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Version: Accepted Version

Article:
D'Ambrosio, L, Touati, N, Blay, J et al. (25 more authors) (Cover date: June 1, 2020) Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: A propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Cancer, 126 (11). cncr.32795. pp. 2637-2647. ISSN 0008-543X

https://doi.org/10.1002/cncr.32795

© 2020 American Cancer Society. This is the peer reviewed version of the following article:D'Ambrosio, L., Touati, N., Blay, J.-Y., Grignani, G., Flippot, R., Czarnecka, A.M., Piperno-Neumann, S., Martin-Broto, J., Sanfilippo, R., Katz, D., Duffaud, F., Vincenzi, B., Stark, D.P., Mazzeo, F., Tuchscherer, A., Chevreau, C., Sherriff, J., Estival, A., Litière, S., Sents, W., Ray-Coquard, I., Tolomeo, F., Le Cesne, A., Rutkowski, P., Stacchiotti, S., Kasper, B., Gelderblom, H., Gronchi, A. and (2020), Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: A propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Cancer, 126: 2637-2647., which has been published in final form at https://doi.org/10.1002/cncr.32795. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions. This article may not be enhanced, enriched or otherwise transformed into a derivative work, without express permission from Wiley or by statutory rights under applicable legislation. Copyright notices must not be removed, obscured or modified. The article must be linked to Wiley's version of record on Wiley Online Library and any embedding, framing or otherwise making available the article or pages thereof by third parties from platforms,

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Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as first-line treatment for advanced leiomyosarcoma: a propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group.

Running title: First-line treatments for leiomyosarcoma

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FUNDING

No external funding supported this study. Nathan Touati received a fellowship from the EORTC Cancer Research Fund through a grant from the EORTC Soft Tissue and Bone Sarcoma Group.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Other Relationship:Innate Pharma.

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Research Funding:PharmaMar,GlaxoSmithKline;Novartis(Inst);Eisai(Inst);Lilly(Inst).

Expert Testimony:PharmaMar;Novartis.

Travel/Accommodations/Expenses:PharmaMar;Pfizer.

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Research Funding:PharmaMar.

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Research Funding:PharmaMar(Inst).

Travel/Accommodations/Expenses:Nanobiotix;PharmaMar.

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ACKNOWLEDGEMENTS

Nathan Touati received a fellowship from the EORTC Cancer Research Fund through a grant from the EORTC Soft Tissue and Bone Sarcoma Group. Lorenzo D'Ambrosio research activity was partially supported by FRPC 5xmille 2014, Giovanni Grignani research activity was partially supported by FPRC 5xmille 2015. We thank all data managers and study coordinators from the participating centers for their great help.

COUNT

- Text pages: 25
- Abstract word count: 249
- Main text word count: 2771
- Tables: 2 (uploaded as separate files)
- Figures: 3 (including CONSORT diagram)
- Supplementary appendix: 1

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- In this propensity score-adjusted multi-Institutional series, doxorubicin+dacarbazine showed the better outcomes for the first-line treatment of advanced leiomyosarcoma warranting further studies
- This series represent a benchmark for the future development of trials in leiomyosarcoma

ABSTRACT

Background: Optimal treatment for advanced leiomyosarcoma is still debated. In the lack of histotype-specific prospective controlled data, we retrospectively evaluated doxorubicin+dacarbazine, doxorubicin+ifosfamide and doxorubicin alone as first-line treatment for advanced/metastatic leiomyosarcoma treated within EORTC-STBSG sites.

Methods: Inclusion criteria: confirmed histological diagnosis, treatment between 1/2010 and 12/2015, measurable disease (RECIST1.1), ECOG performance status ≤2, age ≥18 years. Endpoints: progression-free survival (PFS), overall survival (OS), overall response rate (ORR). PFS was analyzed using methods for interval-censored data. Patients were matched according to their propensity scores estimated using a logistic regression model accounting for histology, grade, age, gender, performance status, tumor site and extent.

