Original Article

Adjuvant Therapy for High-Grade, Uterus-Limited Leiomyosarcoma

Results of a Phase 2 Trial (SARC 005)

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BACKGROUND: Between 30% and 50% of women who have high-grade uterine leiomyosarcoma (uLMS) limited to the uterus at diagnosis remain progression-free at 2 years. Adjuvant pelvic radiation does not improve outcome. The objective of the current study was to determine the 2-year and 3-year progression-free survival (PFS) among a prospective cohort of women who received adjuvant gemcitabine plus docetaxel followed by doxorubicin. **METHODS:** Women with uterus-limited, high-grade uLMS and adequate organ function were eligible. Within 12 weeks of complete resection and after confirmation that they had no evidence of disease on computed tomography (CT) images, the patients received 4 cycles of fixed-dose-rate gemcitabine plus docetaxel. Those who were confirmed disease-free on CT scans after cycle 4 received 4 cycles of doxorubicin. CT imaging for recurrence was performed every 3 months for 2 years, then every 6 months for 3 years. **RESULTS:** In total, 47 women were enrolled (46 evaluable) in 3 years. Characteristics included a median age of 53 years; 1988 International Federation of Gynecology and Obstetrics stage I disease in 81% of patients, stage II disease in 15%, and serosa-only stage IIIA disease in 4%; American Joint Committee on Cancer stage II disease in 13% of patients and stage III disease in 87%; a median tumor size of 8 cm (range, 2.5-30 cm); and a median mitotic rate of 18 mitoses per 10 high-power fields (range, 5-83 mitoses per 10 high-power fields). At a median follow-up of 39.8 months, 21 of 46 patients developed recurrent disease (45.7%). The median time to recurrence was 27.4 months (range, 3-40 months). Seventy-eight percent of patients (95% confidence interval, 67%-91%) were progression-free at 2 years, and 57% (95% confidence interval, 44%-74%) were progression-free at 3 years. The median PFS was not reached and exceeded 36 months. **CONCLUSIONS:** Among women with high-grade, uterus-limited uLMS who received treatment with adjuvant gemcitabine plus docetaxel followed by doxorubicin, 78% remained progression-free at 2 years, and 57% remained progression-free at 3 years. A randomized trial of adjuvant chemotherapy versus observation to determine whether adjuvant chemotherapy can improve survival in women with uterus-limited uLMS is underway. ***Cancer*** **2013;119:1555-61.** © *2013 American Cancer Society.*

KEYWORDS: adjuvant, chemotherapy, uterine, leiomyosarcoma, survival.

INTRODUCTION

Uterine leiomyosarcoma is a rare tumor arising from the smooth muscle of the uterus. Although the majority of women have uterus-limited disease at the time of diagnosis, patients are at substantial risk for both local and distant recurrent disease. Survival after recurrence is poor. In 1 study, the 5-year survival rate for women with 1988 International Federation of Gynecology and Obstetrics (FIGO) stage I disease (tumor limited to the uterus) was only 51%; and, for patients with stage II disease (tumor in uterus and cervix), the 5-year survival rate was 25%.[1] Precise estimates of the risk for recurrence among women who have undergone hysterectomy for uterus-limited leiomyosarcoma are difficult to ascertain. Retrospective studies generally have included small numbers of patients, reporting recurrence rates ranging from 30% to 80% at 2 or 3 years after diagnosis.[2-5] Adjuvant pelvic radiation was studied in a prospective phase 3 trial for women with uterus-limited leiomyosarcoma or carcinosarcoma and did not demonstrate a progression-free survival (PFS) or overall survival (OS) benefit. Among all patients enrolled, the 3-year disease-free survival rate was 52%.[6] Although some retrospective[5,7] and prospective studies have suggested that adjuvant chemotherapy yields a PFS benefit, small patient sample sizes,

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Presented in part at the 2010 Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, IL; and at the 2011 Meeting of the Connective Tissue Oncology Society; October 26-29, 2011; Chicago, IL.

