

Randomized Multicenter and Stratified Phase II Study of Gemcitabine Alone Versus Gemcitabine and Docetaxel in Patients with Metastatic or Relapsed Leiomyosarcomas: A Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study)

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ABSTRACT

Background. This study aimed to evaluate the efficacy and toxicity of single-agent gemcitabine versus gemcitabine plus docetaxel as second-line therapy in patients with uterine and nonuterine leiomyosarcoma (LMS).

Patients and Methods. Patients had metastatic or unresectable LMS and had received one prior anthracycline-based regimen. A total of 90 patients received either single-agent gemcitabine (arm A; gemcitabine, 1,000 mg/m² i.v. for 100 minutes on days 1, 8, and 15 of a 28-day cycle) or a combination of gemcitabine and docetaxel (arm B; gemcitabine, 900 mg/m² i.v. for 90 minutes on days 1 and 8, plus docetaxel, 100 mg/m² i.v. for 1 hour on day 8 of a 21-day cycle with lenograstim). The primary endpoint was the objective response rate.

Results. The objective response rates were 19% and 24% in arm A (gemcitabine) and arm B (gemcitabine plus docetaxel), respectively, for patients with uterine LMS. For patients with nonuterine LMS, the objective response rates were 14% and 5% for arms A and B, respectively. The median progression-free survival times for arms A and B were 5.5 months and 4.7 months, respectively, for patients with uterine LMS. For patients with nonuterine LMS, the median progression-free survival times were 6.3 months and 3.8 months for arms A and B, respectively. One toxic death occurred in arm B.

Conclusions. Both single-agent gemcitabine and gemcitabine plus docetaxel were found to be effective second-line therapies for leiomyosarcomas, with a 3-month

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progression-free survival rate of 40% for LMS with both uterine and nonuterine sites of origin. Single-agent gemcitabine yielded results similar to those of gemcitabine plus

docetaxel in this trial, but patients using single-agent gemcitabine experienced less toxicity. *The Oncologist* 2012;17:1213–1220

INTRODUCTION

Leiomyosarcoma (LMS) is the most common form of uterine sarcoma, comprising 25% of soft-tissue sarcomas [1]. Patients with locally advanced or metastatic LMS have a poor prognosis [2–6], with a median overall survival (OS) time of ~17 months after first-line treatment with a doxorubicin-based regimen [7]. LMS has a wide anatomical distribution and exhibits complex nonrecurring genomic alterations; no specific molecular targets are known to serve as drivers for these sarcomas.

Some phase II studies indicated that LMS patients may exhibit higher rates of objective response than patients with other histological subtypes of soft-tissue sarcoma. In addition, LMS that originates in the uterus may be more chemosensitive than LMS in other sites [8]. Given the known heterogeneity of soft-tissue sarcomas (except for gastrointestinal stromal tumors), studies exploring therapeutic agents in sarcomas should be stratified or specifically designed for particular histological subtypes and sites of disease origin.

In the metastatic setting, the highest response rates reported to be associated with single-agent chemotherapies or combination regimens (i.e., doxorubicin, ifosfamide, cisplatin, gemcitabine, trabectedin, doxorubicin plus ifosfamide, gemcitabine plus docetaxel) are in the range of 15%–53% for uterine LMS [3, 9–15]. Note that response rates vary in the range of 10%–50% for soft-tissue sarcomas in trials without stratification by histological subtype [16–21]. Several phase II studies have investigated gemcitabine alone in a 30-minute infusion and reported low response rates in the range of 3%–18% [22–27].

A fixed-dose-rate infusion of gemcitabine at 10 mg/m² per minute may offer a pharmacologic advantage and has also been explored [25, 28, 29]. The activity of single-agent docetaxel has been reported to be quite limited, with response rates of 0%–18% [30–32]. The combination of fixed-dose-rate infusion gemcitabine plus docetaxel has documented activity against metastatic LMS, particularly uterine LMS [29, 33–36]. However, it is unclear whether this effect results from the prolonged infusion of gemcitabine or the synergy between the two drugs. Maki et al. [35] demonstrated that the combination of gemcitabine and docetaxel may be superior to a higher dose of gemcitabine; the adaptively randomized phase II study included all sarcoma subtypes with broad pretreatment characteristics ranging from zero to three prior chemotherapy regimen(s).