Results: 303 patients from 18 EORTC-STBSG sites were identified. 117(39%) received doxorubicin+dacarbazine, 71(23%) doxorubicin+ifosfamide, and 115(38%) doxorubicin. In the 2:1:2 propensity score-matched population (205 patients), estimated median PFS was 9.2 (5.2-97), 8.2 (5.2-10.1), and 4.8 months (2.3-6.0), with an ORR of 30.9%, 19.5%, and 25.6% for doxorubicin+dacarbazine, doxorubicin+ifosfamide, and doxorubicin alone, respectively. PFS was significantly longer for doxorubicin+dacarbazine *vs.* doxorubicin [HR 0.72(0.52-0.99)]. Doxorubicin+dacarbazine reported longer OS [median 36.8 months(27.9-47.2)] compared to both doxorubicin+ifosfamide [21.9 (16.7-33.4), HR 0.65(0.40-1.06)] and doxorubicin [30.3 (21.0-36.3), HR 0.66(0.43-0.99]. Adjusted analyses retained effect for PFS but not for OS. None of the factors selected for multivariate analysis had significant interaction with the received treatment for both PFS and OS.

Conclusions: This is the largest retrospective study on first-line treatment for advanced leiomyosarcoma. In the propensity score-matched population doxorubicin+dacarbazine showed favorable activity in terms of both ORR and PFS warranting further evaluation in prospective trials.

KEYWORDS

leiomyosarcoma; sarcoma; doxorubicin; dacarbazine; ifosfamide; propensity score; retrospective study.

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of tumors encompassing more than 50 different entities. Leiomyosarcoma is one of the most common histotypes representing about 10-20% of all STS.[1,2] This tumor may arise in any site of the body, being retroperitoneum, limbs/girdles, and uterus more frequently affected.[1,2] Despite the absence of distinctive morphologic features, there is some genetic and clinical evidence supporting that site of origin may affect both sensitivity to treatments and prognosis.[1-7]

Overall, leiomyosarcoma management is multidisciplinary, but surgery still represents the cornerstone of treatment in localized disease. Unfortunately, despite optimal locoregional treatments, leiomyosarcoma may relapse.[1,2,8-10] For patients with metastatic disease, first-line chemotherapy is currently based on anthracyclines, including doxorubicin alone or in combination with ifosfamide or dacarbazine.[11-13]

Whatever treatment is used, complete remission is a rare event and second- and further-line therapies obtain poor results with only anecdotal long-term survivors.[14] Furthermore, chemosensitivity in STS may vary substantially according to histotype and administered drug. On this basis, cytotoxics for the second- and further-line setting are now increasingly chosen following a histology-driven approach.[15] Indeed, the latest randomized phase 3 trials that led to drug approval (pazopanib,[16] trabectedin,[17,18] and eribulin[19,20]) have emphasized this strategy. Unfortunately, the histotype-tailored approach failed to overcome the results of anthracyclines-based regimens in the neoadjuvant setting.[21,22]

In this context, it has been retrospectively observed that ifosfamide has limited activity in leiomyosarcomas,[23] whereas dacarbazine demonstrated favorable results both as single agent and in combination with gemcitabine.[18,20,24,25] More than 30 years ago, doxorubicin was compared to doxorubicin+dacarbazine in patients affected by advanced uterine sarcomas and carcinosarcomas. No significant survival advantage or response rate improvement was demonstrated with the combination over doxorubicin considering all histotypes together. Nevertheless, in uterine

leiomyosarcoma the combination achieved a response rate of 30% (6 out 20 evaluable patients).[26] Hence, dacarbazine is increasingly used in combination with doxorubicin as first-line treatment for advanced leiomyosarcoma,[11,12,27-31] despite we lack a formal prospective evidence to support this choice.

In this scenario of relative uncertainty and in the lack of ongoing controlled prospective studies, we have gathered a large retrospective series of patients affected by advanced/metastatic leiomyosarcoma treated with first-line anthracycline-based regimens within EORTC Soft Tissue and Bone Sarcoma Group (STBSG) referral centers to compare doxorubicin+dacarbazine with doxorubicin either alone or in combination with ifosfamide.

