Original Article

Phase 2 Study of Dasatinib in Patients With Alveolar Soft Part Sarcoma, Chondrosarcoma, Chordoma, Epithelioid Sarcoma, or Solitary Fibrous Tumor

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BACKGROUND: Alveolar soft part sarcoma (ASPS), chondrosarcoma (CS), chordoma, epithelioid sarcoma, and solitary fibrous tumor (SFT) are malignant tumors that are relatively resistant to chemotherapy and for which more effective drug therapy is needed. **METHODS:** The 5 listed subtypes were enrolled into a single indolent sarcoma cohort in a phase 2 study of dasatinib using a Bayesian continuous monitoring rule for enrollment. The primary objective was to estimate the 6-month progression-free survival (PFS) rate according to the Choi criteria with a target of ≥50%. Cross-sectional imaging was performed before the start of treatment, every 2 months for 6 months, and then every 3 months during treatment. The 2- and 5-year survival rates were determined. **RESULTS:** One hundred sixteen patients were enrolled within 45 months, and 109 began treatment with dasatinib. The 6-month PFS rate and the median PFS were 48% and 5.8 months, respectively. The PFS rate at 6 months was highest with ASPS (62%) and lowest with SFT (30%). More than 10% of the patients with ASPS, CS, or chordoma had stable disease for more than 1 year. Collectively, for all 5 subtypes, the 2- and 5-year overall survival rates were 44% and 13%, respectively. An objective response was observed in 18% of the patients with CS or chordoma. **CONCLUSIONS:** Dasatinib failed to achieve control of sarcoma growth for at least 6 months in more than 50% of the patients in this trial according to the Choi tumor response criteria. An objective tumor response and prolonged stable disease was observed in >10% of patients with CS or chordoma. ***Cancer* 2017;123:90-7.** *© 2016 American Cancer Society.*

KEYWORDS: Bayesian, chemotherapy, Choi, chondrosarcoma, chordoma, dasatinib, phase 2, sarcoma.

INTRODUCTION

Sarcomas are a diverse group of stromal cancers, of which the large majority are derived from mesodermal tissue. A number of distinct histologic subtypes of sarcoma share the unusual behavior of a low cell proliferation rate but a high risk of local recurrence and systemic spread, which may occur years after definitive treatment of the primary cancer. The lifespan of individuals with one of these indolent sarcomas after the development of metastasis is often years. For example, the rate of metastasis in patients with alveolar soft part sarcoma (ASPS) is greater than 50%, but the median survival is more than 3 years after the diagnosis of metastases.[1,2] Solitary fibrous tumor (SFT) and epithelioid sarcoma (ES) are other soft tissue sarcomas with an indolent growth rate but a high propensity for recurrence and metastasis.[3,4] Chordoma and low- to intermediate-grade chondrosarcoma (CS) are types of sarcoma arising in the bone that also exhibit a low mitotic rate but have a risk of local recurrence and metastasis. With few notable exceptions, these sarcomas are resistant to chemotherapy, and patients afflicted with one of these sarcomas are in great need of more effective drug treatment when the disease cannot

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See editorial on pages 20-4, this issue.

We thank the patients who participated in this study and their families as well as the staff and investigators of the Sarcoma Alliance Through Research and Collaboration.

DOI: 10.1002/cncr.30379, **Received:** April 29, 2016; **Revised:** June 27, 2016; **Accepted:** July 6, 2016, **Published online** October 3, 2016 in Wiley Online Library (wileyonlinelibrary.com)

be excised and is refractory to radiation or is widely metastatic. Cediranib and sunitinib have activity in ASPS.[5,6] Bevacizumab combined with temozolomide and sunitinib have activity in SFT.[7,8] Imatinib has activity in chordoma.[9] In clinical trials of these drugs as treatment for ASPS, SFT, and chordoma, objective responses were observed in a minority of patients, but more than 50% of patients survived free of sarcoma progression 6 months after they had started therapy.