To expand on these investigations, the French Sarcoma Group designed the TAXOGEM study in 2004. This multicentric, open-label, phase II study included patients with metastatic or relapsed LMS after failure of one prior anthracycline-based regimen. Patients were randomized to receive either a fixed-dose-rate infusion of gemcitabine alone or a combination of gemcitabine and docetaxel. Stratification of LMS by uterine and nonuterine sites of origin was planned so that two

distinct phase II studies could be efficiently conducted in one trial, taking into account possible differences in clinical behavior for the two sites of origin.

PATIENTS AND METHODS

Eligibility

Patients were eligible if they had metastatic or unresectable LMS that was histologically confirmed by an expert sarcoma pathologist at the local center and originated in either the uterus or another site (nonuterine LMS). Patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 and had previously received only one doxorubicin-containing chemotherapy regimen. Patients who had received adjuvant therapy <1 year before a relapse were considered to have received first-line therapy for metastatic disease.

Inclusion criteria included the following: at least one progressive target lesion outside the radiation field based on computed tomography or magnetic resonance imaging; adequate organ function, defined as an absolute neutrophil count (ANC) $\geq 1,000/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, total bilirubin ≤ 1.5 -fold the institutional upper limit of normal (ULN), alanine transaminase, aspartate aminotransferase, and alkaline phosphatase ≤ 2.5 -fold the institutional ULN; serum creatinine ≤ 1.5 -fold the institutional ULN; and an Eastern Cooperative Oncology Group performance status score ≤ 2 . Patients had to have completed any previous chemotherapy, radiotherapy, or hormonotherapy at least 4 weeks before enrollment. Pregnant or lactating women and patients with a history of malignancy, a history of grade 3 or 4 neuropathy, or known central nervous system metastases were excluded. All patients provided written informed consent. Histological diagnoses were centrally reviewed by a pathologist from the French Sarcoma Group after inclusion.

Study Design

This randomized phase II study (ClinicalTrials.gov identifier, EU 20518, NCT00227669) was stratified according to the primary tumor location (uterine LMS versus nonuterine LMS). Each stratum of the study was considered to be an independent randomized phase II study. Treatments were administered in the outpatient setting and planned for eight cycles, unless there was evidence of disease progression or unacceptable toxicity.

In the gemcitabine-only arm, 1,000 mg/m² of gemcitabine was administered at a fixed-dose rate of 10 mg/m² per minute via a 100-minute i.v. infusion on days 1, 8, and 15 every 28 days. In the gemcitabine plus docetaxel arm, gemcitabine was administered at a fixed-dose rate of 900 mg/m² in a 90-minute infusion on days 1 and 8, with docetaxel at 100 mg/m² in a 60-minute infusion on day 8 after gemcitabine, every 21 days with lenograstim, a recombinant human G-CSF, in a daily injection

of 150 $\mu\text{g}/\text{m}^2$ from day 9 to day 15. Patients who had previously received pelvic radiation therapy received gemcitabine at a dose of 675 mg/m^2 infused over 68 minutes on days 1 and 8, followed by docetaxel, 75 mg/m^2 , on day 8 infused over 1 hour. The recommended premedication for docetaxel was 8 mg of dexamethasone administered orally twice daily for 4 days starting the day before docetaxel. Treatment was planned to be stopped after eight cycles, unless there was evidence of disease progression or unacceptable toxicity.

Dose Adjustments

Treatment toxicities were graded by National Cancer Institute Common Toxicity Criteria. In the gemcitabine-only arm, treatment was cancelled on day 8 or day 15 for grade >2 ANC or grade >1 platelet count. A 25% reduction in the previous dose was permitted for persistent ANC of grade >2 or platelet count of grade ≥ 1 . Two reductions of the previous dose were permitted. Recombinant G-CSF could be used in all subsequent cycles.