PATIENTS AND METHODS

Patients Selection

This was a multicenter, retrospective study involving reference Institutions within the EORTC STBSG (Table S1). After approval from the Institutional Review Board and/or Ethic Committee of participating Institutions, patients who met the following criteria were included: histologically confirmed and non-surgically resectable or metastatic leiomyosarcoma (including leiomyosarcoma with pleomorphic features);[1] first-line treatment for metastatic disease with doxorubicin either alone or in combination with ifosfamide or dacarbazine started between January 2010 and December 2015; measurable disease (RECIST 1.1); Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2; age ≥18 years. Patients with major comorbidities that might jeopardize the interpretation of the data were excluded (*i.e.*, another malignancy within the previous 5 years, or other severe and/or uncontrolled concurrent medical disease).

Outcomes

The primary objective of this study was to explore the activity of doxorubicin+dacarbazine, doxorubicin+ifosfamide and doxorubicin alone as first-line treatments for non-resectable/metastatic leiomyosarcomas. Endpoints of the study included progression-free survival (PFS), overall survival

(OS), and RECIST 1.1 overall response rate (ORR). PFS duration was estimated by an interval-censoring method that accounts for the variable schedules of follow-up measurements in the routine clinical practice.[32] Details on endpoints measurement are reported in the appendix (page 2). Data on subsequent treatments were keenly collected.

Due to the absence of randomization we performed matching of patients across treatment arms using a propensity score, *i.e.* an estimate of the probability of each patient to receive one of the three treatments. [33-35] We used a 2:1:2 matching ratio resembling the distribution of treatments between the three arms observed in the dataset and then, as a sensitivity analysis, we conducted pairwise 1:1 matching of the three possible treatment pairs. Details on the propensity score methods are available in the appendix (page 2, 7-19; Figure S1-S3; Table S5-S11).

Statistical Analysis

Statistical analyses were performed using SAS statistical software v9.4. A p-value ≤ 0.05 was considered statistically significant. We provide descriptive statistics for population characteristics. Qualitative variables were compared using the χ^2 and Fisher's exact tests. Tests were two-sided and results were reported with 95% confidence intervals (95%CI) or interquartile ranges (IQR) whenever indicated. ORRs were compared among treatment arms by means of the odds ratio (OR) estimates obtained from logistic regression. In order to determine potential predictive factors (histology, site of primary, age, gender, ECOG performance status, tumor extent, and FNCLCC grade) and their related effects, a full multivariate analysis with the administered chemotherapy as additional covariate was run using the interval-censored and the Cox model with Firth adjustment for PFS and OS, respectively. Wald p-values were computed to evaluate the interaction between administered chemotherapy and each factor.

RESULTS

303 patients treated at 18 different EORTC STBSG Institutions from nine European countries were deemed eligible and were included in the present analysis (Figure 1). Marked differences in the

distribution of chemotherapy across the 18 contributing institution were observed (Table S1). The first-line treatment was doxorubicin plus dacarbazine for 117 (38.6%), doxorubicin plus ifosfamide for 71 (23.4%), and doxorubicin alone for 115 (38.0%) patients. Baseline characteristics of the studied population are reported in Table 1. As expected, fewer patients younger than 50-year-old and more patients over 70-year-old were treated with doxorubicin alone compared to combination regimens. Other characteristics were similar across the three arms with the exception of an excess of inoperable, locally advanced disease without metastases for doxorubicin+ifosfamide arm. At the time of data cutoff (December 22, 2017), only one patient in the doxorubicin+dacarbazine arm was still on treatment. Median number of administered cycles were six, three, and five for doxorubicin+dacarbazine, doxorubicin+ifosfamide and doxorubicin alone, respectively. Table 2 reports further details on chemotherapy regimens.

At the time of analysis, the overall median follow-up was 41 months for the whole series (IQR: 26.3-56.7), with shorter follow-up for doxorubicin+dacarbazine [31.7 months (IQR: 23.1-47.2)] compared to both doxorubicin+ifosfamide and doxorubicin alone [50 months (IQR: 37.3-72.7), and 46.1 months (IQR: 31.3-58.4), respectively]. Indeed, patients receiving doxorubicin+dacarbazine were treated more recently and more patients who received this regimen were lost to follow-up or censored for OS. Notably, subsequent treatments were well balanced across the three arms (Table S2).