DOI: 10.1002/cncr.27942, **Received:** October 18, 2012; **Revised:** November 12, 2012; **Accepted:** November 27, 2012, **Published online** January 18, 2013 in Wiley Online Library (wileyonlinelibrary.com)

histologic heterogeneity among enrolled patients, and variations in patterns of follow-up for evidence of recurrence have made these data difficult to interpret.[8-10]

Among the chemotherapy regimens with evidence of efficacy in advanced, metastatic uterine leiomyosarcoma are fixed-dose rate gemcitabine plus docetaxel,[11,12] gemcitabine,[13] doxorubicin,[14] and ifosfamide.[15] We sought to determine whether adjuvant treatment of women with uterus-limited, high-grade leiomyosarcoma who receive 4 cycles of fixed-dose-rate gemcitabine followed by 4 cycles of doxorubicin would result in at least 50% of women remaining progression-free at 2 years. This study was designed to enroll only patients with uterine leiomyosarcoma who were confirmed disease-free by on computed tomography (CT) scans before enrollment and to follow all patients prospectively with CT scan imaging to accurately ascertain the time of recurrence. The results from this study were intended to be used to determine whether this regimen would be worthy of testing in a subsequent phase 3 trial with an observation control arm.

MATERIALS AND METHODS

Patient Eligibility

Women aged ≥18 years with high-grade uterine leiomyosarcoma (1988 FIGO stage I [confined to the uterine corpus], stage II [confined to corpus and cervix], or stage IIIA-serosa involvement only [disease could involve the uterine serosa, but patients must have had no other evidence of local spread]) were eligible. Patients should have undergone at least a complete hysterectomy no more than 12 weeks before enrollment. Histologic review was required by the enrolling institution, pathology review had to have indicated that tumor was high-grade leiomyosarcoma,[16] and the mitotic rate was required to be ≥5 mitoses per 10 high-power fields. All patients were required to have no evidence of residual disease or metastatic disease on postresection imaging by CT of the chest/abdomen/pelvis performed within 3 weeks of enrollment on study. Patients were not permitted to have received or to be planning to receive adjuvant pelvic radiation. Other eligibility requirements were: an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate bone marrow function, with an absolute neutrophil count (ANC) >1500/μL, platelets >100,000/μL, and hemoglobin >8 mg/dL; adequate renal function, with a creatinine level ≤1.5 times the institutional upper limit of normal (ULN); adequate hepatic function, with a bilirubin level less than or equal to institutional normal limits; serum aspartate and alanine aminotransferase levels could be up to 5 times the ULN provided the alkaline phosphatase was within normal limits; alkaline phosphatase could be up to 5 times the ULN provided the aspartate and alanine aminotransferase levels both were within normal limits; and adequate neurologic function, with no neuropathy worse than Common Toxicity Criteria grade 1. Exclusion criteria included: the presence of other invasive malignancy within the last 5 years, a history of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80, a history of prior therapy with docetaxel or gemcitabine or doxorubicin, a history of congestive heart failure or cardiac ejection fraction <50%. Treatment with hormone replacement therapy or antihormone agents (tamoxifen, medroxyprogesterone, aromatase inhibitors) or other cytotoxic agents was not permitted for patients on this study either during active adjuvant treatment or in follow-up for as long as the patient was considered disease-free.

The treatment protocol was reviewed by the Institutional Review Boards of all participating institutions and was approved annually. All patients signed written, informed consent before enrollment.

Treatment

Patients received gemcitabine 900 mg/m^2 intravenously over 90 minutes on days 1 and 8, and docetaxel 75 mg/m^2 intravenously vein over 1 hour on day 8. The recommended premedication for docetaxel was dexamethasone 4 to 8 mg orally twice daily for 3 days, starting 12 to 24 hours before docetaxel. All patients received white blood cell growth factor support with either filgrastim (granulocyte-colony–stimulating factor) 5 μg/kg (rounded to nearest the vial size) subcutaneously on days 9 through 15 or pegfilgrastim 6 mg subcutaneously on day 9 or 10. A complete blood count was performed before each cycle and on day 15 of each 21-day cycle. Patients received 4 cycles of gemcitabine-docetaxel.

After cycle 4, all patients underwent a CT scan of the chest/abdomen/pelvis to confirm that they continued with no evidence of disease. Patients who remained disease-free proceeded, no sooner than 3 weeks but no longer than 6 weeks from cycle 4/day 1 of gemcitabine/docetaxel, to receive doxorubicin 60 mg/m^2 intravenously every 21 days for 4 cycles. Within 6 weeks after the last doxorubicin dose, all patients had a repeat CT scan of the chest/abdomen/pelvis to confirm that they had no evidence of disease.