The mechanism of the antitumor activity of cediranib, sunitinib, and imatinib in ASPS, SFT, and chordoma has not been definitively established to our knowledge. A number of preclinical studies suggest that a platelet-derived growth factor pathway is active in ASPS, SFT, and chordoma.[5,10-12] The Src pathway is active in CS, and inhibition of Src in vitro by dasatinib has led to reduced CS viability, reduced cell motility, and induced apoptosis.[13,14] Dasatinib is a small molecule inhibitor of the Src family of kinases, platelet-derived growth factor receptors α and β, c-KIT, BCR-ABL, and ephrin receptor kinases, and it has significant clinical activity in chronic myelogenous leukemia.[15] We evaluated the clinical activity of dasatinib in patients with locally advanced or metastatic ASPS, CS, chordoma, ES, or SFT because of an unmet need for more effective drug therapy. At the time the trial was designed, on the basis of preclinical studies and clinical experience with imatinib and sunitinib in the treatment of sarcoma, we felt that there was a reasonable chance for dasatinib to have antitumor activity in ASPS, CS, chordoma, and SFT. Patients with ES were included because of a lack of effective drugs against this cancer.

MATERIALS AND METHODS

Study

We performed a multi-institutional, open-label, single-arm trial of dasatinib in patients with advanced sarcoma. We conducted 3 parallel trials focused on different sarcoma histologic types (aggressive sarcoma subtypes, indolent sarcoma subtypes, and gastrointestinal stromal tumors) under 1 parent study (SARC009) coordinated by the Sarcoma Alliance Through Research and Collaboration (SARC). The results for dasatinib in patients with aggressive sarcoma subtypes are reported elsewhere.[16] SARC provided central coordination of study conduct, patient enrollment, study monitoring, and auditing. Cancer Research and Biostatistics (http://www.crab.org/) developed and maintained an electronic study database. Statistical support was provided by V. Bolejack for the indolent subtype analysis. Bristol-Myers Squibb provided dasatinib and financial support. The trial was registered with ClinicalTrials.gov (NCT00464620). The study was approved by all participating sites' institutional review boards.

Patients

Enrollment in the indolent substudy was restricted to patients who were 13 years old or older, weighed at least 50 kg, and had measurable ASPS, grade 1 or 2 CS of the bone, chordoma, ES, or SFT that was incurable with conventional treatment. Confirmed disease progression based on standard imaging criteria before enrollment was not required. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance score ≤ 2; an ability to swallow whole tablets; an absolute neutrophil count $\geq 1500/\mu$L; a platelet count $\geq 75{,}000/\mu$L; a serum creatinine level ≤ 2 times the institutional upper limit of normal; prothrombin and partial thromboplastin times ≤ 1.5 times the institutional upper limit of normal; serum magnesium, potassium, and calcium levels at least at the lower limit of the normal range; a corrected QT interval ≤ 450 milliseconds; and a left ventricular ejection fraction of at least 45%. All patients provided written informed consent. Local site investigators determined patient eligibility; however, patients' pathology slides were centrally reviewed, and diagnoses were retrospectively confirmed for all subjects by the study pathologist (D.R.L.) within 2 months of patient enrollment and therapy initiation.

Study Treatment and Evaluations

Oral dasatinib was started at 100 mg twice daily. The study amended the starting dose to 70 mg twice daily because of toxicity observed in other trials of dasatinib.[17] A cycle of treatment was 28 days. Dose and schedule adjustments were allowed for toxicity (50 mg twice daily and then 100 mg once daily). Drug treatment was continued until the disease progressed according to the Choi criteria,[18] unacceptable toxicity occurred, or the patient or provider decided to stop. The extent of disease was assessed with computed tomography or magnetic resonance imaging within 2 weeks of treatment, every 2 months for 6 months, and then every 3 months until disease progression was documented in patients remaining on treatment. An electrocardiogram was performed during screening and after the first month of treatment. Correction of the QT interval was performed by local sites with Bazett's formula. Safety evaluations included complete blood counts and comprehensive metabolic panels performed monthly for 6 months, every 6 weeks for the next 6 months, and then every 12 weeks during treatment.

Adverse events were recorded according to the Common Terminology Criteria for Adverse Events (version 3.0).

