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

D'Ambrosio, L.; Touati, N.; Blay, J.Y.; Grignani, G.; Flippot, R.; Czarnecka, A.M.; ... ; Treatment Canc Soft Tissue Bone Sa

Original Article

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

Lorenzo D'Ambrosio, MD, PhD [1,2]; Nathan Touati, PhD[3]; Jean-Yves Blay, MD [4]; Giovanni Grignani, MD [2]; Ronan Flippot, MD[5]; Anna M. Czarnecka, MD[6,7]; Sophie Piperno-Neumann, MD[8]; Javier Martin-Broto, MD[9]; Roberta Sanfilippo, MD[10]; Daniela Katz, MD[11]; Florence Duffaud, MD[12]; Bruno Vincenzi, MD[13]; Daniel P. Stark, MD[14]; Filomena Mazzeo, MD[15]; Armin Tuchscherer, MD[16]; Christine Chevreau, MD [17]; Jenny Sherriff, MD[18]; Anna Estival, MD[19]; Saskia Litière, PhD[3]; Ward Sents, PhD[3]; Isabelle Ray-Coquard, MD, PhD[4]; Francesco Tolomeo, MD[2]; Axel Le Cesne, MD[5]; Piotr Rutkowski, MD[6,7]; Silvia Stacchiotti, MD [10]; Bernd Kasper, MD [20]; Hans Gelderblom, MD[21]; and Alessandro Gronchi, MD [22]; on behalf of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

BACKGROUND: The optimal treatment for advanced leiomyosarcoma is still debated. Given histotype-specific prospective controlled data lacking, this study retrospectively evaluated doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone as first-line treatments for advanced/metastatic leiomyosarcoma treated at European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) sites. **METHODS:** The inclusion criteria were a confirmed histological diagnosis, treatment between January 2010 and December 2015, measurable disease (Response Evaluation Criteria in Solid Tumors 1.1), an Eastern Cooperative Oncology Group performance status ≤2, and an age ≥ 18 years. The endpoints were progression-free survival (PFS), overall survival (OS), and overall response rate (ORR). PFS was analyzed with methods for interval-censored data. Patients were matched according to their propensity scores, which were estimated with a logistic regression model accounting for histology, grade, age, sex, performance status, tumor site, and tumor extent. **RESULTS:** Three hundred three patients from 18 EORTC-STBSG sites were identified. One hundred seventeen (39%) received doxorubicin plus dacarbazine, 71 (23%) received doxorubicin plus ifosfamide, and 115 (38%) received doxorubicin. In the 2:1:2 propensity score–matched population (205 patients), the estimated median PFS was 9.2 months (95% confidence interval [CI], 5.2-9.7 months), 8.2 months (95% CI, 5.2-10.1 months), and 4.8 months (95% CI, 2.3-6.0 months) with ORRs of 30.9%, 19.5%, and 25.6% for doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone, respectively. PFS was significantly longer with doxorubicin plus dacarbazine versus doxorubicin (hazard ratio [HR], 0.72; 95% CI, 0.52-0.99). Doxorubicin plus dacarbazine was associated with longer OS (median, 36.8 months; 95% CI, 27.9-47.2 months) in comparison with both doxorubicin plus ifosfamide (median, 21.9 months; 95% CI, 16.7-33.4 months; HR, 0.65; 95% CI, 0.40-1.06) and doxorubicin (median, 30.3 months; 95% CI, 21.0-36.3 months; HR, 0.66; 95% CI, 0.43-0.99). Adjusted analyses retained an effect for PFS but not for OS. None of the factors selected for multivariate analysis had a significant interaction with the received treatment for both PFS and OS. **CONCLUSIONS:** This is the largest retrospective study of first-line treatment for advanced leiomyosarcoma. In the propensity score–matched population, doxorubicin and dacarbazine showed favorable activity in terms of both ORR and PFS and warrants further evaluation in prospective trials. ***Cancer* 2020;126:2637-2647**. © *2020 American Cancer Society*.

KEYWORDS: dacarbazine, doxorubicin, ifosfamide, leiomyosarcoma, sarcoma, propensity score, retrospective study.

Corresponding Author: Lorenzo D'Ambrosio, MD, PhD, Sarcoma Unit, Division of Medical Oncology, Candiolo Cancer Institute, Strada Provinciale 142, Km 3.95, 10060 Candiolo (Turin), Italy (lorenzo.dambrosio.md@gmail.com).

Daniela Katz's current address: Oncology Institute, Assaf Harofeh Medical Center, Zrifin, Israel

[1]Department of Oncology, University of Turin, Turin, Italy; [2]Sarcoma Unit, Division of Medical Oncology, Candiolo Cancer Institute–FPO, IRCCS, Candiolo, Italy; [3]European Organization for Research and Treatment of Cancer, Brussels, Belgium; [4]Leon Berard Center and Claude Bernard Lyon I University, EURACAN, LYRICAN, Lyon, France; [5]Department of Medicine, Gustave Roussy, Villejuif Cedex, France; [6]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute–Oncology Center, Gliwice, Poland; [7]Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland; [8]Medical Oncology Department, Curie Institute, Paris, France; [9]Virgen del Rocio University Hospital, Institute of Biomedicine Research/CSIC/University of Seville, Seville, Spain; [10]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [11]Oncology Department, Sharett Institute of Oncology, Hadassah-Hebrew University, Jerusalem, Israel; [12]Medical Oncology - University Hospital Timone, Aix-Marseille University, Marseille, France; [13]Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy; [14]St James's Institute of Oncology, Leeds Institute of Cancer and Pathology, University of Leeds and Leeds Teaching Hospitals National Health Service Trust, Leeds, United Kingdom; [15]Medical Oncology, Clinique Universitaire Saint-Luc, Woluwe-Saint-Lambert, Belgium; [16]Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany; [17]Claudius Regaud Institute, University Cancer Institute of Toulouse, Toulouse, France; [18]Cancer Centre, Queen Elizabeth Hospital, Birmingham, United Kingdom; [19]Catalan Institute of Oncology, Barcelona, Spain; [20]Sarcoma Unit, Interdisciplinary Tumor Center, Mannheim University Medical Center, University of Heidelberg, Mannheim, Germany; [21]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands; [22]Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

We thank all data managers and study coordinators from the participating centers for their great help.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32795, **Received:** September 11, 2019; **Revised:** January 5, 2020; **Accepted:** January 24, 2020, **Published online** March 4, 2020 in Wiley Online Library (wileyonlinelibrary.com)

