (DCR), response rate (RR), response duration, all assessed based on RECIST v1.1 criteria, toxicities, overall survival (OS), and progression-free survival of patients in second-line therapy after progression (PFS2). DCR (RECIST criteria 1.1) was defined as proportion of objective responses (complete (CR) and partial (PR) responses) and stable diseases. For both DCR and RR, the response taken into consideration was the best response during the 6 induction cycles. Response duration was defined as the time

from first CR/PR before end of cycle 6 until first documented PD. Toxicities were graded with the NCI common terminology criteria (CTCAE version 4). Overall survival of patients was defined as the time from the date of randomisation to the date of death from any cause. PFS2 was defined as the time from date of randomisation to date of second progression (radiological or clinical progression assessed by investigator) or death,[22] whichever occurred first. Early data on PFS2 and OS are immature and will be presented with longer follow-up. Exploratory objectives were to identify biomarkers potentially predictive of response and resistance in archived tumor biopsies (not presented here).

Sample size

To evaluate the primary endpoint, 150 patients were planned to be included. The targeted difference was based on a literature overview. The median progression-free survivals were expected to be 6 months in arm A and 9.7 months in arm B (corresponding hazard ratio=0.62). With a two-sided alpha set to 5%, 136 events (local relapse, metastases progression, new metastasis and death) were needed to provide the study 80% power (nQuery® 7.0). With an inclusion duration of 24 months, an assumption that patients will enter the study uniformly over the accrual period, a minimum follow-up of 24 months (total study duration = 48 months, median follow-up of 36 months), and an expected rate of 3% of included but not randomized patients, 150 patients were needed (75 patients in each arm).

In July 28th 2021, it was decided to lock the database since the results had to be presented at the ESMO meeting, although the number of PFS RECIST events was 134 instead of 136 initially planned. The power loss was considered negligible (decrease of 0.5%).

Statistical analysis

Efficacy analyses were performed on all randomized patients, based on intention-to-treat principle. Safety population included all randomized patients who received at least one dose of treatment. Median follow-up and associated IQR were estimated using the reversed Kaplan-Meier method (appendix 11, Schemper method).[22]

For the primary analysis, treatment effect on PFS was assessed using Cox proportional-hazards model, with adjustment for the stratification factors used for randomisation. Hazard ratio from Cox model, as well as 95% confidence intervals and p-values (Wald method) are

provided. Proportionality of hazards assumption was graphically assessed by plotting log(-log(S(t)) (appendix 10). The same Cox regression model was used to perform sensitivity analyses to assess robustness of results on PFS (appendix 7). Pre-planned subgroup analyses of the treatment effect according to stratification factors (LMS subtype and disease characteristics) were implemented (appendix 4 and 9).

A post-hoc analysis of PFS at 12 and 24 months and associated 95% bilateral confidence intervals were given (Kaplan-Meier method and Greenwood formula). Response rates in each group were compared with the Chi-square test (appendix 15). The Hazard Ratio for the duration of response was estimated with an univariate Cox regression model (appendix 14). A post-hoc multivariate analysis with adjustment for stratification factors and bone metastases was performed using a Cox regression model (appendix 13).

Safety analyses were performed on all adverse events occurring from randomisation until first progression. No imputation of missing data was performed. No interim analysis was planned. A p-value ≤ 0.05 was considered statistically significant. SAS® software version 9.4 was used for statistical analysis. This trial is registered with ClinicalTrials.gov, number NCT02997358, LMS04 study. Statistical Analysis Plan includes all details on secondary endpoints (appendix 3).

Concerning data handling, a DMP (Data Management Plan) was written which complies with the French law on protection of participant data and with Good Clinical Practices.

There was no protocol amendment affecting trial during the study.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 18, 2017 and Mar 21, 2019, 150 patients were included (67 U-LMS and 83 ST-LMS) (Figure 1, trial profile) with a median age of 61 years [IQR 52-68] and mostly metastatic (n=135, 90%), and were analyzed according to intent-to-treat principles: 76 in the

doxorubicin arm (arm A) and 74 in the doxorubicin+trabectedin arm (arm B) (characteristics of patients are presented in Table 1). Median duration of follow-up was 37 months (IQR [31;44]).