The primary study endpoint was the 6-month progression-free survival (PFS) rate according to the Choi criteria (10% or greater increase in the sum of the greatest dimension without a greater than 15% reduction in the average tumor density of the target lesions). We chose to assess the tumor response with the Choi criteria instead of the Response Evaluation Criteria in Solid Tumors (RECIST) or the World Health Organization criteria 1) because improvements in the resolution of cross-sectional imaging allowed more precise tumor measurements and thus we felt a change in the tumor size of more than 10% could be reliably determined and 2) because of prior experience assessing the responses of gastrointestinal stromal tumors treated with another tyrosine kinase inhibitor, imatinib.[18] Secondary endpoints included a patient safety assessment by the adverse event rate, the 2- and 4-month PFS rates, the median time to progression, and the 2- and 5-year overall survival (OS) rates. Study endpoints were assessed by participating investigators; a central radiology review was not performed. Patients were censored for PFS at the date of the last radiology evaluation if progression had not occurred. Patients were censored for survival at the date of last contact, with the survival time calculated from the date of registration to death. Patients were contacted at least every 12 months for survival information until 5 years after registration.

Statistical Methods

Patients with one of the eligible indolent sarcoma subtypes were enrolled into a single cohort: the relative rarity and uncertainty of the rate of accrual of each of the sarcoma subtypes under study made it hard to justify enrollment in subtype-specific cohorts. The study was designed to estimate the PFS and OS for the group. A post hoc analysis was performed for each sarcoma subtype. We estimated a 6-month PFS rate of 30% to 40% for inactive therapies and a rate greater than 50% for active therapy. A Bayesian monitoring rule was used to stop enrollment if the probability that the 6-month PFS rate was at least 50% fell to less than 0.85%. The stopping rule was chosen to provide no higher than a 10% chance that the trial would be terminated early if the true 6-month PFS was $\geq$ 50%. We estimated that the trial would terminate early more than 88% of the time with fewer than 30 patients enrolled if the 6-month PFS rate was 30%. A minimum of 10 patients and a maximum of 116 patients were to be enrolled. We anticipated an accrual rate of 1 to 3 patients per month.

TABLE 1. Patient Characteristics

Age at registration, median (range), y	54 (22-87)
Sex: male/female, No.	76/33
Race (n = 109), No. (%)	
White	94 (86)
Black	8 (7)
Asian	3 (3)
Other	4 (4)
Sarcoma subtype (n = 109), No. (%)	
Alveolar soft part sarcoma	12 (11)
Chondrosarcoma	33 (30)
Chordoma	32 (29)
Epithelioid sarcoma	7 (6)
Solitary fibrous tumor	25 (23)
Prior drug therapy, No. (%)	
Alveolar soft part sarcoma	10 (83)
Chondrosarcoma	11 (34)
Chordoma	20 (61)
Epithelioid sarcoma	6 (86)
Solitary fibrous tumor	11 (44)

RESULTS

Patient Demographics

One hundred sixteen patients were registered over the course of 45 months (starting in July 2007), and this provided an average rate of accrual of 2.6 subjects per month. No patient under 21 years of age enrolled. Two patients were excluded because of an ineligible sarcoma subtype (extraskeletal myxoid CS) according to the central pathology review, 2 were ineligible because of the use of a prohibited concomitant medication, and 3 chose not to start therapy after registration. The characteristics of the 109 patients who started dasatinib are shown in Table 1. Chordoma and CS were the commonest subtypes studied. All surviving patients who started dasatinib have completed 5 years of follow-up since enrollment.

Dasatinib Treatment and Safety

As of June 2016, all patients were off treatment. A median of 4 cycles of dasatinib (range, 1-87 months) were administered. The median number of cycles completed by patients was 7.5 for ASPS, 6 for chordoma, 4 for CS, 9 for ES, and 2 for SFT. Treatment interruption was reported in 62 patients (57%), and a reduction in dose was reported in 36 patients (33%). A reduction in the dasatinib dose was more frequent in patients with SFT (52%) in comparison with patients with ES (14%), ASPS (17%), CS (27%), or chordoma (34%). Most patients discontinued dasatinib because of sarcoma progression. Hematologic adverse events were infrequent (see Table 2). Nonhematologic adverse events occurring in more than 5% of the patients included fatigue, fever, anorexia, weight loss, rash, nausea, vomiting, constipation,

TABLE 2. Number of Patients With Hematologic Toxicities From Dasatinib

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	10	8	4	0
Leukocytes	2	3	1	0
Lymphopenia	1	2	1	0
Neutrophils	1	1	1	2
Platelets	5	0	2	0