Unmatched population

Overall, in the 303 patients included in the database, unadjusted median PFS was 9.4 (95%CI 6.1-9.7), 6.8 (4.5-9.5), 5.4 (3.8-6.8) months (Figure 2A, p=0.0723, df=2) with a 6-month PFS rate of 57.9% (48.0-66.5%), 43.9% (23.9-57.3%), 45% (35.3-54.2%), and an observed ORR of 36.8%, 21.5%, and 25.9%, for doxorubicin+dacarbazine, doxorubicin+ifosfamide and doxorubicin alone, respectively. Median OS was 35.4 (28.7-45.7), 21.4 (16.7-26.7), and 29.3 (21.4-33.4) months (Figure 3A, p=0.0258), with a 24-month OS rate of 68.8% (58.9-76.8%), 41.9% (30.0-53.3%) and

56.0% (46.1-64.8%) for doxorubicin+dacarbazine, doxorubicin+ifosfamide and doxorubicin alone, respectively.

Adjusting for all baseline factors (histology, site of primary, age, gender, ECOG performance status, tumor extent, and FNCLCC grade) revealed a significant difference in terms of PFS for doxorubicin+dacarbazine vs. doxorubicin (HR 0.60, 95%CI:0.44-0.82, p=0.0014) but not for doxorubicin+ifosfamide vs. doxorubicin HR 0.79 (95%CI: 0.56-1.10). There was no significant difference between groups in terms of OS (HR for doxorubicin + dacarbazine and for doxorubicin + ifosfamide vs. doxorubicin were 0.78 (95%CI: 0.52-1.16) and 1.21 (95%CI: 0.82-1.79), respectively).

Predictive factors

None of the factors included in the multivariate analysis (age, sex, ECOG PS, histotype, site of primary tumor, tumor grade, and tumor extent) appeared predictive for treatment effect in terms of both PFS and OS based on interaction tests (appendix pages 5-6, Table S3-S4). We observed a trend toward a worse outcome for uterine vs. non-uterine origin especially for patients who received doxorubicin alone. Nonetheless, this difference did not reach significance in the overall population and the number of patients affected by uterine leiomyosarcoma did not allow to further explore differences based on site of origin of the primary tumor.

Matched population

After propensity score matching of 205 patients with a 2:1:2 ratio, demographic and baseline tumor characteristics were well balanced with no significant differences between the three arms with the exception of tumor extent that retained an excess of patients with locally advanced disease without metastases in the doxorubicin+ifosfamide arm (Table 1, Figure S1-S3).

In the 2:1:2 matched population, doxorubicin+dacarbazine showed a significantly longer PFS compared to doxorubicin alone [median 9.2 months (95%CI 5.2-9.7) *vs.* 4.8 (2.3-6.0); HR 0.72 (0.52-0.99)], but not to doxorubicin+ifosfamide [8.2 months (5.2-10.1), HR 1.01 (0.68-1.50)]. PFS did not differ significantly between doxorubicin+ifosfamide and doxorubicin alone [HR 0.71 (0.48-

1.06)]. Estimated 6-month PFS rates were 58.2% (46.4-68.3%), 47.1% (31.5-61.2%), and 42.4% (31.0-53.1%) for doxorubicin+dacarbazine, doxorubicin+ifosfamide, and doxorubicin alone, respectively (Figure 2B).

In the same 2:1:2 matched population, ORR was 30.9% with doxorubicin+dacarbazine, 19.5% with doxorubicin+ifosfamide, and 25.6% with doxorubicin alone [OR 1.70 (0.68-4.24) for doxorubicin+dacarbazine *vs.* doxorubicin+ifosfamide; OR 1.26 (0.63-2.50) for doxorubicin+dacarbazine *vs.* doxorubicin alone; and OR 0.74 (0.29-1.86) for doxorubicin+ifosfamide vs. doxorubicin alone].

The estimated median OS was longer with doxorubicin+dacarbazine [36.8 months (95%CI 27.9-47.2)] compared to both doxorubicin+ifosfamide [21.9 months (95%CI 16.7-33.4), HR 0.65 (95%CI 0.40-1.06)] and doxorubicin alone [30.3 months (95%CI 21.0-36.3), HR 0.66 (95%CI 0.43-0.99)] (Figure 3B). OS rates at 12- and 24-month were 81.5% (70.8-88.6%) and 69.6% (57.8-78.7%) with doxorubicin+dacarbazine, 82.9% (67.5-91.5%) and 49.5% (33.1-63.9%) with doxorubicin+ifosfamide, 76.3% (65.4-84.2) and 59.0% (47.2-69.1%) with doxorubicin alone. Indeed, survival curves started to separate after 18 months (Figure 3B).