For grade 3–4 hepatic toxicity, treatment was delayed up to a maximum of 14 days until toxicity dropped to grade ≤ 2 . In the gemcitabine plus docetaxel arm, the doses of both gemcitabine and docetaxel were reduced to 75% if patients experienced febrile neutropenia or thrombopenia of grade ≥ 3 for >5 days, neutropenia of grade 3, or platelet count of grade 2 at day 8. If the patient experienced grade 3–4 neurotoxicity, treatment was delayed for 1 week, with a 25% dose reduction of docetaxel (if neurotoxicity had resolved to grade ≤ 2). If the patient's bilirubin level was >1.5 mg/dL , docetaxel was withheld during that cycle.

Evaluation During Treatment

Pretreatment evaluations included a medical history, a physical examination, laboratory tests, an electrocardiogram, computed tomography scans of the pelvis and abdomen, and disease evaluation. During treatment, CBCs were performed weekly. Biochemical profiles were obtained every 3 weeks. The tumor status was assessed every two cycles (every 8 weeks in the gemcitabine-only arm and every 6 weeks in the gemcitabine plus docetaxel arm). To be considered assessable for response, patients had to receive at least one injection of the treatment regimen.

Statistical Analysis

The primary endpoint of the study was the objective response rate. Secondary endpoints were the progression-free survival (PFS) interval, the duration of response, toxicity, and the OS duration.

A Simon phase II study design was used to calculate the number of patients, with stratification according to the primary tumor location in two parallel phase II studies (uterine and nonuterine LMS). Each stratified substudy (uterine or nonuterine LMS) planned to include 20 evaluable patients per arm (gemcitabine versus gemcitabine plus docetaxel), for a total of 80 patients in the study overall. The probability of selecting the best treatment for uterine LMS (response rate of 50%) was 74%, assuming an underlying response rate of 40%. The probability of selecting the best treatment for nonuterine LMS (re-

sponse rate of 40%) was 91.8%, assuming an underlying response rate of 20%.

Rates of response and 95% confidence intervals (CIs) were determined. The survival analysis was performed on the intent-to-treat population and on the population evaluable for therapy. OS and PFS times were calculated using the Kaplan–Meier method. The PFS interval was calculated from the date of randomization until the date of the first progression, date of death, or last documented contact. The OS times was calculated from the date of randomization until the date of death or the date of the last known contact.

RESULTS

Patient Characteristics

Patients were enrolled from February 2006 to December 2008 in 17 institutions across France. In all, 90 patients were included: 46 in the uterine LMS group (Table 1) and 44 in the nonuterine LMS group (Table 2). In total, seven patients were excluded from the efficacy analysis because of major protocol violations: three patients in the nonuterine group (i.e., no prior anthracycline-based regimen, a single target lesion in a previously irradiated field, and three prior chemotherapy regimens for metastases) and four patients in the uterine group (i.e., no measurable target lesion, progression before the first course of treatment [two patients], and an interval >12 months since the end of adjuvant chemotherapy). In all, 73 tumors (81%) were histologically reviewed and confirmed in 95% of cases: 35 (76%) in the uterine group and 38 (86%) in the nonuterine group.

A total of 11 patients (24%) in the uterine LMS group and 11 patients (25%) in the nonuterine LMS group had received prior adjuvant chemotherapy (seven and nine patients, respectively, had received it within 1 year). The median patient age was 63 years (range, 29–78 years) in the nonuterine group and 57 years (range, 41–80 years) in the uterine group. The median Eastern Cooperative Oncology Group performance status score was 1 in the nonuterine group and 0 in the uterine group. In total, 83 patients were evaluated for efficacy: 41 in the nonuterine group and 42 in the uterine group.

In the nonuterine group, most cases of LMS were high-grade tumors. All patients had received first-line anthracycline-based chemotherapy for metastatic disease, except for five patients in the gemcitabine-only arm and four patients in the gemcitabine plus docetaxel arm. For seven patients, the interval between the end of adjuvant anthracycline-based chemotherapy and first-line treatment of metastases was <1 year. Two patients were ineligible.

In the uterine LMS group, all but one patient in the gemcitabine arm and all but seven patients in the gemcitabine plus docetaxel arm had received anthracycline-based chemotherapy for metastatic disease. One patient was ineligible because the interval between the end of adjuvant anthracycline-based chemotherapy and first-line treatment for metastatic disease was >1 year.