INTRODUCTION

Soft-tissue sarcomas (STSs) are a heterogeneous group of tumors encompassing more than 50 different entities. Leiomyosarcoma is one of the most common histotypes and represents approximately 10% to 20% of all STSs.[1,2] This tumor may arise in any site of the body, with the retroperitoneum, limbs/girdles, and uterus being more frequently affected.[1,2] Despite the absence of distinctive morphologic features, there is some genetic and clinical evidence supporting the hypothesis that the 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 for 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-line and further therapies obtain poor results with only anecdotal long-term survivors.[14] Furthermore, chemosensitivity in STS may vary substantially according to the histotype and the administered drug. On this basis, cytotoxics for the second-line and further setting are now increasingly chosen according to a histology-driven approach.[15] Indeed, the latest randomized phase 3 trials leading to drug approval (pazopanib,[16] trabectedin,[17,18] and eribulin[19,20]) have emphasized this strategy. Unfortunately, the histotype-tailored approach has failed to overcome the results of anthracycline-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 has demonstrated favorable results both as a single agent and in combination with gemcitabine.[18,20,24,25] More than 30 years ago, doxorubicin was compared with doxorubicin plus 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 when all histotypes were considered together. Nevertheless, in uterine leiomyosarcoma, the combination achieved a response rate of 30% (6 of 20 evaluable patients).[26] Hence, dacarbazine is increasingly used in combination with doxorubicin as a first-line treatment for advanced leiomyosarcoma[11,12,27-31] even though we lack formal prospective evidence to support this choice.

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

MATERIALS AND METHODS

Patient Selection

This was a multicenter, retrospective study involving reference institutions within the EORTC-STBSG (Supporting Table 1). After approval from the institutional review board and/or ethics committee of participating institutions, patients who met the following criteria were included: histologically confirmed and nonsurgically 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 (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and an age $\geq$ 18 years. Patients with major comorbidities that might jeopardize the interpretation of the data were excluded (ie, 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 plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone as first-line treatments for nonresectable/metastatic leiomyosarcomas. Endpoints of the study included progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) according to RECIST 1.1. The PFS duration was estimated by an interval-censoring method that accounted for the variable schedules of follow-up measurements in routine clinical practice.[32] Details on endpoint measurement are reported in the supporting information (p 2). Data on subsequent treatments were keenly collected.

Because of the absence of randomization, we performed matching of patients across treatment arms with a propensity score, an estimate of the probability of each patient to receive 1 of the 3 treatments.[33-35] We used a 2:1:2 matching ratio, which resembled the distribution of treatments between the 3 arms observed in the data

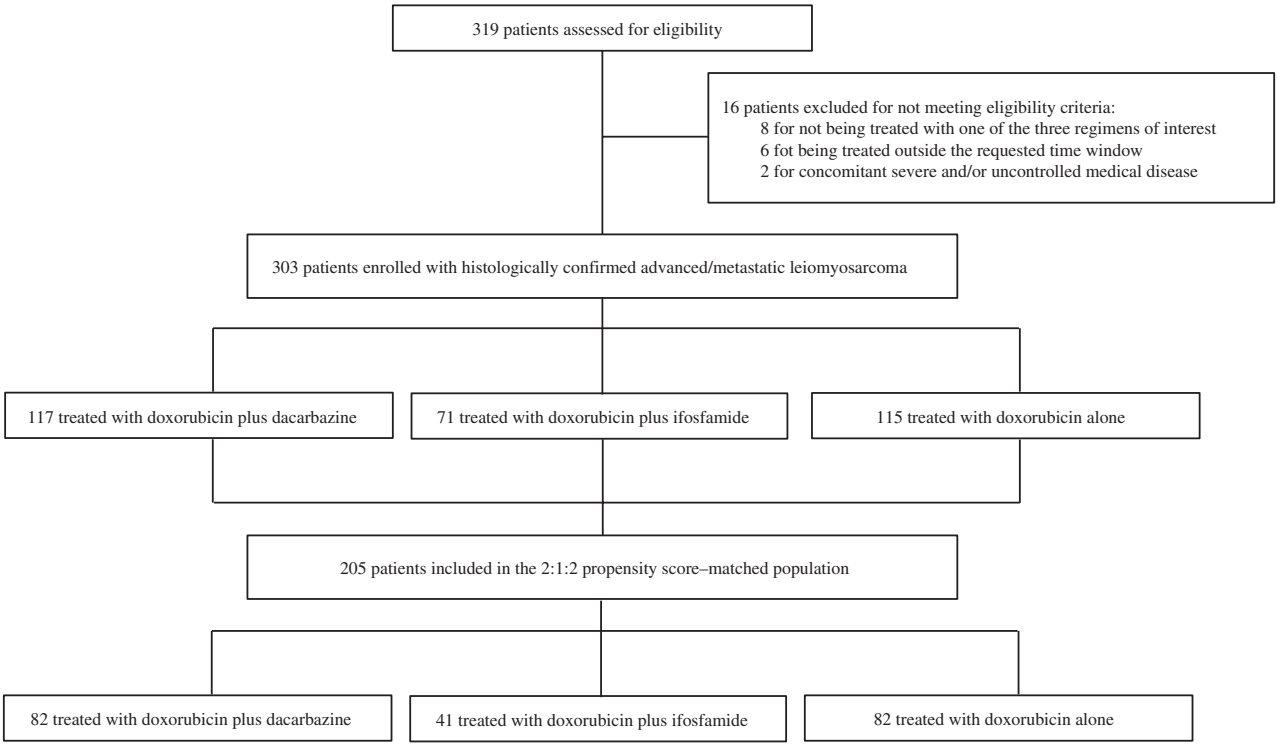

Figure 1. Consolidated Standards of Reporting Trials diagram.

set, and then we conducted pairwise 1:1 matching of the 3 possible treatment pairs as a sensitivity analysis. Details on the propensity score methods are available in the supporting information (pp 2 and 7-19, Supporting Figs. 1-3, and Supporting Tables 5-11).