Analyses are based on database version August 30th 21. 149 patients received at least one cycle of treatment (Figure 1, trial profile). The median number of cycles was 6 in each arm for the induction and 10 for the maintenance part in arm B. 18 (23.68%) patients in arm A and 31 (41.89%) in arm B needed a dose reduction during induction, and 3 patients/76 (4%) (A) and 17 patients/74 (23%) (7 induction including 2 who started a maintenance + 10) (B) respectively stopped treatment for toxicity. 6.3% and 10.2% of cycles respectively needed a dose reduction.

21 of 150 patients (14%) underwent surgery among whom 15 of 74 patients (20%) in arm B and more often with complete surgery (71%) (appendix 8). The study met its primary endpoint with a reduction of 59% of the risk of progression or death with the doxorubicin-trabectedin combination compared to doxorubicin alone. The median progression survival time was statistically improved from 6.2 months (95% CI 4.1-7.1) with doxorubicin alone to 12.2 months (95% CI 10.1-15.6) with doxorubicin combined to trabectedin [HR: 0.41 95% CI 0.29-0.58; *P*<0.0001] (figure 2).

The 12 and 24 months PFS rates were respectively 16% [9.4 ; 25.9] and 5.3% [2.1 ; 12.9] in arm A and 50.7% [39.5 ; 61.9] and 30.2% [20.9 ; 41.5] in arm B. It was also improved according to investigators (appendix 7). Discrepancy concerned 24 on 150 patients (16%), 13 of 76 in arm A (17%) and 11 of 74 in arm B (15%). In the end, 17 of these discrepancies were declared as real progressions (9/13 (69%) in arm A, 8/11 (73%) in arm B).

Similar results were observed in both the uterine and the soft tissue populations, in locally advanced and metastatic population (appendix 4).

The response rate was 13.2% with 10 partial responses/76 in the doxorubicin arm compared to 36.5% with 3 complete responses and 24 partial responses/74 in the combination arm (appendix 5). The difference in response rate was 23 %, 95% C.I [10%-37%], p=0.0009. The response rate was 25% (17/67) in the U-LMS subgroup (15% in arm A and 36% in arm B) and 24% (20/83) in the ST-LMS group (12% in arm A and 37% in arm B) (appendix 12).

The median duration of response was prolonged from 5.6 months (95% CI 3.5-6.9) with doxorubicin to 12.7 months (95% CI 7.9-18.4) with doxorubicin-trabectedin combination (H.R: 0.36, 95%C.I. [0.17;0.77],p=0.009).

The proportion of patients achieving disease control (complete response, partial response, or stable disease) was 79% (95% CI 69.1- 88.8) in the doxorubicin alone group *versus* 91.9% (95% CI 85.0-98.8) in the doxorubicin + trabectedin group. The difference in disease control rate was 13%, 95% C.I [2%-24%], p=0.03.

The comparison of overall survival is planned to be performed later. The number of deaths observed so far is 50 in arm A (47/76 (62%) of disease vs 42 in arm B (40/74 (54%) of disease) (detailed in appendix 16).

Safety was assessed in 149 patients (table 2, appendix 6). 18 patients/76 (24%) in arm A versus 47/74 (62%) (31 during the induction (42%) and 16 during the maintenance (22%)) in arm B required dose reduction. The association of doxorubicin and trabectedin was more toxic than doxorubicin alone with grade 3-4 adverse events reported in 39 of 75 patients (52.0%) in arm A *versus* 71 of 74 patients (96.0%) in arm B (Table 2, appendix 6), with mostly hematologic events (neutropenia (10(13%) arm A *vs* 59/74 (80%) arm B), anemia (4/75(3%) arm A *vs* 23/74(31%) arm B, thrombocytopenia 0/75 arm A *vs* (35/75 (47%) arm B), and febrile neutropenia in 7/75 (9%) with doxorubicin alone *vs* 21/74 patients (28%) in arm B . It is to note that aprepitant was contraindicated with trabectedin, explaining partly the excess grade 1-2 GI toxicity. 9 serious adverse events were described in the doxorubicin arm (febrile neutropenia (n=3), grade 5 cardiac failure (n=1), pneumopathy (n=2), pneumothorax (n=2), and extravasation (n=1)) *versus* 15 in arm B (febrile neutropenia (n=7), pneumopathy (n=1), septic shock (n=2), sever cardiotoxicity (n=3), pancytopenia(n=1), and anemia (n=1)); 7 patients (3 in the doxo arm and 5 patients in the doxo + trab arm) received EPO and 4 received IV iron supplementation (1 in the doxo arm and 3 patients in the doxo + trab arm) for anemia.