In the nonuterine LMS group, postoperative radiation had been delivered for nine and 11 patients in the gemcitabine-only and gemcitabine plus docetaxel arms, respectively. In the uterine group, 16 and 12 patients in the gemcitabine-only and gem-

Table 1. Patient characteristics in the uterine group

	Gemcitabine			Gemcitabine + docetaxel		
	<i>n</i>	%	Median (range)	<i>n</i>	%	Median (range)
<i>n</i> of patients	22	100		24	100	
Age, yrs			54 (41–80)			58 (43–76)
ECOG performance status score			0 (0–2)			0 (0–2)
Prior adjuvant chemotherapy	2	9		9	38	
Relapse <1 yr	1			6		
Relapse >1 yr	1			3		
Received first-line anthracycline-based chemotherapy	21	95		18	75	
Prior radiation (primary tumor)	16	73		12	50	
Metastases (lung/liver)	22 (20/10)	100		23 (20/11)	96	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Patient characteristics in the nonuterine group

	Gemcitabine			Gemcitabine + docetaxel		
	<i>n</i>	%	Median (range)	<i>n</i>	%	Median (range)
<i>n</i> of patients	22	100		22	100	
Age, yrs			64 (35–74)			62 (29–78)
Female	10	45		13	59	
ECOG performance status			1 (0–2)			1 (0–2)
Primary tumor site						
Extremity	9	41		9	41	
Retroperitoneal/abdominal/GI	8	36		7	32	
Trunk	1	4.5		3	13.5	
Other	4	18		3	13.5	
FNCLCC primary tumor grade 2/3	20	91		16	73	
Prior adjuvant chemotherapy	5	23		6	27	
Relapse <1 yr	5			4		
Relapse >1 yr	0			2		
Received first-line anthracycline-based chemotherapy	17	77		18	82	
Prior radiation (primary tumor)	9	43		11	50	
Metastases (lung/liver)	20 (18/6)	91		21 (17/12)	95	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FNCLCC, Fédération Nationale des Centres de lutte Contre le Cancer; GI, gastrointestinal.

citabine plus docetaxel arms, respectively, had received postoperative radiation. More than 90% of the patients had distant metastases at inclusion in both groups. The lung and liver were the two most common metastatic sites.

Treatment Delivery and Toxicity

The median numbers of administered cycles were four in the nonuterine LMS group and five in the uterine group (Table 3). The rate of the dose received compared with the dose planned

in the nonuterine group was 85% in the gemcitabine-only arm; in the gemcitabine plus docetaxel arm, the rates were 95% for gemcitabine and 86% for docetaxel. In the uterine group, the rate of the dose received compared with the dose planned was 96% in the gemcitabine-only arm; in the gemcitabine plus docetaxel arm, the rates were 89% for gemcitabine and 82% for docetaxel.

A small percentage of cycles were delayed in both arms; the median lengths of delay were 7 days and 9 days for the no-

Table 3. Toxicity for the uterine group, nonuterine group, and all sarcomas

	Uterine				Nonuterine				All sarcomas			
	G		G + D		G		G + D		G		G + D	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Leukocytes	54	37	50	11	42	13	53	7	48	25	52	9
Neutrophils	46	32	35	14	31	11	27	6	38	21	31	10
Platelets	63	11	47	26	41	7	41	9	52	8	44	18
Hemoglobin	94	1	82	8	74	2	85	12	84	1	84	10
Nausea/vomiting	20	0	26	0	9	0	18	0	14	0	22	0
Fever/infection	16	1	23	3	20	0	16	0	18	0	19	1
Asthenia	28	0	63	4	29	1	46	7	29	0	55	4
Alopecia	5	0	31	0	9	0	18	0	7	0	25	0
Mucositis	3	0	10	0	10	1	10	1	6	0	10	0
Diarrhea	3	0	16	0	4	0	10	1	3	0	13	0
Cutaneous	4	0	24	0	9	0	23	1	6	0	23	0
Pulmonary	6	1 (4)	8	1 (4)	9	1 (3)	7	0	7	1	7	1
Hepatic	0	1	5	0	14	0	2	2	7	0	3	1
Neurological	7	0	15	0	8	0	15	2	7	0	15	1
Retention	1	0	10	0	0	0	11	0	0	0	11	0