Statistical Analysis

Statistical analyses were performed with SAS statistical software (version 9.4). A P value $\leq$.05 was considered statistically significant. We provide descriptive statistics for population characteristics. Qualitative variables were compared with chi-square and Fisher exact tests. Tests were 2-sided, and results were reported with 95% confidence intervals (CIs) or interquartile ranges (IQRs) whenever indicated. ORRs were compared among treatment arms by means of the odds ratio (OR) estimates obtained from logistic regression. To determine potential predictive factors (histology, site of primary, age, sex, ECOG performance status, tumor extent, and Fédération Nationale des Centres de Lutte Contre Le Cancer [FNCLCC] grade) and their related effects, a full multivariate analysis with the administered chemotherapy as an additional covariate was run with the interval-censoring method 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

Three hundred three patients treated at 18 different EORTC-STBSG institutions from 9 European countries were deemed eligible and were included in the current analysis (Fig. 1). Marked differences in the distribution of chemotherapy across the 18 contributing institution were observed (Supporting Table 1). The first-line treatment was doxorubicin plus dacarbazine for 117 patients (38.6%), doxorubicin plus ifosfamide for 71 patients (23.4%), and doxorubicin alone for 115 patients (38.0%). The baseline characteristics of the studied population are reported in Table 1. As expected, fewer patients younger than 50 years and more patients older than 70 years were treated with doxorubicin alone in comparison with combination regimens. Other characteristics were similar across the 3 arms with the exception of an excess of inoperable, locally advanced disease without metastases for the doxorubicin-ifosfamide arm. At the time of data cutoff (December 22, 2017), only 1 patient in the doxorubicin-dacarbazine arm was still on treatment. The median numbers of administered cycles were

TABLE 1. Baseline Population Characteristics

Characteristic	Full Population					2:1:2 Matched Population				
	Doxorubicin Alone (n = 115)	Doxorubicin + Ifosfamide (n = 71)	Doxorubicin + Dacarbazine (n = 117)	Total (n = 303)	*P*	Doxorubicin Alone (n = 82)	Doxorubicin + Ifosfamide (n = 41)	Doxorubicin + Dacarbazine (n = 82)	Total (n = 205)	*P*
Age at diagnosis, y										
Median	63	53	57	58		62.5	56	58	59	
Range	32-84	20-78	25-87	20-87		32-84	27-78	29-87	27-87	
Age at diagnosis, No. (%)										
≤40 y	2 (1.7)	10 (14.1)	10 (8.5)	22 (7.3)	<.001	1 (1.2)	1 (2.4)	7 (8.5)	9 (4.4)	.211
>40 to 50 y	9 (7.8)	17 (23.9)	26 (22.2)	52 (17.2)		8 (9.8)	6 (14.6)	14 (17.1)	28 (13.7)	
>50 to 70 y	80 (69.6)	39 (54.9)	72 (61.5)	191 (63.0)		62 (75.6)	30 (73.2)	52 (63.4)	144 (70.2)	
>70 y	24 (20.9)	5 (7.0)	9 (7.7)	38 (12.5)		11 (13.4)	4 (9.8)	9 (11.0)	24 (11.7)	
Sex, No. (%)					.317					.333
Male	28 (24.3)	20 (28.2)	39 (33.3)	87 (28.7)		22 (26.8)	11 (26.8)	30 (36.6)	63 (30.7)	
Female	87 (75.7)	51 (71.8)	78 (66.7)	216 (71.3)		60 (73.2)	30 (73.2)	52 (63.4)	142 (69.3)	
ECOG PS at start, No. (%)					.580					.518
0	49 (42.6)	30 (42.3)	59 (50.4)	138 (45.5)		30 (36.6)	23 (56.1)	39 (47.6)	92 (44.9)	
1	31 (27.0)	25 (35.2)	52 (44.4)	108 (35.6)		23 (28.0)	16 (39.0)	38 (46.3)	77 (37.6)	
2	6 (5.2)	2 (2.8)	4 (3.4)	12 (4.0)		5 (6.1)	1 (2.4)	3 (3.7)	9 (4.4)	
Missing	29 (25.2)	14 (19.7)	2 (1.7)	45 (14.9)		24 (29.3)	1 (2.4)	2 (2.4)	27 (13.2)	
Site of primary tumor, No. (%)					.446					.453
Extremities	19 (16.5)	12 (16.9)	16 (13.7)	47 (15.5)		14 (17.1)	9 (22.0)	14 (17.1)	37 (18.0)	
Thoracic/ abdominal wall	6 (5.2)	4 (5.6)	6 (5.1)	16 (5.3)		4 (4.9)	3 (7.3)	3 (3.7)	10 (4.9)	
Retroperitoneum (including vessels)	37 (32.2)	20 (28.2)	45 (38.5)	102 (33.7)		19 (23.2)	8 (19.5)	23 (28.0)	50 (24.4)	
Uterus	36 (31.3)	22 (31.0)	32 (27.4)	90 (29.7)		25 (30.5)	14 (34.1)	20 (24.4)	59 (28.8)	
Other	11 (9.6)	9 (12.7)	7 (6.0)	27 (8.9)		20 (24.4)	7 (17.1)	22 (26.8)	49 (23.9)	
Head and neck	4 (3.5)	2 (2.8)	1 (0.9)	7 (2.3)						
GI tract	2 (1.7)	2 (2.8)	10 (8.5)	14 (4.6)						
Histology, No. (%)					.369					.309
Leiomyosarcoma	93 (80.9)	54 (76.1)	101 (86.3)	248 (81.8)		65 (79.3)	32 (78.0)	74 (90.2)	171 (83.4)	
Leiomyosarcoma with pleomorphic features	22 (19.1)	17 (13.9)	16 (13.7)	55 (18.1)		17 (20.7)	9 (21.4)	8 (9.8)	34 (16.6)	
Grade (FNCLCC), No. (%)					.610					.645
1	6 (5.2)	6 (8.5)	12 (10.3)	24 (7.9)		5 (6.1)	4 (9.8)	11 (13.4)	20 (9.8)	
2	40 (34.8)	22 (31.0)	41 (35.0)	103 (34.0)		28 (34.1)	14 (34.1)	27 (32.9)	69 (33.7)	
3	56 (48.7)	36 (50.7)	51 (43.6)	143 (47.2)		40 (48.8)	20 (48.8)	36 (43.9)	96 (46.8)	
Missing	13 (11.3)	7 (9.9)	13 (11.1)	33 (10.9)		9 (11.0)	3 (7.3)	8 (9.8)	20 (9.8)	
Tumor extent, No. (%)					.036					.016
Locally advanced	27 (23.5)	24 (33.8)	26 (22.2)	77 (25.4)		21 (25.6)	13 (31.7)	15 (18.3)	49 (23.9)	
Metastatic/ inoperable	58 (50.4)	33 (46.5)	75 (64.1)	166 (54.8)		36 (43.9)	22 (53.7)	55 (67.1)	113 (55.1)	
Both	30 (26.1)	14 (19.7)	16 (13.7)	60 (19.8)		25 (30.5)	6 (14.6)	12 (14.6)	43 (21.0)	
Surgery of primary tumor, No. (%)					.599					.830
No	30 (26.1)	14 (19.7)	29 (24.8)	73 (24.1)		20 (24.4)	8 (19.5)	19 (23.2)	47 (22.9)	
Yes	85 (73.9)	57 (80.3)	88 (75.2)	230 (75.9)		62 (75.6)	33 (80.5)	63 (76.8)	158 (77.1)	
Neoadjuvant chemotherapy, No. (%)					.270					.413
No	114 (99.1)	68 (95.8)	115 (98.3)	297 (98.0)		81 (98.8)	40 (97.6)	82 (100.0)	203 (99.0)	
Yes	1 (0.9)	3 (4.2)	2 (1.7)	6 (2.0)		1 (1.2)	1 (2.4)	0 (0.0)	2 (1.0)	
Adjuvant chemotherapy, No. (%)					.580					.826
No	112 (97.4)	68 (95.8)	115 (98.3)	295 (97.4)		80 (97.6)	40 (97.6)	81 (98.8)	201 (98.0)	
Yes	3 (2.6)	3 (4.2)	2 (1.7)	8 (2.6)		2 (2.4)	1 (2.4)	1 (1.2)	4 (2.0)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FNCLCC, Fédération Nationale des Centres de Lutte Contre Le Cancer; GI, gastrointestinal; PS, performance status.