There was only one toxic death in the doxorubicin arm linked to infection and cardiac failure. 3 patients/76 (4%) in the doxorubicin arm A stopped for toxicity, for renal failure (n=1), and for grade 3 cardiac failure (n=2) *versus* 17/74 patients (23%) of the combination arm, 7/74 (9%) in the induction phase and 10/74 (14%) during maintenance for thrombocytopenia (n=4), neutropenia (n=2), hemorrhagic shock (n=1), sepsis (n=2), gr2 acute myeloid leukemia (n=1) (but dead from sarcoma one year later), performance status degradation/fatigue (n=2), grade 1 left ventricular dysfunction (n=1), grade 3 gamma-glutamyl-transferase increase (n=1), vomiting (n=1), intestinal obstruction (n=1), and for oesophagal ulcer (n=1),

Table 2: adverse events (n=149)

	Arm A Doxo N=75				Arm B Doxor + Trab N = 74			
	Gr 1-2*	Gr 3	Gr4	Gr 5	Gr 1-2*	Gr 3	Gr4	Gr 5
Anaemia	55(73%)	0	4(5%)	0	51(69%)	20(27%)	3(4%)	0
Febrile neutropenia	3(4%)	4(5%)	3(4%)	0	5(7%)	7(9%)	14(19%)	0
Leukopenia	24(32%)	2(3%)	1(1%)	0	10(14%)	24(32%)	32(43%)	0
Lymphopenia	0	1(1%)	0	0		4(5%)	0	0
Neutropenia	20(27%)	7(9%)	3(4%)	0	5(7%)	14(19%)	45(61%)	0
Thrombocytopenia	6(8%)	0	0	0	24(32%)	17(23%)	18(24%)	0
Cardiac failure	0	1(1%)	1(1%)	1(1%)	0	1(1%)	0	0
Dyspnoea	9(12%)	1(1%)	0	0	10(14%)	1(1%)	0	0
Constipation	17(23%)	1(1%)	0	0	28(38%)	1(1%)	0	0
Diarrhoea	10(13%)	1(1%)	0	0	26(35%)	2(3%)	0	0
Dysgeusia	10(13%)	0	0	0	10(14%)	0	0	0
Enteritis	0	0	0	0	0	1(1%)	0	0
Faecaloma	0	0	0	0	0	0	1(1%)	0
Intestinal obstruction	0	1(1%)	0	0	0	1(1%)	0	0
Nausea	46(61%)	1(1%)	0	0	59(80%)	5(7%)	0	0
Vomiting	10(13%)	0	0	0	59(80%)	4(5%)	0	0
Oesophageal ulcer	0	0	0	0		1(1%)	0	0
Decreased appetite	14(19%)	0	0	0	21(28%)	1(1%)	0	0
Device related infection	0	0	0	0		3(4%)	0	0
Fatigue	60(80%)	8(11%)	0	0	72(96%)	8(11%)	0	0
Mucosal inflammation	24(32%)	2(3%)	0	0	27(36%)	3(4%)	0	0
Pain	5(7%)	3(4%)	1(1%)	0	15(20%)	2(3%)	0	0
Pyrexia	7(9%)	1(1%)	0	0	18(24%)	1(1%)	0	0
Infection	2(3%)	3(4%)	0	0	0	2(3%)	0	0
Pneumococcal sepsis	0	1(1%)	1(1%)	0	0	0	0	0
Septic shock	0	0	0	0	0	0	2(3%)	0
Hemorragic shock	0	0	0	0	0	0	1(1%)	0
Alanine aminotransferase	19(25%)	1(1%)	0	0	36(28%)	28(38%)	3(4%)	0
Aspartate aminotransferase	17(23%)	0	1(1%)	0	52(70%)	6(8%)	1(1%)	0
Blood alkaline phosphatase	23 (31%)	0	0	0	46(62%)	2(3%)	0	0
Blood bilirubin	5(9%)	0	0	0	27(36%)	6(8%)	0	0