Dose reductions of gemcitabine and docetaxel were required for patients who experienced febrile neutropenia, grade 3 thrombocytopenia with bleeding, or grade 4 thrombocytopenia; docetaxel was held in patients who developed significant liver dysfunction; both gemcitabine and docetaxel were discontinued for grade 2 or worse

pulmonary toxicity; the docetaxel dose was reduced for grade 2 neuropathy and was discontinued for grade 3 or worse neuropathy unless the symptoms improved to grade 2 or better with treatment interruption for up to 2 weeks; both gemcitabine and docetaxel were discontinued in patients who developed grade 4 edema; and docetaxel was discontinued in patients with grade 4 hypersensitivity reactions. Dose reductions for doxorubicin were required for febrile neutropenia, grade 3 thrombocytopenia with bleeding, or grade 4 thrombocytopenia; doxorubicin was held for up to 2 weeks in patients whose bilirubin increased to >1.5 times the ULN and was discontinued if the bilirubin did not improve in 2 weeks' time; and doxorubicin was held for up to 2 weeks for grade 2 or worse mucositis.

Monitoring for Evidence of Disease Recurrence After the Completion of Chemotherapy

All patients were followed by physical examination and CT scan of the chest/abdomen/pelvis every 3 months until 2 years after the completion of study treatment, then every 6 months for the next 3 years.

Correlative Studies

The following parameters were ascertained for all patients with the intent to determine whether any of these factors correlated with PFS outcomes: menopausal status, patient age, tumor size, mitotic rate, FIGO stage, and estrogen receptor (ER) and progesterone receptor (PR) status. ER and PR status was determined by immunohistochemistry performed on paraffin-embedded tissue at a single institution and interpreted by a single pathologist as positive or negative for each receptor.

Statistical Considerations

This was a single-arm, phase 2 trial with a target enrollment of up to 45 patients. Safety monitoring was based on PFS duration with the intent of closing the study early if the PFS rate was so poor that continuing the study would be deemed futile. The monitoring rules were based on a Bayesian model. An early stopping rule in terms of the posterior mean PFS duration was applied continuously throughout the trial, and the stopping rule was applied based on accumulated data when each new patient was ready to be accrued. The trial had an 80% probability of being stopped early if the true 2-year PFS rate was no better than 30%.

PFS, OS, and toxicity were evaluated using summary statistics, including Kaplan-Meier plots of PFS and OS. Both PFS and OS were analyzed using time-to-event regression. In each regression analysis, patient covariates (menopausal status, age) and tumor characteristics (ER and PR status, tumor size, mitotic rate, uterine serosal involvement) were included to determine whether these variables correlated with PFS outcome.

TABLE 1. Patient Demographics, Tumor Characteristics, and Stage Distribution for Patients With Uterine Leiomyosarcoma (n = 47)

Characteristic	Value
Patient demographics	
Age: Median (range), y	53 (37-70)
Menopausal status, no. of women	
Postmenopausal	43
Premenopausal	4
Tumor characteristics	
Tumor size: Median (range), cm	8 (2.5-30)
Mitotic rate: Median mitoses per10 high-power fields (range)	18 (5-83)
ER status, n = 38 evaluable	63% Positive
PR status, n = 38 evaluable	50% Positive
Either ER or PR	29% Negative for both
1988 FIGO stage	
I	81%
II	15%
III, serosa only	4%
AJCC stage	
I	0%
II	13%
III	87%

Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; PR, progesterone receptor.

OS was calculated from the on-study date to date of death or was censored at the date of last follow-up. PFS was calculated from the on-study date to the date of documented recurrence. Recurrence of disease was defined as the development of tumor on physical examination and/or CT scan that was considered consistent with recurrent leiomyosarcoma. Abnormalities that were considered equivocal were further evaluated for confirmation that they represented recurrence: biopsy was recommended as ideal; however, additional or follow-up imaging was acceptable. If follow-up imaging confirmed that a suspicious finding was indeed a recurrence, then the date of recurrence was the date that recurrence was first documented.