TABLE 2. Chemotherapy Data

	Chemotherapy of Interest			
	Doxorubicin Alone (n = 115)	Doxorubicin + Ifosfamide (n = 71)	Doxorubicin + Dacarbazine (n = 117)	Total (n = 303)
Total No. of cycles				
Median	5.0	3.0	6.0	
Range	1.0-7.0	1.0-7.0	1.0-27.0	
Doxorubicin starting dose per cycle, mg				
Median	75.0	62.0	60.0	
Range	25.0-78.0	12.0-75.0	27.0-75.0	
Ifosfamide starting dose per cycle, g				
Median		9.0		
Range		1.5-10.0		
Dacarbazine starting dose per cycle, mg				
Median			900.0	
Range			300.0-1125.0	
Dose modifications, No. (%)				
Dose reduction > 10%	21 (18.3)	22 (31.0)	24 (20.5)	67 (22.1)
Dose escalation > 10%	0 (0.0)	1 (1.4)	4 (3.4)	5 (1.7)
Dose delayed for >72 h	17 (14.8)	21 (29.6)	24 (20.5)	62 (20.5)
G-CSF use	36 (31.3)	47 (66.2)	63 (53.8)	146 (48.2)
Reason for interruption, No. (%)				
Scheduled treatment completed	49 (42.6)	31 (43.7)	57 (49.1)	137 (45.2)
Disease progression	40 (34.8)	23 (32.4)	39 (33.6)	102 (33.8)
Toxicity	10 (8.7)	7 (9.9)	8 (6.9)	25 (8.3)
Physician's choice	8 (7.0)	7 (9.9)	6 (5.2)	21 (7.0)
Patient's refusal to continue	3 (2.6)	2 (2.8)	3 (2.6)	8 (2.6)
Other	5 (4.3)	1 (1.4)	3 (2.6)	9 (3.0)

Abbreviation: G-CSF, granulocyte colony-stimulating factor.

6, 3, and 5 for doxorubicin plus dacarbazine, doxorubicin plus 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 months), with shorter follow-up for doxorubicin plus dacarbazine (31.7 months; IQR, 23.1-47.2 months) in comparison with both doxorubicin plus ifosfamide (50 months; IQR, 37.3-72.7 months) and doxorubicin alone (46.1 months; IQR, 31.3-58.4 months). Indeed, patients receiving doxorubicin plus 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 3 arms (Supporting Table 2).

Unmatched Population

Overall, for the 303 patients included in the database, the unadjusted median PFS was 9.4 months (95% CI, 6.1-9.7 months), 6.8 months (95% CI, 4.5-9.5 months), and 5.4 months (95% CI, 3.8-6.8 months; $P = .0723$; $df = 2$; Fig. 2A) with 6-month PFS rates of 57.9% (48.0%-66.5%), 43.9% (23.9%-57.3%), and 45% (35.3%-54.2%) and observed ORRs of 36.8%, 21.5%, and 25.9% with doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone, respectively. The median OS was 35.4 months (95% CI, 28.7-45.7 months), 21.4 months (95% CI, 16.7-26.7 months), and 29.3 months (95% CI, 21.4-33.4 months; $P = .0258$; Fig. 3A) with 24-month OS rates of 68.8% (58.9%-76.8%), 41.9% (30.0%-53.3%), and 56.0% (46.1%-64.8%) with doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone, respectively.

Adjusting for all baseline factors (histology, site of primary, age, sex, ECOG performance status, tumor extent, and FNCLCC grade) revealed a significant difference in terms of PFS for doxorubicin plus dacarbazine versus doxorubicin (hazard ratio [HR], 0.60; 95% CI, 0.44-0.82; $P = .0014$) but not for doxorubicin plus ifosfamide versus doxorubicin (HR, 0.79; 95% CI, 0.56-1.10). There was no significant difference between groups in terms of OS (HR for doxorubicin plus dacarbazine vs doxorubicin, 0.78; 95% CI, 0.52-1.16; HR for doxorubicin plus ifosfamide vs doxorubicin, 1.21; 95% CI, 0.82-1.79).

Predictive Factors

None of the factors included in the multivariate analysis (age, sex, ECOG performance status, histotype, site of primary tumor, tumor grade, and tumor extent) appeared predictive for a treatment effect in terms of both PFS and OS according to interaction tests (pp 5 and 6 and