Blood creatine phosphokinase	8(11%)	0	0	0	24(32%)	5(7%)	0	0
Renal creatinine clearance	8(11%)	0	0	0	1(1%)	23(31%)	0	0
Gamma-glutamyltransferase	2(3%)	0	0	0	8(11%)	6(8%)	2(3%)	0
Rhabdomyolysis	0	0	0	0	0	1(1%)	0	0
Depression	0	0	0	0	3(4%)	1(1%)	0	0
Cough	15(20%)	0	0	0	15(20%)	0	0	0

*Occuring in at least 10% of patients

Discussion

LMS-04 met its primary endpoint, demonstrating a statistically significant improvement in progression-free-survival with the doxorubicin + trabectedin combination compared with standard-of-care doxorubicin alone in first-line treatment of metastatic leiomyosarcomas. Such improvement was observed both in the uterine and the soft tissue populations.

These data support the previous LMS-02 phase 2 results, possibly resulting from synergistic activity of the combination.[13,14] The LMS-02 trial, a phase 2 combination of doxorubicin and trabectedin in the same population as the LMS04 study, demonstrated a high response rate, an interesting median PFS of 10.1 months and an OS of 34.4 months supporting that the combination was feasible despite the toxicity.[18,19] The LMS04 study confirms in a prospective randomized trial the superiority of the doxorubicin-trabectedin combination against doxorubicin alone. We report the same response rate and a non-statistical difference in PFS between uterine and soft tissue LMS, contrary to what has been already described.[17] Indeed, LMS-02 study showed that OS was respectively of 27.5 months (95% CI 17.9- 38.2) in the uterine group *versus* 38.7 months (95% CI 31.0 - 52.9) in the soft tissue group, while LMS-04 study showed that median PFS in the doxorubicin-trabectedin arm was 10.0 months [4.9-16.6] in the U-LMS subgroup and 13.5 months [10.5-21.6] in the ST-LMS group.

To our knowledge, no randomised phase 3 study has been published in first-line therapy for metastatic/relapsed LMSs, except for uterine LMSs.[23]

Drug development in sarcoma has evolved to focus on histotype specific trials in an effort to detect more robust effects in well defined soft-tissue sarcoma subtypes, such as trabectedin in liposarcoma and leiomyosarcoma,[11] eribulin in liposarcoma,[24] or weekly paclitaxel in angiosarcoma.[25] Since those tumors are rare, we decided first to focus on one specific histological subtype and two subgroups (uterine and non-uterine).

A propensity score matching analysis of the EORTC STBSG group compared the results of different doxorubicin-based regimens (doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone) given as first line treatment for advanced leiomyosarcoma in a retrospective observational study.[5] Doxorubicin plus dacarbazine, showed favorable activity in terms of both ORR (30.9%) and PFS (9.2 months). No data on doses, nor on toxicities were reported in this study, and no published report show clear data on toxicity with this combination, but it is possibly less toxic than the doxorubicin trabectedin combination. The major limitation of these results is the retrospective analysis of observational data collected in different EORTC centers, without randomisation of treatments, nor central review. Still, these results warrant further evaluation in prospective trials. Since the beginning of LMS04 trial, several randomised controlled trials in first line treatment in metastatic STS (combining several histologies) were published, but none of them showed a survival advantage of any schedule over single-agent doxorubicin treatment.