RESULTS

Patient Demographics and Tumor Characteristics

Between February 2006 and February 2009, 47 patients were enrolled at 10 participating institutions. The median age of participants was 53 years (range, 37-70 years); and 1988 FIGO stage distribution was 81% stage I, 15% state II, and 4% serosa-only stage IIIA, as detailed in Table 1. According to the American Joint Committee on Cancer staging system for soft tissue sarcomas, the stage

distribution was as follows: 0% stage I, 13% stage II, and 87% and stage III. The median size of the primary uterine tumor was 8 cm (range, 2.5-30 cm), and the median mitotic rate was 18 mitoses per 10 high-power fields (range, 5-83 mitoses per 10 high-power fields). To be eligible for study participation, all patients were required to have disease that was considered "high grade" by the enrolling institution. Tumor tissue was obtained for immunohistochemistry to determine ER and PR status in 38 patients. Sixty-three percent of tumors were positive for ER, and 50% of tumors were positive for PR. Only 4 patients were premenopausal at diagnosis. The median follow-up for all patients in the cohort was 39.8 months. All 47 patients were considered evaluable for PFS and OS. One patient died during cycle 1 of treatment because of infectious complications of acquired immunodeficiency syndrome (AIDS), and 1 patient was lost to follow-up. PFS and OS data from these patients were censored at the time of death (the patient with AIDS) and at the time of last patient contact (the patient who was lost to follow-up).

Treatment Delivery and Toxicities

Eighty-nine percent of patients received all 8 planned cycles of adjuvant therapy. Reasons for receiving fewer than all 8 planned cycles were: 1 patient with AIDS died during cycle 1 of treatment; 2 patients had a mild increase in bilirubin to above the ULN and were not able to receive either additional docetaxel or doxorubicin (1 patient received only 2 cycles of gemcitabine-docetaxel, and 1 patient received 4 cycles of gemcitabine-docetaxel); 1 patient recurred after gemcitabine-docetaxel and, thus, did not receive adjuvant doxorubicin; and it was believed that 1 patient had a recurrence based on imaging studies after 4 cycles of gemcitabine-docetaxel, but it was determined subsequently that this patient did not have evidence of recurrence. The major toxicities observed during gemcitabine plus docetaxel were myelosuppression (grade 3 in 30% of patients; grade 4 in 4%), hypersensitivity reactions to docetaxel (grade 2 in 21% of patients; grade 3 in 2%), neuropathy (grade 2 in 6% of patients, grade 3 in 0%), and edema (grade 3 in 4% of patients). No patient developed pulmonary toxicity. Doxorubicin-related toxicities included myelosuppression (grade 3 in 30% of patients, grade 4 in 13%) and mucositis (grade 2 in 2% of patients, grade 3 in 2%).

Recurrence and Survival Outcomes

Twenty-one of 46 evaluable patients developed recurrent disease (45.7%), and 8 patients died (17%). The median time to recurrence was 27.4 months (range, 3-40 months). The sites of first recurrence were lung alone in 5 patients, pelvis alone in 8 patients, bone alone in 1 patient, liver alone in 1 patient, para-aortic region in 1 patient, and a combinations of sites in 5 patients. Details of the 21 patients who developed recurrent disease are provided in Table 2.

TABLE 2. Patients With Recurrent Disease: Stage, Site, and Time to Recurrence (n = 21)

Patient No.	FIGO Stage	AJCC Stage	Site of First Recurrence	Time to First Recurrence, mo
1	I	III	Lung	30
2	I	III	Lung	39.8
3	I	III	Lung	17.2
4	I	III	Lung	6.7
5	I	II	Lung	36.4
6	I	III	Pelvis	10.7
7	I	III	Pelvis	21.2
8	I	III	Pelvis	30.3
9	I	III	Pelvis	8.8
10	I	III	Pelvis	9.3
11	I	III	Pelvis	32.7
12	I	III	Pelvis	36.4
13	III	III	Pelvis	20.8
14	II	III	Bone (vertebral body)	32.8
15	I	III	Liver	3.2
16	II	III	Para-aortic area	13.3
17	I	III	Pelvis, bone	38
18	I	III	Pelvis, lung	31.3
19	I	III	Liver, lung	35.6
20	II	III	Bone, liver, small bowel	15.4
21	I	II	Lung, bone	27.4

Abbreviations: AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynecology and Obstetrics.