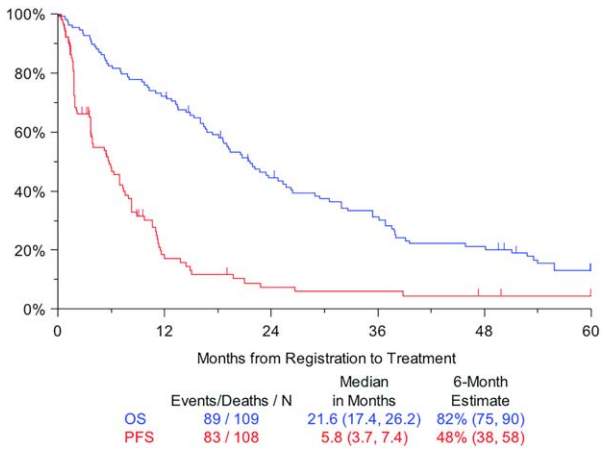

Figure 1. Kaplan-Meier progression-free survival (PFS) and overall survival (OS) curves for the patients.

TABLE 3. Survival According to the Sarcoma Subtype

Sarcoma Subtype	6-mo PFS	2-y OS	5-y OS
Alveolar soft part sarcoma	62%	50%	30%
Chondrosarcoma	47%	56%	9%
Chordoma	54%	43%	18%
Epithelioid sarcoma	57%	21%	0%
Solitary fibrous tumor	30%	34%	8%

Abbreviations: OS, overall survival; PFS, progression-free survival.

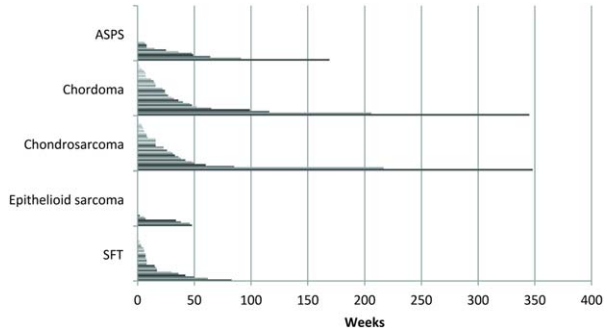

Figure 2. Time on treatment with dasatinib by sarcoma subtype: alveolar soft part sarcoma (ASPS), chordoma, chondrosarcoma, epithelioid sarcoma, and solitary fibrous tumor (SFT).

diarrhea, edema, pleural effusion, dyspnea, cough, headache, pain, serum creatinine elevation, hyperglycemia, and hyponatremia. Grade 3 and 4 adverse events were reported in 46 and 8 patients, respectively. Grade 3 adverse events occurring in at least 5% of the patients included pain in 17%, dyspnea in 11%, pleural effusion in 6%, and diarrhea in 5%. Nonhematologic grade 4 adverse events included 1 episode each of cardiac infarction, intracranial hemorrhage, meningitis, pyelonephritis, dyspnea, serum creatinine elevation, and hypokalemia. Six patients died during therapy; 2 deaths were due to the general progression of sarcoma, 3 were related to pulmonary complications from sarcoma, and 1 death was unrelated to sarcoma or dasatinib. The mean and median pretreatment corrected QT intervals were 421 and 422 milliseconds, respectively. After 4 weeks of dasatinib, the mean and median corrected QT intervals were not significantly different from the baseline values and measured 429 and 427 milliseconds, respectively, in 93 patients for whom data were available.

Dasatinib Activity

The 6-month PFS rate was 48%. The median PFS and OS times were 5.8 and 21.6 months, respectively (Fig. 1). The median PFS was 2 months for SFT, 5.5 months for CS, 6.3 months for chordoma, 7.9 months for ES, and 11 months for ASPS. The 6-month PFS rate and the 2- and 5-year OS rates by subtype are shown in Table 3. The duration of dasatinib therapy by patient is shown in Figure 2. One patient with ASPS, 3 with chordoma, and 3 with CS remained on treatment for more than 2 years. One patient with ASPS, 6 with CS, 6 with chordoma, 2 with ES, and 5 with SFT had an objective tumor response according to the Choi criteria. Nineteen of the patients with a response started treatment with dasatinib at 70 mg twice daily, and 1 started with 100 mg twice daily. In a post hoc analysis, 1 patient with chordoma had a RECIST objective response.