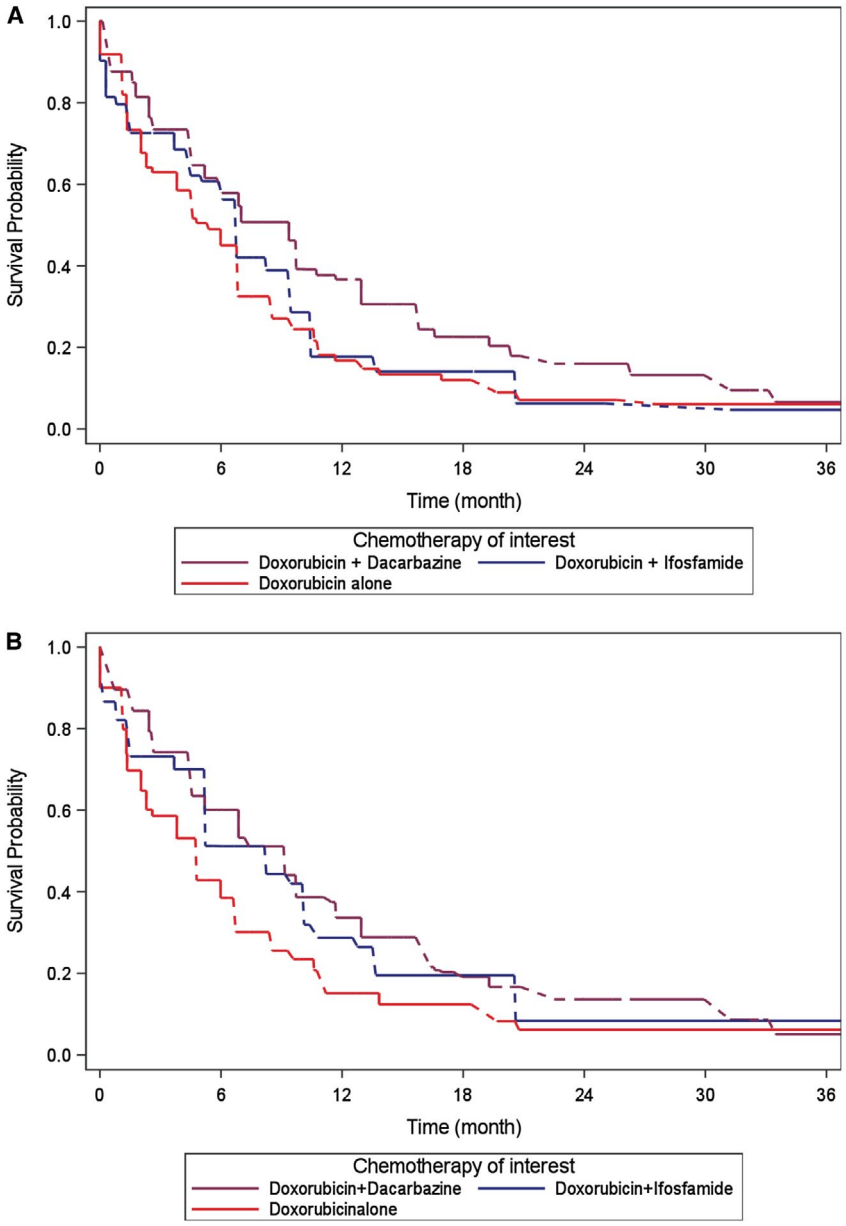

Figure 2. Progression-free survival: (A) unadjusted population and (B) 2:1:2 propensity score–matched population for the 3 treatment arms.

Supporting Tables 3 and 4 in the supporting information). We observed a trend toward a worse outcome with a uterine origin versus a nonuterine 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 us to further explore differences based on the 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 3 arms with the exception of tumor extent, which retained an excess of patients with locally advanced disease without metastases in the doxorubicin-ifosfamide arm (Table 1 and Supporting Figs. 1-3).

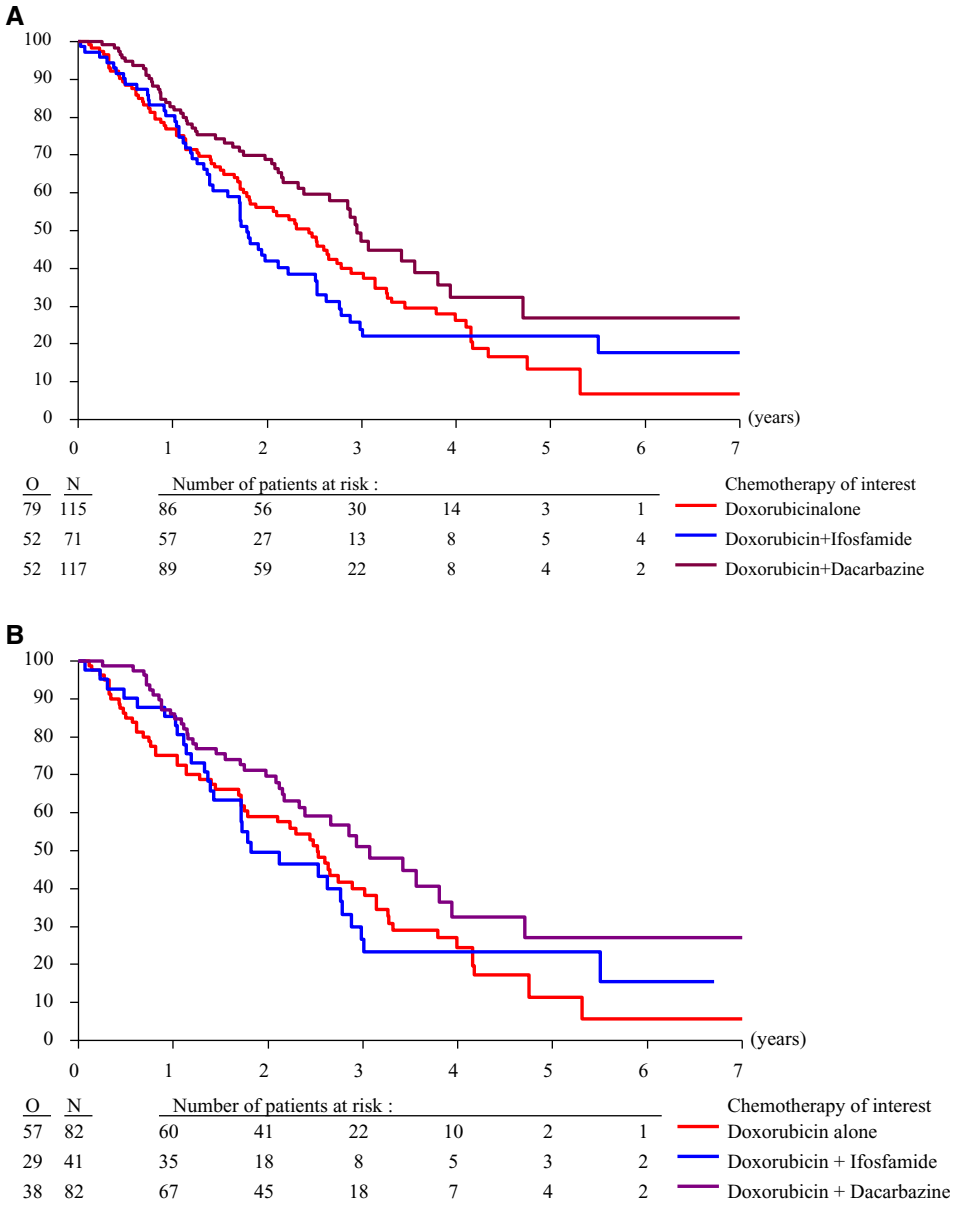

Figure 3. Overall survival: (A) unadjusted population and (B) 2:1:2 propensity score–matched population for the 3 treatment arms. O, total number of events observed; N, number of patients in each treatment arm.