At a median follow-up of 39.8 months, 78% of patients remained progression-free at 2 years (95% confidence interval, 67%-91%). At 3 years, 57% of patients remained progression-free (95% confidence interval, 44%-74%). The median PFS and OS have not been reached (Figs. 1 and 2, respectively). In univariate analysis, no variable (patient age, menopausal status, FIGO stage, uterine serosal involvement, mitotic rate, ER status, or PR status) was associated significantly with PFS (Table 3).

DISCUSSION

Uterus-confined, high-grade leiomyosarcoma is a high-risk disease, and at least half of patients with these tumors develop recurrent disease. Patients who develop metastatic uterine leiomyosarcoma have a poor prognosis, with an estimated median survival of approximately 12 months for those with stage IV disease. Fixed-dose-rate gemcitabine plus docetaxel and doxorubicin are active in patients with metastatic uterine leiomyosarcoma. Whether the use of agents that have activity in metastatic disease can improve

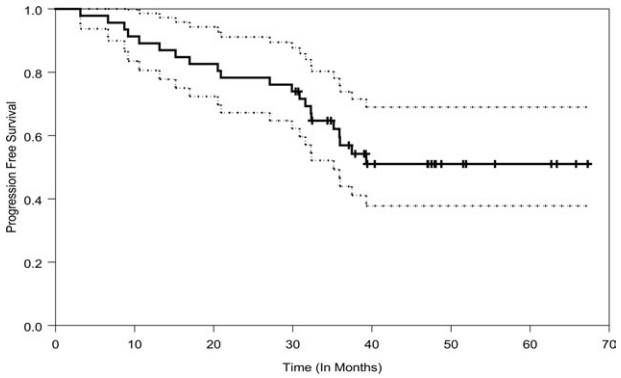

Figure 1. Progression-free survival is illustrated (n = 47). At 2 years, 75% of patients remained progression-free (95% confidence interval, 67%-91%); and, at 3 years, 57% of patients remained progression-free (95% confidence interval, 44%-74%). The median progression-free survival has not been reached.

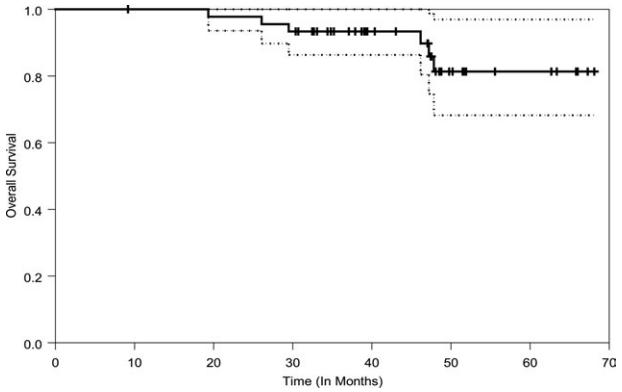

Figure 2. Overall survival is illustrated (n = 47). The median overall survival has not been reached.

survival outcomes for women with uterus-limited disease is not known. The current prospective phase 2 trial, which enrolled a homogeneous population of patients with high-grade, uterus-limited disease and was designed with standardized imaging intervals to capture PFS, yielded a PFS rate of 78% at 2 years and 57% at 3 years, and the median PFS has not been reached.

Although some limited data were collected to explore potential predictors of survival outcomes, no variable was identified as an independent predictor of recurrence. This may be because of the relatively small sample size or the number of observed events. It is of potential interest that the median time to recurrence exceeded 2 years (27.4 months), with some recurrences appearing as late as 40 months after enrollment. Also of potential interest are the numbers of patients with bone recurrences. Whether adjuvant chemotherapy had an impact on the location or timing of recurrences could be ascertained from the current single-arm study. The distribution of metastatic sites (preponderantly lung and pelvis; 4 patients with bone metastasis) appears to be similar to the expectation for sarcoma.