DISCUSSION

SARC conducted a unique clinical trial focused on patients with locally advanced or metastatic sarcomas of subtypes that usually exhibit an indolent rate of growth and for which there are very limited accepted standard chemotherapy treatments. Collectively, ASPS, ES, and SFT represent approximately 1% of soft tissue sarcomas, and chordoma represents approximately 5% of bone sarcomas.[19] Because of the rarity of the different subtypes, patients were enrolled into 1 cohort rather than indolent

TABLE 4. Comparison of Reported Patient Outcomes in Selected Phase 2 and Retrospective Sarcoma Studies

Sarcoma	Drug	No. of Patients	Choi Response Criteria			RECIST		
			ORR	6-mo PFS	Median PFS	ORR	6-mo PFS	Median PFS
ASPS	Dasatinib	12	8%	62%	11 mo	0%	ND	ND
	Sunitinib[5]	9	NR	NR	NR	56%	88%	17 mo
	Cediranib[6]	43	NR	NR	NR	35%	84%	NR
CS	Dasatinib	33	15%	47%	5.5 mo	0%	ND	ND
	GDC-0449[21]	39	NR	NR	NR	0%	28%	3.5 mo
Chordoma	Dasatinib	32	19%	54%	6.3 mo	0%	ND	ND
	Imatinib[9]	50	NR	NR	NR	2%	66%	9.2 mo
	Imatinib[22]	46	NR	NR	NR	0%	65%	9.9 mo
	Lapatinib[23]	18	33%	50%	6 mo	0%	60%	8 mo
SFT	Dasatinib	25	20%	30%	2 mo	0%	ND	ND
	Sunitinib[8]	31	48%	NR	7 mo	6%	45%	6 mo
	TMZ/BEV[7]	14	79%	79%	9.7 mo	14%	93%	10.8 mo

Abbreviations: ASPS, alveolar soft part sarcoma; CS, chondrosarcoma; ND, not done; NR, not reported; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SFT, solitary fibrous tumor; TMZ/BEV, temozolomide and bevacizumab.

histology subtype–specific cohorts. This study demonstrated that SARC, as a cooperative clinical research group, was able to enroll patients with very rare subtypes at a rate consistent with a priori expectations and successfully complete accrual. SARC members are predominantly medical oncologists who have expertise in the treatment of patients with sarcomas, are committed to sarcoma clinical research, and practice at medical centers with demonstrated multidisciplinary management of sarcoma patients. Most of the SARC-associated members see a high volume of sarcoma patients and function as regional or national experts in the management of sarcoma; this likely contributed to the successful enrollment. In addition, most of the member institutions support pathologists with special expertise in the diagnosis of soft tissue and bone tumors; this accounted for the low rate (<2%) of discrepancies in diagnosis between local and central pathologists.

Before the start of this trial, very few objective responses had been reported in clinical trials of chemotherapy or tyrosine kinase inhibitor therapy in patients with ASPS, chordoma, or SFT, and to our knowledge, the results of prospective clinical trials of chemotherapy in patients with ES or CS had not been reported. Because of a lack of objective responses observed in previous trials, we used the 6-month PFS rate as an estimate of dasatinib activity in this trial. Previous drug studies in patients with ASPS, chordoma, or SFT demonstrated 6-month PFS rates of 50% or higher according to RECIST.[8,9,20] Therefore, we set the primary goal for preliminary evidence of dasatinib activity as a 6-month PFS rate of at least 50%. Dasatinib treatment resulted in a 6-month PFS rate of 48% in the group of patients enrolled in this phase 2 trial. One reason for the relatively low 6-month PFS rate is the use of the Choi criteria rather than RECIST: disease progression according to the Choi criteria occurs when tumor growth is at least 10% and thus occurs earlier than RECIST disease progression, which requires a 20% increase in tumor size. A minority of patients met the criteria for sarcoma progression per RECIST: 1 patient with ASPS, 3 patients with chordoma, 13 patients with CS, 1 patient with ES, and 8 patients with SFT had RECIST progressive disease. This trial would likely have had a 6-month PFS rate greater than 50% if RECIST had been used to assess the tumor response and thus would have been viewed as a trial with a positive primary endpoint. The differential activity of dasatinib within sarcoma subtypes and/or the variability in the natural growth rates of sarcoma subtypes also likely affected PFS. Patients with SFT experienced the shortest median PFS time and the lowest 6-month PFS rate, whereas patients with ASPS, chordoma, or ES had a 6-month PFS rate greater than 50%. If the study had been designed to enroll patients into subtype-specific cohorts, dasatinib may have been declared potentially active in ASPS, chordoma, and ES. Patients with ASPS had a relatively long median PFS and OS in comparison with many of the other subtypes, but only 1 objective response from treatment with dasatinib was observed. In comparison, recent trials using sunitinib or cediranib in patients with advanced ASPS demonstrated RECIST objective responses in more than 30% and a lack of progression for at least 6 months in more than 80% of patients (Table 4).[5,6] A randomized trial of cediranib versus sunitinib (NCT01391962) that is in progress

should help to define a standard therapy for advanced/metastatic ASPS.