In the 2:1:2 matched population, doxorubicin plus dacarbazine showed significantly longer PFS (median, 9.2 months; 95% CI, 5.2-9.7 months) in comparison with doxorubicin alone (median, 4.8 months; 95% CI, 2.3-6.0 months; HR, 0.72; 95% CI, 0.52-0.99) but not in comparison with doxorubicin plus ifosfamide (median, 8.2 months; 95% CI, 5.2-10.1 months; HR, 1.01; 95% CI, 0.68-1.50). PFS did not differ significantly between doxorubicin plus ifosfamide and doxorubicin alone (HR, 0.71; 95% CI, 0.48-1.06). The 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%) with doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone, respectively (Fig. 2B).

In the same 2:1:2 matched population, the ORR was 30.9% with doxorubicin plus dacarbazine, 19.5% with doxorubicin plus ifosfamide, and 25.6% with doxorubicin alone (OR for doxorubicin plus dacarbazine vs doxorubicin plus ifosfamide, 1.70; 95% CI, 0.68-4.24; OR for doxorubicin plus dacarbazine vs doxorubicin alone, 1.26;

95% CI, 0.63-2.50; OR for doxorubicin plus ifosfamide vs doxorubicin alone, 0.74; 95% CI, 0.29-1.86).

The estimated median OS was longer with doxorubicin plus dacarbazine (36.8 months; 95% CI, 27.9-47.2 months) in comparison with both doxorubicin plus ifosfamide (21.9 months; 95% CI, 16.7-33.4 months; HR, 0.65; 95% CI, 0.40-1.06) and doxorubicin alone (30.3 months; 95% CI, 21.0-36.3 months; HR, 0.66; 95% CI, 0.43-0.99; Fig. 3B). The OS rates at 12 and 24 months were 81.5% (70.8-88.6%) and 69.6% (57.8%-78.7%) with doxorubicin plus dacarbazine, 82.9% (67.5%-91.5%) and 49.5% (33.1%-63.9%) with doxorubicin plus ifosfamide, and 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 (Fig. 3B).

Adjusted Analysis in the Matched Population

Because 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 ($P = .0023$ overall) with an HR of 0.53 (95% CI, 0.36-0.77; $P = .0009$) for doxorubicin plus dacarbazine versus doxorubicin and an HR of 0.58 (95% CI, 0.38-0.89; $P = .0135$) for doxorubicin plus ifosfamide versus doxorubicin. There was no significant difference between groups in terms of OS ($P = .2089$) with an HR of 0.70 (95% CI, 0.44-1.13; $P = .1433$) for doxorubicin plus dacarbazine versus doxorubicin and an HR of 1.07 (95% CI, 0.67-1.71; $P = .7789$) for doxorubicin plus ifosfamide versus doxorubicin.

Sensitivity Analyses

Population characteristics of the new data set of patients (Supporting Figs. 1-3 and Supporting Tables 5-11) as well as results of the 3 pairwise matched populations obtained with a 1:1 ratio are reported in the supporting information (Supporting Figs. 4-9 and Supporting Tables 12-14).

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 the doxorubicin and dacarbazine combination both in the unadjusted population and in the propensity score–matched population. In particular, the median PFS and ORR were greater than 9 months and 30%, respectively. These results favorably compare with both historical controls and the results observed with either doxorubicin plus ifosfamide or doxorubicin alone in our study.[13,36-38]

Notably, the 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 arm and the doxorubicin-ifosfamide arm are consistent with the ones reported in the randomized European Organization for Research and Treatment of Cancer (EORTC) 62012 study using the same regimens (median PFS for patients with leiomyosarcoma, 6.1 and 6.6 months, respectively; Litiere and Touati, unpublished data).[13]

When we look 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 the lowest median OS among the 3 arms, with only a nonsignificant trend toward improved PFS in comparison with 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, we think that the use of this drug in leiomyosarcomas should be considered with caution.

Notably, we observed a marked difference in treatment choices 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 was delivered as monotherapy (nearly 60 vs 75 mg/m^2). Nonetheless, this difference was not statistically significant.

To put our data in the clinical context of advanced leiomyosarcoma, doxorubicin alone or gemcitabine plus docetaxel (with or without bevacizumab) has demonstrated a median PFS of approximately 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 and docetaxel or the mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) protocol[30] because very few patients had been treated in the first-line setting with these regimens across the 18 reference centers that contributed to 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 nonuterine origins reported median PFS times of 8 and 13 months with ORRs of approximately 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 a 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 for all STSs as well as leiomyosarcoma.[36,41]

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

In our multi-institutional series, the doxorubicin-dacarbazine arm showed the longest survival both in the unadjusted population and in the propensity score–matched population, but the shorter follow-up of this arm weakened the comparison among the 3 regimens. Although a median follow-up of 32 months could be considered adequate in the STS setting, being more than 2 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 the Kaplan-Meier method. Despite this potential issue in OS evaluation, the follow-up length does not affect PFS estimation.

The limitations of the current study are mainly related to its retrospective nature. As mentioned previously, 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 were confirmed by reference sarcoma pathologists in each country, and disease responses were reviewed by the involved investigator or investigators 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 computed tomography scans, which could have delayed 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 previously, was superimposable to the outcomes observed in the prospective EORTC 62012 trial for both doxorubicin alone and doxorubicin-ifosfamide arms.[13]

With the lack of prospective randomized studies and in light of the negative results of the ANNOUNCE trial, data from analyses based on adjustments for baseline covariates and propensity score matching represent a relevant source of information, although they should remain mainly hypothesis-generating. Propensity scores allowed us to reduce the bias related to treatment allocation in a nonrandomized, retrospective study and were based on the most relevant covariates available in our database. However, matching has the limitation of diminishing the total number of matched patients to the arm with the lowest recruitment (in our study, doxorubicin plus ifosfamide) and thus reducing the power of the analysis and limiting the generalizability 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 plus dacarbazine versus doxorubicin alone.

In conclusion, our study has shown that the doxorubicin and dacarbazine combination is an intriguing treatment option for leiomyosarcoma that deserves further investigations in prospective trials. Indeed, on the basis of these results, a phase 3 randomized study is currently being developed within the framework of the EORTC-STBSG with the aim of exploring the role of neoadjuvant doxorubicin plus dacarbazine versus surgery alone in patients affected by high-grade, >5-cm, localized retroperitoneal leiomyosarcoma (the STRASS2 study).