Data are presented as the percentage of cycles for which patients experienced toxicity. Total number of cycles for each regimen is as follows: 103 gemcitabine-only and 111 gemcitabine + docetaxel for the uterine group; 104 gemcitabine-only and 95 gemcitabine + docetaxel for the nonuterine group; and 207 gemcitabine-only and 206 gemcitabine + docetaxel for all sarcomas.
Abbreviations: D, docetaxel; G, gemcitabine.

uterine group and 11 days and 7 days for the uterine group in the gemcitabine-only and gemcitabine plus docetaxel arms, respectively. The main reasons for these delays were personal convenience in the gemcitabine-only arm and grade 2–3 toxicities in the gemcitabine plus docetaxel arm. The main reasons for the interruption of treatment were progression and completion of therapy after eight cycles (in both arms) and toxicity (mainly in the combination arm). No differences in toxicity were observed between the two LMS locations (uterine versus nonuterine). One toxic death occurred from a hemorrhage related to grade 4 thrombocytopenia.

Treatment Responses and Survival

In the uterine LMS group, one complete response and three partial responses were observed in the gemcitabine-only arm (19%; 95% CI, 5%–42%). Five partial responses were observed in the gemcitabine plus docetaxel arm (24%; 95% CI, 8%–47%) (Table 4).

In the nonuterine LMS group, three partial responses were observed (14%; 95% CI, 3%–35%) in the gemcitabine-only arm. Only one partial response was observed in the gemcitabine plus docetaxel arm (5%; 95% CI, 0%–26%).

The nonprogression rates (responses and stable disease) were 68% and 63%, respectively, in the gemcitabine and gemcitabine plus docetaxel arms for the nonuterine group, respectively. For

the uterine group, nonprogression rates were 62% and 71% in the gemcitabine and gemcitabine plus docetaxel arms, respectively.

For the uterine group, the median PFS times were 5.5 months in the gemcitabine arm and 4.7 months in the gemcitabine plus docetaxel arm (Fig. 1). For the nonuterine group, the median PFS times were 6.3 months in the gemcitabine arm and 3.4 months in the gemcitabine plus docetaxel arm (Fig. 2). PFS rates at 3 months and 6 months were not statistically different for either the two drug regimens or the two sites of origin (Table 4). Moreover, the median OS times were 15 months and 13 months in the gemcitabine and gemcitabine plus docetaxel arms, respectively, for the nonuterine group. The median OS times seemed to be better in the uterine group: 20 months and 23 months in the gemcitabine and gemcitabine plus docetaxel arms, respectively.

DISCUSSION

Clinical management of soft-tissue sarcomas has changed considerably since the advent of molecular-targeted therapies (e.g., imatinib and sunitinib) for specific sarcoma subtypes, such as gastrointestinal stromal tumors and dermatofibrosarcoma protuberans. It is increasingly recognized that different sarcoma subtypes may exhibit unique clinical behaviors that may justify different forms of therapy [37]. Doxorubicin and ifosfamide, either alone or in combination, have served as the

	Uterine group (%)		Nonuterine group (%)	
	Gemcitabine	Gemcitabine + docetaxel	Gemcitabine	Gemcitabine + docetaxel
<i>n</i>	21	21	22	19
Assessable patients	21	21	22	19
Complete response, <i>n</i> (%)	1 (5)	0	0	0
Partial response, <i>n</i> (%)	3 (14)	5 (24)	3 (14)	1 (5)
Stable disease	9 (43)	10 (48)	12 (54)	11 (58)
Progression	8 (38)	6 (28)	7 (32)	7 (37)
Objective response, % (95% CI)	19 (5–42)	24 (8–47)	14 (3–35)	5 (0–26)
Nonprogression rate, % (95% CI)	62 (38–82)	71 (48–89)	68 (45–86)	63 (38–84)
Progression-free survival, % (95% CI)				
3 mos	57 (37–76)	71 (50–86)	68 (47–84)	53 (32–73)
6 mos	48 (28–68)	48 (28–68)	50 (31–69)	47 (27–68)
Median progression-free survival (mos)	5.5	4.7	6.3	3.4
Median overall survival (mos)	20	23	15	13

Abbreviation: CI, confidence interval.