Preclinical studies suggest that the tyrosine kinase Src plays a role in CS pathogenesis, and dasatinib had antitumor activity in preclinical CS models.[13,14] In our study, patients with low- or intermediate-grade CS of the bone had a median PFS of 5.5 months and a 6-month PFS rate of 47%. Six patients had an objective tumor response, and 4 patients (12%) had stable disease on treatment for more than a year; this suggests that a small subset of patients may have had some tumor control with dasatinib. Prospective trials of drug therapy in metastatic CS have been too infrequently conducted to provide a basis for a comparison of results. In a phase 2 trial of the hedgehog pathway inhibitor GDC-0449 in patients with progressive, advanced CS, no objective tumor responses were observed, and the 6-month PFS rate was only 28%.[21] Eighty-seven percent of patients had grade 1 or 2 CS, 11% had dedifferentiated CS, and 1 patient had clear cell CS in the trial of GDC-0449. The median OS in the GDC-0449 trial was 12 months, whereas it was 27 months in our study of dasatinib. Our preliminary clinical data from dasatinib treatment of CS patients along with an absence of a standard effective drug therapy for this group of patients support further study of dasatinib in CS.

Chordomas express platelet-derived growth factor receptor α and epidermal growth factor receptor and have been the subject of clinical trial research using tyrosine kinase inhibitors. The treatment of 56 patients with advanced chordoma with imatinib in a phase 2 trial demonstrated 1 objective partial response by RECIST, a 6-month PFS rate of 64%, and a median PFS time of 9 months.[9] Similar results were noted in a retrospective case series analysis of 48 patients treated with imatinib.[22] The authors also noted that 16.5% of the patients remained on treatment with stable disease for more than 18 months. In a phase 2 trial of lapatinib treatment of patients with advanced epidermal growth factor receptor–positive chordoma, no objective responses per RECIST were seen, but 33% of the patients had a partial response per the Choi response criteria, and the median PFS was 6 months.[23] In our trial of dasatinib using the Choi response criteria, the median PFS time and the 6-month PFS rate for patients with chordoma were 6.3 months and 54%, respectively, which are not substantially different from results with imatinib or lapatinib. Moreover, 14% of the patients treated with dasatinib were surviving without tumor progression for more than 2 years, and 18% of the patients were alive at 5 years; this highlights the very indolent course of disease that is seen in a subset of patients.

The groups of patients with ES or SFT had the lowest survival rates in our study. The 6-month survival rates were remarkably similar among the histologic subtypes and ranged from 71% for ES patients to 88% for patients with conventional CS; however, the 2- and 5-year survival rates for ES patients were 21% and 0%, respectively, whereas the survival rates for patients with conventional CS were 56% and 9%, respectively. Similarly poor survival rates for patients with metastatic ES were reported in an analysis of cases in the Surveillance, Epidemiology, and End Results database.[24] Doxorubicin-based regimens and gemcitabine combined with docetaxel have limited activity in ES, and more effective drugs are needed.[25,26] The response of SFT to dasatinib was worse than the results in previous reports of treatment with temozolomide and bevacizumab or sunitinib with the Choi response criteria.[7,8] Treatment with either regimen resulted in objective partial responses in approximately 50% of the patients, a median PFS of at least 50%, and a 6-month PFS rate of at least 50%, whereas a median PFS time of 2 months and a 6-month PFS rate of 30% were achieved with dasatinib.