There are few studies in previously untreated STS with LMS cohorts or in specific LMS population. All studies compared an association (with or without doxorubicin) to doxorubicin alone in first-line therapy for metastatic or advanced soft tissue sarcomas. In the SARC021 trial, [26] authors reported results in subgroups, in particular LMS *versus* non-LMS population; in the GeDDIS study,[8] patients were stratified by histological subtype (leiomyosarcoma *versus* synovial sarcoma *versus* pleomorphic sarcoma *versus* other eligible sarcomas); in the ANNOUNCE trial,[7] the analysis was preplanned to be in all randomised patients (total STS population) and in the subset of randomised patients with LMS.

In these three phase 3 trials (SARC021, GeDDIS and ANNOUNCE) with doxorubicin alone and in the LMS population, the reported median PFS was 6.2, 5.8, 6.9 months respectively, and median OS was 28.9, 19.1, 28.9 months respectively *versus* 6.6, 5.9, 4.3 months of median PFS and 23.2, 16.8, 21.6 months of median OS with combinations (doxorubicin +

evofosfamide, gemcitabine + docetaxel, doxorubicin + olaratumab).[7,8,26] The median OS was longer than the previous published ones,[22] partly due to better second-line or beyond therapies.

In these studies, the combinations did not show better efficacy than doxorubicin alone, in terms of median PFS, or median OS, but resulted in a higher toxicity.

A randomised phase 2 trial[27] compared doxorubicin to doxorubicin and trabectedin in different histological STS subtypes, but without published data on OS.

The interest of the LMS-04 study was also to integrate a different strategy to enhance efficacy of treatment with surgery and maintenance therapy.

A retrospective study analysed the factors affecting the survival of patients with metastatic leiomyosarcoma treated with doxorubicin-containing chemotherapy.[28] Authors found that maintain appropriate doxorubicin dose intensity and metastectomy were associated with improved survival. In the LMS-04 study, surgery was allowed in both arms as it is a part of management for patients in first-line treatment. Twenty percent of patients in the combination arm (*versus* 8% with doxorubicin alone) underwent surgery after the 6 induction cycles. Even if surgery impacts PFS and OS, a better response to treatment with the combination may render more patients candidate to surgery or locoregional therapies; but a bias, linked to the unblinded treatments, can not be excluded.

Objectives of maintenance therapy are to maintain response, and prevent or delay progression. The key difference between maintenance therapy and further line is that maintenance therapy is given in patients experiencing non-progressive disease, whereas further lines are given in those experiencing progressive disease. The only randomised phase 3 study in sarcoma patients questioning the usefulness of maintenance is the RMS 2005 trial which tested vinorelbine plus low-dose continuous cyclophosphamide maintenance treatment for patients with high-risk rhabdomyosarcoma.[29] Traditionally, for advanced stage diseases not amenable to curative-intent strategy, systemic treatment could be administered until severe toxicity, disease progression, or cumulative doses have been reached (e.g., like in the case of doxorubicin). If it is not possible to perform more than 6 cycles of doxorubicin 75 mg/m², however trabectedin can be continued after 6 cycles in the

absence of cumulative toxicity. Moreover, in the particular case of trabectedin, continuation of treatment for patients who have not progressed after 6 cycles is better than stopping after 6 cycles and reintroduction in case of progression, as shown by the results of the T-DIS study (with an improvement of 4 months in median PFS and an impact on overall survival).[20] These data provided the rationale for exploring maintenance treatment with trabectedin in the LMS-04 study. In LMS-04, 27 of 76 patients (35.5%) in arm A received trabectedin in second-line, but data on PFS2 are immature and will be presented later; we shall see whether results tend –or not– in favor of the front-line association of doxorubicin + trabectedin followed by trabectedin, rather than a sequential use of the two drugs. However, it is not possible to extrapolate fully, as the systematic cross-over was not possible in the absence of reimbursement in France for this indication.