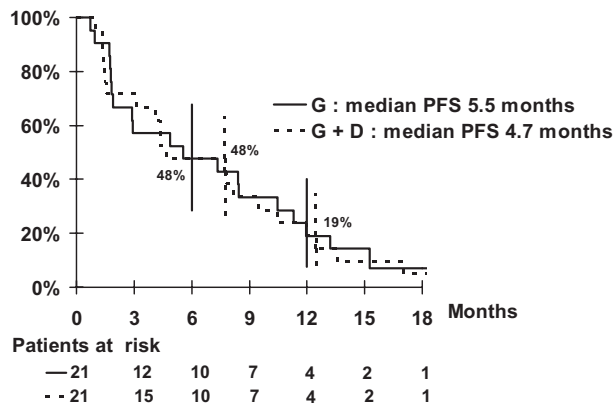


Figure 1. Kaplan–Meier curve of progression-free survival for the uterine leiomyosarcoma group.

chemotherapy backbone for metastatic sarcoma therapy for >15 years. With the limited number of drugs available for sarcoma, there has been an ongoing search for new agents for specific sarcoma subtypes, both cytotoxic and cytostatic.

Great enthusiasm has been generated by the clinical activity reported in a single-institution phase II study of gemcitabine in combination with docetaxel in patients with metastatic and/or unresectable LMS (originating in either the uterus or other soft-tissue sites) [33]. That study enrolled 34 patients, 84% of whom had uterine LMS, and demonstrated that the combination was tolerable and highly active in treated and untreated patients with LMS. A fixed-dose-rate infusion of gemcitabine seemed to result in a higher response rate.

Our TAGOXEM study focused only on LMS patients to test the activity of a true second-line treatment, following failure of a first-line anthracycline-based regimen, in a multi-

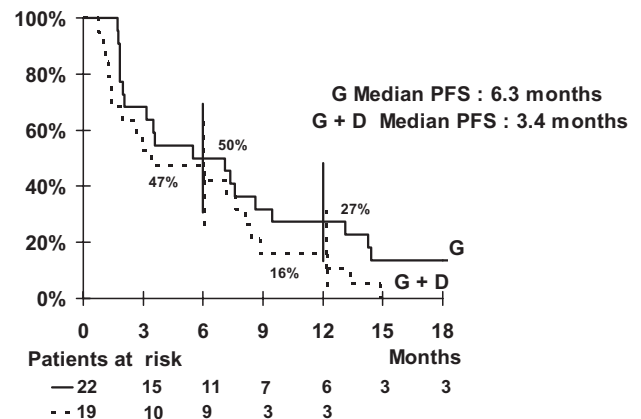


Figure 2. Kaplan–Meier curve of progression-free survival for the nonuterine leiomyosarcoma group.

institutional setting. This trial documented a modest (<25%) objective response rate per the RECIST for both uterine and nonuterine LMS using either gemcitabine alone or a gemcitabine plus docetaxel combination regimen as second-line therapy for metastatic disease. Interestingly, these results are relatively consistent with a retrospective study by the French Sarcoma Group, which reported an objective response rate of 24% with gemcitabine plus docetaxel in LMS patients [36]. Although this study was not stratified, the results are similar to some phase II studies, indicating that LMS originating in the uterus may be more chemosensitive than other sites of LMS [8], with a higher response rate and better OS outcome than in the nonuterine group.

The relative benefits of the gemcitabine plus docetaxel combination versus gemcitabine alone are not so clear in our conventionally randomized phase II trial, in contrast with the Bayesian

randomized phase II trial performed by the SARC (Sarcoma Alliance for Research through Collaboration) group [35]. There are many differences between these trials; for example, the TAXOGEM study was performed in 17 centers in France, whereas the SARC study was performed in eight U.S. centers. Perhaps more importantly, the TAXOGEM study enrolled purely second-line patients after only one prior chemotherapy regimen, whereas the SARC trial enrolled patients who received a variety of prior chemotherapy regimens, ranging from chemotherapy-naïve patients to patients with up to three prior failed chemotherapy regimens. In addition, LMS histology was restricted in the TAXOGEM study, whereas all histologies were present in the SARC study. Moreover, the SARC study included only nine cases (18%) of LMS in the gemcitabine arm, versus 29 cases (40%) in the gemcitabine plus docetaxel arm. Results could have been influenced if gemcitabine is more effective for LMS. More liver localizations were included in the gemcitabine plus docetaxel arm of the nonuterine group in the TAXOGEM study. No significant differences in activity were described for the metastatic localizations.