In summary, SARC conducted a single-arm trial of dasatinib in patients with rare sarcoma subtypes for whom there is an unmet medical need for more effective chemotherapy to manage locally advanced or metastatic disease, and it was able to meet the anticipated enrollment rate and accrual goal for a trial of very rare cancers through a collaborative effort. Adverse events experienced by patients were similar in type and rate to events previously reported.[16] Although the 6-month PFS rate fell short of the 50% goal for the group with the Choi response criteria, more than 50% of patients with ASPS or ES were free of disease progression for more than 6 months, and 50% of the ASPS patients were alive for at least 2 years after enrollment. In addition, approximately 15% of the patients with chordoma or CS had an objective tumor response, and a few had stable disease for more than 2 years on treatment. Dasatinib should not be used as a standard treatment for SFT, but a comparative study with cediranib or sunitinib may be worthwhile; this will depend on results from the ongoing ASPS trial. The low rate of OS for patients with ES highlights the urgent need to identify active drugs to treat patients with metastatic ES. Because of a lack of defined drug therapy for the treatment of patients with locally advanced, unresectable, or metastatic CS of the bone or chordoma and the results discussed previously, a further evaluation of dasatinib for CS and chordoma should be considered in future clinical trials.

FUNDING SUPPORT

This work was supported by the Sarcoma Alliance Through Research and Collaboration and Bristol-Myers Squibb. Dasatinib was provided by Bristol-Myers Squibb to the participating sites. Funding for the study was provided to the Sarcoma Alliance Through Research and Collaboration by Bristol-Myers Squibb.

CONFLICT OF INTEREST DISCLOSURES

Scott M. Schuetze reports grants from Janssen R&D, Lilly, and Amgen and personal fees from Janssen R&D and Amgen outside the submitted work. Edwin Choy reports personal fees from EMD Serono, Bayer, and Amgen outside the submitted work. Hussein A. Tawbi reports grants from Bristol-Myers Squibb, Novartis, and Merck and personal fees from Bristol-Myers Squibb and Novartis outside the submitted work. Shreyaskumar R. Patel reports grants from Janssen, Eisai, and Morphotek and personal fees from Janssen, EMD Serono, CytRx, Bayer, and Eli Lilly outside the submitted work. Mohammed M. Milhem reports personal fees from Bristol-Myers Squibb, Novartis, Eisai, Genentech, Amgen, and EMD Serono outside the submitted work. Daniel A. Rushing reports personal fees from Bayer Pharmaceutical and Daiichi Sankyo outside the submitted work. Rashmi Chugh reports grants from Novartis, Lilly, Morphotek, MabVax, BioMarin, and AADi outside the submitted work. Laurence H. Baker reports personal fees from Morphotek and Teva outside the submitted work.

AUTHOR CONTRIBUTIONS

Scott M. Schuetze: Study concept, study design, provision of patients, data collection, study oversight, data analysis, manuscript writing, and approval of final manuscript. **Vanessa Bolejack**: Statistical analysis, data analysis, manuscript writing, and approval of final manuscript. **Edwin Choy**: Provision of patients, data collection and analysis, and approval of final manuscript. **Kristen N. Ganjoo**: Provision of patients, data collection and analysis, and approval of final manuscript. **Arthur P. Staddon**: Provision of patients, data collection and analysis, and approval of final manuscript. **Warren A. Chow**: Provision of patients, data collection and analysis, and approval of final manuscript. **Hussein A. Tawbi**: Provision of patients, data collection and analysis, and approval of final manuscript. **Brian L. Samuels**: Provision of patients, data collection and analysis, and approval of final manuscript. **Shreyaskumar R. Patel**: Provision of patients, data collection and analysis, and approval of final manuscript. **Margaret von Mehren**: Provision of patients, data collection and analysis, and approval of final manuscript. **Gina D'Amato**: Provision of patients, data collection and analysis, and approval of final manuscript. **Kirsten M. Leu**: Provision of patients, data collection and analysis, and approval of final manuscript. **David M. Loeb**: Provision of patients, data collection and analysis, and approval of final manuscript. **Charles A. Forscher**: Provision of patients, data collection and analysis, and approval of final manuscript. **Mohammed M. Milhem**: Provision of patients, data collection and analysis, and approval of final manuscript. **Daniel A. Rushing**: Provision of patients, data collection and analysis, and approval of final manuscript. **David R. Lucas**: Study design, review of pathology, and approval of final manuscript. **Rashmi Chugh**: Provision of patients, study oversight, manuscript writing, and approval of final manuscript. **Denise K. Reinke**: Study concept, study design, funding, oversight of study, and approval of final manuscript. **Laurence H. Baker**: Study concept, study design, data analysis, manuscript writing, and approval of final manuscript.

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