Adjusted analysis in the matched population

Since there remained minor imbalances in baseline characteristics after matching (Table 1), we also performed comparisons adjusted for baseline factors. The difference between treatments in terms of PFS was statistically significant (p=0.0023 overall) with HR 0.53 (95%CI 0.36-0.77, p=0.0009) for doxorubicin+dacarbazine *vs*. doxorubicin and HR 0.58 (95%CI 0.38-0.89, p=0.0135) for doxorubicin+ifosfamide *vs.* doxorubicin. There was no significant difference between groups in terms of OS (p=0.2089) with HR 0.70 (95%CI 0.44-1.13, p=0.1433) for doxorubicin+dacarbazine *vs.* doxorubicin and HR 1.07 (95%CI: 0.67-1.71, p=0.7789) for doxorubicin+ifosfamide *vs*. doxorubicin.

Sensitivity analyses

Population characteristics of the new dataset of patients (Figure S1-S3, Table S5-S11) as well as results of the three pairwise matched populations obtained with a 1:1 ratio are reported in the supplementary appendix (Figure S4-S6; Table S12-S14; Figure S7-S9).

DISCUSSION

To our knowledge, this is the largest retrospective study investigating the value of first line treatment for advanced leiomyosarcoma. Despite the limitations of a retrospective study, we observed intriguing signs of activity for doxorubicin and dacarbazine combination both in the unadjusted and in the propensity-score-matched population. In particular, median PFS and ORR were above 9 months and 30%, respectively. These results favorably compare with both historical controls and the results observed with either doxorubicin+ifosfamide or doxorubicin alone in our study.[13,36-38]

Notably, outcomes of the doxorubicin+dacarbazine arm were also consistent with the few data previously reported for this combination in leiomyosarcomas.[26,29] Furthermore, although retrospective, the outcomes observed in the doxorubicin alone and in the doxorubicin+ifosfamide arms are consistent with the ones reported in the randomized EORTC 62012 study using the same regimens [median PFS for leiomyosarcoma patients: 6.1 and 6.6 months, respectively (unpublished data)].[13]

Looking at our data from another perspective, this study confirms the limited role of ifosfamide in leiomyosarcoma.[23,39] Indeed, patients who received this drug reported the lowest response rate and lowest median OS among the three arms, with only a non-significant trend toward an improved PFS compared to doxorubicin alone. Given the retrospective nature of the study, we cannot draw definitive conclusions. Nonetheless, taking also into consideration the relevant toxicities associated with ifosfamide, the use of this drug in leiomyosarcomas should be considered with caution.

Notably, we observed a marked difference in treatment choice across reference Centers in Europe that reflects the current uncertainty on the topic that prompted our study. In particular, some Centers used mainly doxorubicin in combination with either dacarbazine or ifosfamide, whereas others preferentially delivered doxorubicin as monotherapy. The median delivered doses of chemotherapy

are consistent with guidelines and literature data.[12,39] As frequently observed in clinical practice, doxorubicin in combination with either ifosfamide or dacarbazine was seldom used at a slightly lower dose than the one used when the drug is delivered as monotherapy (nearly 60 vs. 75 mg/m2, respectively). Nonetheless, this difference was not statistically significant.