Additionally, there are differences in drug delivery and dose intensity between these studies. In the gemcitabine arm of the SARC trial, the dose intensity of gemcitabine was somewhat higher than in our TAXOGEM study (800 mg/m² per week in the SARC study versus 750 mg/m² per week in the TAXOGEM study) but remained the same in the gemcitabine plus docetaxel arm. However, the dose intensity of gemcitabine was lower in the combination arm for the SARC study but the same in the TAXOGEM study (750 mg/m²). The possible impact is the same in the SARC study.

It should also be noted that the schedules of drug administration were different between the studies. Gemcitabine was administered at 1,200 mg/m² per week for two of 3 weeks in the SARC study and 1,000 mg/m² per week for three of 4 weeks in the TAXOGEM study, with differences in staging intervals. Moreover, TAXOGEM had a different staging interval between the two arms (“every two cycles” equates to every 8 weeks in the gemcitabine arm versus every 6 weeks in the gemcitabine plus docetaxel arm). The TAXOGEM study was designed to evaluate the response rate as the primary endpoint; these staging intervals may have inflated time to progression in the gemcitabine arm but had no impact on the response rate and OS time.

Despite these differences, the classical randomization design of TAXOGEM allows important comparative insights about the relative safety and efficacy of gemcitabine plus docetaxel versus single-agent gemcitabine without the possible confounding variables associated with changes in patient-related variables that occurred over the duration of the SARC study. Results may be disproportionately influenced by a study with a Bayesian design [38].

The results from the TAXOGEM study confirm prior observations that the objective response rate is higher for uterine LMS (24%) than for nonuterine LMS using a combination of gemcitabine and docetaxel [33–35]. The statistical design of the TAXOGEM study took this into account prospectively, using statistical hypotheses based on the anatomic origin of primary tumors (uterine versus nonuterine LMS).

Interestingly, PFS rates were high in the TAXOGEM study, with 3-month PFS rates in the gemcitabine and gemcitabine plus docetaxel arms of 57% and 71% in the uterine group and 68% and 53% in the nonuterine group, respectively. PFS rates were ~50% at 6 months in both arms and both groups. These results support the hypothesis that both regimens are active as second-line therapy for LMS and match the criteria defining active agents proposed by Van Glabekke et al. [39]. The EORTC STBSG group (EORTC and Soft Tissue and Bone Sarcoma Group) reported that agents used in second-line therapy for metastatic soft-tissue sarcomas should demonstrate a 3-month PFS rate > 40% and a 6-month PFS rate of 14% to be considered active.

Moreover, the TAXOGEM study reported median PFS durations in the gemcitabine and gemcitabine plus docetaxel arms, respectively, of 6.3 months and 3.4 months for nonuterine LMS and 5.5 months and 4.7 months for uterine LMS. To put this in the context of prior studies, Hensley et al. [33] in 2002 reported a median PFS time of 5.6 months with a gemcitabine plus docetaxel combination in metastatic LMS only, with a 47% 6-month PFS rate. In 2007, the SARC study reported median PFS intervals of 3 months and 6.2 months in the gemcitabine and gemcitabine plus docetaxel arms, respectively, for all sarcoma subtypes with a Bayesian study design and heterogeneity in inclusion criteria.

Furthermore, despite the fact that the RECIST-defined response rates were low for both the gemcitabine-only and gemcitabine plus docetaxel treatments in the TAXOGEM study, a significant number of patients experienced the clinical benefit of prolonged stable disease. These findings confirm the hypothesis that durable stable disease in response to systemic therapy is an important clinical endpoint for patients with metastatic LMS. Moreover, efforts should be made to enhance results with other new drugs or new associations, such as gemcitabine plus dacarbazine (already tested in phase II studies [40]) or gemcitabine plus pazopanib (an association tested on second-line LMS in the new LMS03 French Sarcoma Group study).

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