FUNDING SUPPORT

Lorenzo D'Ambrosio's research activity was partially supported by Fodazione Piemontese per la Ricerca Sul Cancro (FPRC) 5xmille 2014. Nathan Touati received a fellowship from the Cancer Research Fund of the European Organization for Research and Treatment of Cancer through a grant from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Giovanni Grignani's research activity was partially supported by FPRC 5xmille 2015.

CONFLICT OF INTEREST DISCLOSURES

Lorenzo D'Ambrosio reports travel/accommodations/expenses from PharmaMar and Lilly. Jean-Yves Blay reports honoraria from Bayer, GlaxoSmithKline, Lilly, Novartis, PharmaMar, and Roche; consulting or advisory roles with Bayer, GlaxoSmithKline, Merck, Novartis, PharmaMar, and Roche; research funding from Bayer (institutional), GlaxoSmithKline (institutional), Novartis (institutional), PharmaMar (institutional), and Roche (institutional); and another relationship with Innate Pharma. Giovanni Grignani: reports honoraria from Bayer, Eisai, Lilly, Novartis, Pfizer, and PharmaMar; consulting or advisory roles with Bayer, Eisai, Lilly, Novartis, Pfizer, and PharmaMar; research funding from Bayer, Novartis, and PharmaMar; and travel/accommodations/expenses from PharmaMar.

Ronan Flippot reports travel/accommodations/expenses from Pfizer and Novartis. Anna M. Czarnecka reports participation in speakers' bureaus for Bristol-Myers Squibb, MSD, and Roche and travel/accommodations/expenses from Bristol-Myers Squibb, Lilly, MSD, Novartis, Pfizer, and Roche. Javier Martin-Broto reports honoraria from Lilly and PharmaMar; consulting or advisory roles with PharmaMar, GlaxoSmithKline, Novartis, Amgen, and Bayer; participation in a speakers' bureau for PharmaMar; research funding from Bayer (institutional), Karyopharm (institutional), Celgene (institutional), Pfizer (institutional), Bristol-Myers Squibb (institutional), PharmaMar (institutional), GlaxoSmithKline (institutional), Novartis (institutional), Eisai (institutional), Lixte (institutional), Lilly (institutional), and Roche; expert testimony for PharmaMar and Novartis; travel/accommodations/expenses from PharmaMar and Pfizer; and participation in clinical trials for Blueprint, Deciphera, Nektar, Forma, Amgen, and Daichii-Sankyo. Daniela Katz reports honoraria from Lilly and Roche, consulting or advisory roles with Novartis, and research funding from Bristol-Myers Squibb and Novartis. Florence Duffaud reports honoraria from Bayer and PharmaMar; consulting or advisory roles with Bayer, Lilly, Novartis, and PharmaMar; and travel/accommodations/expenses from PharmaMar. Daniel P. Stark reports research funding from PharmaMar. Filomena Mazzeo reports honoraria from Novartis, PharmaMar, Lilly, Eisai, and Pfizer; a consulting or advisory role with Lilly; and travel/accommodations/expenses from PharmaMar. Christine Chevreau reports consulting or advisory roles with Bristol-Myers Squibb, Novartis, and Pfizer; travel/accommodations/expenses from Ipsen; and participation on boards for AstraZeneca, Bristol-Myers Squibb, Ipsen, MSD, Novartis, and Pfizer. Anna Estival reports travel and conference expenses from PharmaMar, Roche, and Lilly and personal fees from Roche. Isabelle Ray-Coquard reports honoraria from AstraZeneca, PharmaMar, Roche and consulting or advisory roles with AbbVie, Amgen, and Pfizer. Axel Le Cesne reports honoraria from Novartis, Lilly, PharmaMar, Amgen, Pfizer, and Eisai and personal fees from Bayer. Piotr Rutkowski reports honoraria from Amgen, Blueprint Medicines, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Pierre Fabre, Pfizer, and Roche; consulting or advisory roles with Amgen, Blueprint Medicines, Eli Lilly, MSD, Pierre Fabre, and Novartis; participation in speakers' bureaus for Bristol-Myers Squibb, Novartis, and Pfizer; research funding from BMS Brazil (institutional) and Novartis (institutional); and travel/accommodations/expenses from Orphan Europe. Silvia Stacchiotti reports honoraria from Lilly, PharmaMar, and Takeda; consulting or advisory roles with Bayer, Epizyme, Immune Design, Lilly, MaxiVax, and PharmaMar; research funding from Advenchen Laboratories (institutional), Amgen (institutional), Bayer (institutional), Daiichi-Sankyo (institutional), GlaxoSmithKline (institutional), Eisai (institutional), Epizyme (institutional), Lilly (institutional), Novartis (institutional), Pfizer (institutional), and PharmaMar (institutional); and travel/accommodations/expenses from PharmaMar. Bernd Kasper reports honoraria from Bayer, Lilly, Novartis, and PharmaMar; consulting or advisory roles with Bayer, Eisai, and Lilly; and research funding from PharmaMar. Alessandro Gronchi reports honoraria from Lilly, Novartis, Pfizer, and PharmaMar; consulting or advisory roles with Bayer, Lilly, Nanobiotix, Novartis, Pfizer, and PharmaMar; research funding from PharmaMar (institutional); personal fees from SpringWorks; and travel/accommodations/expenses from Nanobiotix and PharmaMar. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Lorenzo D'Ambrosio: Conceptualization, data curation, methodology, resources, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Nathan Touati:** Data curation, formal analysis, methodology, validation, visualization, and writing–review and editing. **Jean-Yves Blay:** Data curation, resources, and writing–review and editing. **Giovanni Grignani:** Data curation, resources, and writing–review and editing. **Ronan Flippot:** Data curation, resources, and writing–review and editing. **Anna M. Czarnecka:** Data curation, resources, and writing–review and editing. **Sophie Piperno-Neumann:** Data curation, resources, and writing–review and editing. **Javier Martin-Broto:** Data curation, resources, and writing–review and editing. **Roberta Sanfilippo:** Data curation, resources, and writing–review and editing. **Daniela Katz:** Data curation, resources, and writing–review and editing. **Florence Duffaud:** Data curation, resources, and writing–review and editing. **Bruno Vincenzi:** Data curation, resources, and writing–review and editing. **Daniel P. Stark:** Data curation, resources, and writing–review and editing. **Filomena Mazzeo:** Data curation, resources, and writing–review and editing. **Armin Tuchscherer:** Data curation, resources, and writing–review and editing. **Christine Chevreau:** Data curation, resources, and writing–review and editing. **Jenny Sherriff:** Data curation, resources, and writing–review and editing. **Anna Estival:** Data curation, resources, and writing–review and editing. **Saskia Litière:** Data curation, formal analysis, methodology, project administration, resources, supervision, validation, writing–original draft, and writing–review and editing. **Ward Sents:** Data curation, project administration, resources, and writing–review and editing. **Isabelle Ray-Coquard:** Data curation, resources, and writing–review and editing. **Francesco Tolomeo:** Data curation, resources, and writing–review and editing. **Axel Le Cesne:** Data curation, resources, and writing–review and editing. **Piotr Rutkowski:** Data curation, resources, and writing–review and editing. **Silvia Stacchiotti:** Data curation, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Bernd Kasper:** Data curation, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Hans Gelderblom:** Data curation, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Alessandro Gronchi:** Conceptualization, methodology, supervision, validation, visualization, writing–original draft, and writing–review and editing.