Putting our data in the clinical context of advanced leiomyosarcoma, doxorubicin alone or gemcitabine+docetaxel (+/- bevacizumab) demonstrated a median PFS of about 6 months with a response rate ranging from 10 to 30% at most.[13,37,38] We decided not to include in our analysis the combination of gemcitabine+docetaxel or the MAID protocol (MESNA, doxorubicin, ifosfamide, and dacarbazine)[30] since very few patients have been treated in the first-line setting with these regimens across the 18 reference Centers that contributed in this study. A notable exception in the field of first-line treatments for leiomyosarcoma is represented by the combination of doxorubicin and trabectedin that, up to now, obtained the most promising results. Indeed, in a phase 2, open-label, single-arm study, patients stratified according to uterine and non-uterine origin reported a median PFS of 8 and 13 months with an ORR of about 60% and 40%, respectively.[5] A phase 3 randomized study comparing this combination with doxorubicin alone in advanced leiomyosarcomas is currently ongoing (NCT02997358), whereas a phase 2 randomized trial that included all STS histotypes did not demonstrate benefit from the addition of trabectedin to doxorubicin.[40] More recently, preliminary data from the ANNOUNCE trial did not confirm the survival advantage of adding olaratumab to doxorubicin in all STS as well as in leiomyosarcoma.[36,41]

In our study, the observed OS seems particularly promising and is consistent with the expected longer survival in leiomyosarcoma patients compared to the general sarcoma population.[2,42]

In our multi-institutional series, the doxorubicin+dacarbazine arm showed the longest survival both in the unadjusted and in the propensity-score-matched population, but the shorter follow-up of this arm weakens the comparison among the three regimens. Although a median follow-up of 32 months could be considered adequate in the STS setting being more than two times longer than the expected median survival for this population,[13,36] the observed excess of censored patients in this arm might

indeed lead to an overestimation of OS by means of Kaplan-Meier method. Despite this potential issue in OS evaluation, the follow-up length does not affect PFS estimation.

The limitations of the present study are mainly related to its retrospective nature. As mentioned above, there is a potential bias in center-specific chemotherapy preference. Moreover, as in the great majority of retrospective studies, we did not perform a central pathological review of the diagnosis or a central review of radiological responses. Nonetheless, both these potential issues are limited by the fact that data came from reference centers across Europe. Indeed, the great majority of the diagnoses have been confirmed by reference sarcoma pathologists in each country, and disease responses have been reviewed by the involved investigator(s) at each site according to RECIST 1.1. Another potential bias is related to the risk of PFS overestimation due to longer time intervals between CT scans that could delay disease progression detection. Nonetheless, the risk of this bias was greatly limited by our choice of an interval-censoring approach to the data analysis. This choice allowed for a better PFS estimation that, as mentioned above, was superimposable to the outcomes observed in the prospective EORTC 62012 trial for both doxorubicin alone and doxorubicin+ifosfamide arm.[13]

In the lack of prospective randomized studies and in light of the negative results of the ANNOUNCE trial, data from analyses based on adjustment for baseline covariates and propensity score matching represent a relevant source of information although they should remain mainly hypothesis-generating. Propensity score allowed us to reduce the bias related to treatment allocation in a non-randomized, retrospective study and was based on the most relevant covariates available in our database. However, matching has the limitation to diminish the total number of matched patients to the arm with the lowest recruitment (in our study doxorubicin+ifosfamide), thus reducing the power of the analysis and limiting the generalization of the estimated effect.[33-35] That said, the results of adjusted analyses in the matched and unmatched populations appear consistent and suggest that PFS might be superior in the group of patients treated with doxorubicin+dacarbazine compared to doxorubicin alone.

In conclusion, our study showed that doxorubicin and dacarbazine combination is an intriguing treatment option for leiomyosarcoma that deserves further investigations in prospective trials. Indeed, based on these results, a phase 3 randomized study is currently being developed within the frame of the EORTC Soft Tissue and Bone Sarcoma Group aiming to explore the role of neoadjuvant doxorubicin+dacarbazine compared to surgery alone in patients affected by high grade, >5 cm, localized retroperitoneal leiomyosarcoma (STRASS2 study).

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FIGURES LEGENDS

Figure 1. CONSORT diagram.

Figure 2. Progression-free survival. Panel A, unadjusted population; Panel B, 2:1:2 propensity-score-matched population for the three treatment arms. Purple line doxorubicin plus dacarbazine, blue line doxorubicin plus ifosfamide, red line doxorubicin alone.

Figure 3. Overall survival. Panel A, unadjusted population; Panel B, 2:1:2 propensity-score-matched population for the three treatment arms. Purple line doxorubicin plus dacarbazine, blue line doxorubicin plus ifosfamide, red line doxorubicin alone.