The PFS results from our study may be interpreted in light of results from other recent prospective studies addressing adjuvant treatment for uterine sarcomas. Two studies enrolled patients with early stage disease who had a mix of histologic diagnoses (uterine leiomyosarcomas, carcinosarcomas, and endometrial stromal sarcomas), and 1 study enrolled patients specifically with carcinosarcoma of any stage provided the patient had undergone complete resection. The prognosis, patterns of recurrence, and sensitivity to treatment differs among histologic subtypes of uterine sarcomas, thus making any interpretation of cross-trial comparison of outcomes particularly difficult. In a study of adjuvant pelvic radiation versus observation, 219 patients with uterus-limited carcinosarcoma (n = 91), leiomyosarcoma (n = 103), or endometrial stromal sarcoma (n = 28) were evaluated. The 3-year disease-free survival rate was 57.7% among the 110 patients who were assigned to radiation versus 52% among the 109 who were assigned to observation (the difference was not statistically significant), and the reported OS rates were 58% and 56%, respectively.[6] In a randomized study of combined doxorubicin, ifosfamide, cisplatin, plus pelvic radiation versus radiation alone, 81 patients (53 leiomyosarcoma, 19 carcinosarcoma, 9 undifferentiated sarcoma; FIGO stage I, II, or III) were enrolled. The 3-year PFS rate was 52% (90% confidence interval, 36%-67%) among the 39 patients who were assigned to chemotherapy plus radiation versus 41% (95% confidence interval, 27%-57%) among the 42 patients who were assigned to pelvic radiation alone,[17] and the median PFS was 27 months. In a study that was designed specifically for patients with completely resected stage I, II, III, or IV uterine carcinosarcoma, patients were assigned to receive either adjuvant treatment with 3 cycles of ifosfamide plus cisplatin or whole abdominal radiation. OS was statistically superior in the group that was assigned to

TABLE 3. Univariate Analysis of Tumor Characteristics With Progression-Free Survival

Variable	Coefficient	*P*
Menopausal status at diagnosis	0.02	.9
Age	−0.00269	.92
Uterine serosal involvement	0.101	.066
Mitotic rate	−0.00676	.65
ER status	−0.708	.15
PR status	−0.906	.075
1988 FIGO stage	0.207	.61
Either ER or PR positive	−0.564	.27

Abbreviations: ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; PR, progesterone receptor.

chemotherapy, in which 47% of patients remained alive at 5 years versus 34% of patients who were assigned to radiation.[18]

Among patients with uterine sarcomas, the individual prognosis and relative sensitivity to systemic treatment varies by histologic subtype. Studies that enroll patients who have a mix of uterine sarcoma histologic types may be difficult to interpret, because any benefit may accrue only to 1 subgroup, and potential benefit may be obscured by poorer survival among patients who have histologies with the worst prognosis or by the inclusion of low-grade histologies, such as endometrial stromal sarcomas, which may do well without intervention. Thus, although the observed 3-year PFS rate of 57% in our study appears to be relatively similar to the rate among the mixed group of patients with uterine sarcoma who received adjuvant pelvic radiation (57.7%) and also is similar to the disease-free survival rate among patients who received combined doxorubicin, ifosfamide, cisplatin, and radiation (52%), it cannot be concluded that these adjuvant interventions are equivalent or superior to observation. Rather, the results from these trials highlight the need for histology-specific prospective studies of adjuvant therapy. The strengths of our study include enrollment specifically for patients with uterus-limited, high-grade leiomyosarcoma; confirmation of disease-free status by CT imaging before enrollment; uniform treatment of patients using agents with demonstrated activity in uterine leiomyosarcoma; prospective, quarterly CT imaging to determine the time of disease recurrence; and multi-institution cooperative participation.

The current study demonstrates that an adjuvant regimen of fixed-dose-rate gemcitabine plus docetaxel followed by doxorubicin can be delivered to patients who have uterus-limited, completely resected leiomyosarcoma with acceptable tolerability. The 2-year PFS rate was 78%, which exceeded historic expectations of 50% remaining disease-free at 2 years, based largely on the retrospective data that were available at the time of study design. The 3-year PFS rate was 57%. The adjuvant regimen used in this phase 2 study is currently being compared with the standard approach of observation in an international, prospective, randomized phase 3 trial (National Clinical Trials identifier NCT01533207) to determine whether adjuvant chemotherapy can improve survival for women with uterus-limited, high-grade leiomyosarcoma.

FUNDING SOURCES

Funding for this study was provided by the Sarcoma Alliance for Research through Collaboration (SARC) (clinicaltrials.gov registration NCT00282087).

CONFLICT OF INTEREST DISCLOSURES

Dr. Baker is a consultant for Millennium Pharmaceuticals, Dr. Maki, is a consultant for Lilly, Dr. George is a consultant for GSK, and Dr. Wathen is an employee of Janssen Research and Development, LLC, a pharmaceutical company of Johnson & Johnson.

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