REFERENCES

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. IARC; 2013.
2. George S, Serrano C, Hensley ML, Ray-Coquard I. Soft tissue and uterine leiomyosarcoma. *J Clin Oncol*. 2018;36:144-150.
3. Beck AH, Lee CH, Witten DM, et al. Discovery of molecular subtypes in leiomyosarcoma through integrative molecular profiling. *Oncogene*. 2010;29:845-854.
4. Guo X, Jo VY, Mills AM, et al. Clinically relevant molecular subtypes in leiomyosarcoma. *Clin Cancer Res*. 2015;21:3501-3511.
5. Pautier P, Floquet A, Chevreau C, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. *Lancet Oncol*. 2015;16:457-464.
6. Cancer Genome Atlas Research Network. Comprehensive and integrated genomic characterization of adult soft tissue sarcomas. *Cell*. 2017;171:950-965.e928.
7. Lucchesi C, Khalifa E, Laizet Y, et al. Targetable alterations in adult patients with soft-tissue sarcomas: insights for personalized therapy. *JAMA Oncol*. 2018;4:1398-1404.
8. Brennan MF, Antonescu CR, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. *Ann Surg*. 2014;260:416-421; discussion 421-422.
9. Gronchi A, Lo Vullo S, Colombo C, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. *Ann Surg*. 2010;251:506-511.
10. Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS. Prognostic factors for disease-specific survival after first relapse of soft-tissue sarcoma: analysis of 402 patients with disease relapse after initial conservative surgery and radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003;57:739-747.
11. von Mehren M, Randall RL, Benjamin RS, et al. Soft Tissue Sarcoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16:536-563.
12. Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv51-iv67.
13. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15:415-423.
14. Blay JY, van Glabbeke M, Verweij J, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. *Eur J Cancer*. 2003;39:64-69.
15. Casali PG. Histology- and non–histology-driven therapy for treatment of soft tissue sarcomas. *Ann Oncol*. 2012;23(suppl 10):x167-x169.

16. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379:1879-1886.
17. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol*. 2009;27:4188-4196.
18. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34:786-793.
19. Schoffski P, Ray-Coquard IL, Cioffi A, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. *Lancet Oncol*. 2011;12:1045-1052.
20. Schoffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016;387:1629-1637.
21. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18:812-822.
22. Zaidi MY, Ethun CG, Tran TB, et al. Assessing the role of neoadjuvant chemotherapy in primary high-risk truncal/extremity soft tissue sarcomas: an analysis of the multi-institutional U.S. Sarcoma Collaborative. *Ann Surg Oncol*. 2019;26:3542-3549.
23. Sleijfer S, Ouali M, van Glabbeke M, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). *Eur J Cancer*. 2010;46:72-83.
24. Gottlieb JA, Benjamin RS, Baker LH, et al. Role of DTIC (NSC-45388) in the chemotherapy of sarcomas. *Cancer Treat Rep*. 1976;60:199-203.
25. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29:2528-2533.
26. Omura GA, Major FJ, Blessing JA, et al. A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer*. 1983;52:626-632.
27. Saiki JH, Baker LH, Rivkin SE, et al. A useful high-dose intermittent schedule of Adriamycin and DTIC in the treatment of advanced sarcomas. *Cancer*. 1986;58:2196-2197.
28. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. *J Natl Cancer Inst*. 1991;83:926-932.
29. Bitz U, Pink D, Busemann C, Reichardt P. Doxorubicin (Doxo) and dacarbacin (DTIC) as first-line therapy for patients (pts) with locally advanced or metastatic leiomyosarcoma (LMS) and liposarcoma (LPS). *J Clin Oncol*. 2011;29(15 suppl):10094.
30. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol*. 1993;11:1276-1285.
31. Borden EC, Amato DA, Rosenbaum C, et al. Randomized comparison of three Adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol*. 1987;5:840-850.
32. Finkelstein DM, Wolfe RA. A semiparametric model for regression analysis of interval-censored failure time data. *Biometrics*. 1985;41:933-945.
33. Lechner M. Identification and estimation of causal effects of multiple treatments under the conditional independence assumption. In: Lechner M, Pfeiffer F, eds. Econometric Evaluation of Labour Market Policies. Physica; 2001:43-58.
34. Rassen JA, Glynn RJ, Brookhart MA, Schneeweiss S. Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. *Am J Epidemiol*. 2011;173:1404-1413.
35. Rassen JA, Glynn RJ, Rothman KJ, Setoguchi S, Schneeweiss S. Applying propensity scores estimated in a full cohort to adjust for confounding in subgroup analyses. *Pharmacoepidemiol Drug Saf*. 2012;21:697-709.
36. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet*. 2016;388:488-497.
37. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol*. 2017;18:1397-1410.
38. Hensley ML, Miller A, O'Malley DM, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. *J Clin Oncol*. 2015;33:1180-1185.
39. Le Cesne A, Judson I, Crowther D, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *J Clin Oncol*. 2000;18:2676-2684.
40. Martin-Broto J, Pousa AL, de Las Penas R, et al. Randomized phase II study of trabectedin and doxorubicin compared with doxorubicin alone as first-line treatment in patients with advanced soft tissue sarcomas: a Spanish Group for Research on Sarcoma study. *J Clin Oncol*. 2016;34:2294-2302.
41. Tap W, Wagner A, Papai Z, et al. ANNOUNCE: a randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS) [abstract LBA3]. *J Clin Oncol*. 2019;37(18 suppl):LBA3.
42. Parikh RC, Lorenzo M, Hess LM, Candrilli SD, Nicol S, Kaye JA. Treatment patterns and survival among older adults in the United States with advanced soft-tissue sarcomas. *Clin Sarcoma Res*. 2018;8:8.