The LMS-04 study offered a unique opportunity in a multicentre prospective randomised clinical trial, to assess efficacy of doxorubicin + trabectedin (induction + maintenance) in uterine and soft-tissue LMS patients. Inclusion and non-inclusion criteria were limited, thus allowing the results of LMS04 to be generalized to a real life population of patients with LMS. The study included a high number of patients, followed according to clinical standards, and the primary endpoint was validated by blinded independent central review.

Nevertheless, the study presents some limitations; it is open-label as blinding patients and physicians was not feasible, but central review was implemented to limit the impact of open-label, and sensitivity analyses based on PFS defined by investigators support results from the main analysis (appendix 6 and 7). This corresponds to current clinical and optimal practice, even if it can introduce heterogeneity in patients care after randomisation. Similarly, treatment for second line was left to investigator's judgement and results for overall survival will be interpreted in consequence. The study has also a small sample size and has not shown yet an effect on overall survival. A subsequent analysis of survival with longer follow-up will be updated. No proof of progressing clinically prior to entry in the study was required, and the heterogeneity of the LMS disease itself (locally advanced grade 1 disease, versus multimetastatic grade 3 disease), difficult to integrate in the analysis, could be bias in the final analysis. As the percentage of patients with bony disease (sometime pointed out as prognosis) was not well balanced between the two arms (Table1), we have performed a multivariable analysis to adjust on bone metastases and stratification criteria. The

adjustment for this factor did not impact the HR associated with the treatment (appendix 12).

The safety profile was consistent with previous reports with additional grade 3-4 toxicity. Even if it is manageable, it could affect quality of life.

Doxorubicin + trabectedin could be considered for first-line treatment of metastatic leiomyosarcomas, in particular for patients requiring tumor shrinkage and possibly for patients requiring neoadjuvant therapy; however, further researchs are needed.

Contributors

BA did the statistical analysis. PP wrote the first draft of the report with input from AB, FD and BA and then from all the authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. BA and PP accessed and verified the data

Conceptualization: PP FD, data curation: BA, formal analysis: BA, AB and PP, funding acquisition: PP, methodology: BA, PP, FD, AB, project administration: PP, supervision: PP, AB, validation: PP, BA, AB, writing – original draft: PP, writing – review & editing: FD, all the authors.

Declaration of interests

PP has received research funding from PharmaMar, Onxeo (BMS) (all fees for institution); has received honoraria for lectures and presentations from MSD, Clovis ; has received consultancy fees from MSD, PharmaMar, AstraZeneca, Roche, Onxeo, GSK, Clovis; and has received support for travel or meetings from GSK, PharmaMar, Roche, Astra Zeneca, Amgen. AI has received research funding from astra zeneca, bayer, BMS, MSD, merck, roche ; consulting fees from Astra Zeneca, bayer, BMS, MSD, Merck, Roche. SP-N has received support for travel or meetings from PharmaMar. CC has been on a data safety monitoring board or advisory board for Ipsen, Pfizer, ESAI, MSD, BMS. NP declares no conflict of interest. NF has received support for travel or meetings from PharmaMar. PB-R has received support for travel or meetings from Takeda, Pfizer, Pharmamar ; and has received consultancy fees from Ipsen. FB declares no conflict of interest. CB declares no conflict of interest. VB-L has been on a on a Data Safety Monitoring Board or Advisory Board for Ipsen. IR-C has received research funding from BMS, MSD, GSK ; has received honoraria for lectures and presentations from GSK, Astra Zeneca, Clovis, Agenus, Deciphera, Mersana, MAcrogenics, Pharmamar, Roche, Novartis, ESAI ; support for attending

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Data sharing

The clinical study report is available upon request, after approval by the study principal investigator (corresponding author). Identified individual participant data from this clinical trial, as well as a data dictionary, can be requested by filling out the data request form for Gustave Roussy clinical trials at https://redcap.gustaveroussy.fr/redcap/surveys/?s=DYDTLPE4AM. The process is similar for every trial sponsored by Gustave Roussy. The trial steering committee and the sponsor will review the requests on a case-by-case basis. In the case of approval, a specific agreement between the sponsor and the researcher might be required for a data transfer.

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