Original article

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

Running title: Dasatinib Treatment of Indolent Sarcomas

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BLS: provision of patients, data collection and analysis, approval of final manuscript
SRP: provision of patients, data collection and analysis, approval of final manuscript
MvM: provision of patients, data collection and analysis, approval of final manuscript
GD: provision of patients, data collection and analysis, approval of final manuscript
KL: provision of patients, data collection and analysis, approval of final manuscript
DML: provision of patients, data collection and analysis, approval of final manuscript
CF: provision of patients, data collection and analysis, approval of final manuscript
MM: provision of patients, data collection and analysis, approval of final manuscript
DR: provision of patients, data collection and analysis, approval of final manuscript
DRL: study design, review of pathology, approval of final manuscript
RC: provision of patients, study oversight, manuscript writing, approval of final manuscript
DKR: study concept, study design, funding, oversight of study, approval of final manuscript
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Precis: Dasatinib demonstrated no significant anti-sarcoma activity in patients with epithelioid sarcoma or solitary fibrous tumor. Patients with alveolar soft part sarcoma had prolonged disease progression-free and overall survival but not necessarily caused by dasatinib. A small minority of patients with chondrosarcoma or chordoma experienced objective tumor response or prolonged stabilization of disease suggesting dasatinib treatment should be further evaluated in these sarcoma sub-types.

Abstract

Background: Alveolar soft part sarcoma (ASPS), chondrosarcoma (CS), chordoma, epithelioid sarcoma (ES) and solitary fibrous tumor (SFT) are malignant tumors which are relatively resistant to chemotherapy for which more effective drug therapy is needed.

Patients and methods: The five listed subtypes were enrolled into a single "indolent" sarcoma cohort in a phase II 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 using Choi criteria with a target of $\geq$50%. Cross-sectional imaging was done prior to start of treatment, every 2 months for 6 months and then every 3 months during treatment. Two and 5 year survival rates were determined.

Results: 116 patients were enrolled in 45 months and 109 began treatment with dasatinib. The 6-month PFS rate and median PFS were 48% and 5.8 months, respectively. The rate of PFS at 6 months was highest in ASPS (62%) and lowest in SFT (30%). More than 10% of patients with ASPS, CS or chordoma had stable disease for more than 1 year. Collectively for all 5 sub-types, 2-year and 5-year overall survival rates were 44% and 13%, respectively. Objective response was observed in 18% of 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 using Choi tumor response criteria. Objective tumor response and prolonged stable disease was observed in >10% of patients with CS or chordoma.

Introduction

Sarcomas are a diverse group of stromal cancers of which the large majority is derived from mesodermal tissue. A number of distinct histologic sub-types of sarcoma share the unusual behavior of low cell proliferation rate but high risk of local recurrence and systemic spread which may occur years after definitive treatment of the primary cancer. The life span of individuals with one of these "indolent" sarcomas after development of metastasis is often years. For example, the rate of metastases in patients with alveolar soft part sarcoma (ASPS) is greater than 50% but median survival is more than 3 years after diagnoses 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 metastases.[3, 4] Chordoma and low to intermediate grade chondrosarcoma (CS) are types of sarcoma arising in bone that also exhibit a low mitotic rate but have risk of local recurrence and metastases. 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 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] And imatinib has activity in chordoma.[9] In clinical trials of these drugs to treat ASPS, SFT and chordoma, objective responses were observed in a minority of patients but more than 50% of patients were surviving free from sarcoma progression 6 months after starting therapy.

The mechanism of anti-tumor 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 platelet-derived growth factor pathway is active in ASPS, SFT and chordoma.[5, 10-12] The Src pathway is active in chondrosarcoma and inhibition of Src in vitro by dasatinib has led to reduced chondrosarcoma 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 receptor alpha and beta, c-KIT, BCR-ABL and ephrin receptor kinases that 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, based on pre-clinical studies and clinical experience with imatinib and sunitinib in treatment of sarcoma, we felt there was a reasonable chance for dasatinib to have anti-tumor activity in ASPS, CS, chordoma and SFT. Patients with ES were included because of a lack of effective drugs against this cancer.

Patients 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 sub-types, indolent sarcoma sub-types and gastrointestinal stromal tumor) under one parent study (SARC009) coordinated by Sarcoma Alliance through Research and Collaboration (SARC). Results of dasatinib in patients with aggressive sarcoma sub-types are reported elsewhere.[16] SARC provided central coordination of study conduct, patient enrollment, study monitoring and audit. Cancer Research and Biostatistics (www.crab.org) developed and maintained an electronic study database. Statistical support was provided by V. Bolejack for the indolent sub-type 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

Study enrollment into the "indolent" sub-study was restricted to patients 13 years of age or older weighing at least 50 Kg with measurable, ASPS, grade 1 or 2 CS of bone, chordoma, ES or SFT that was incurable by conventional treatment. Confirmed disease progression based on standard imaging criteria prior to enrollment was not required. Additional eligibility criteria included ECOG performance score $\leq$2, ability to swallow whole tablets, absolute neutrophil count $\geq$1,500/ul, platelet count $\geq$75,000/ul, serum creatinine $\leq$2 times institutional upper limit of normal (IULN), prothrombin and partial thromboplastin times $\leq$1.5 times IULN, serum magnesium, potassium and calcium at least the lower limit of normal range, corrected QT interval $\leq$450 msec, and left ventricular ejection fraction 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. Lucas) within 2 months of patient enrollment and initiation of therapy.

Study treatment and evaluations

Dasatinib was started at 100 mg orally 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 to 50 mg twice daily then to 100 mg once daily. Drug treatment was continued until disease progression by Choi criteria[18], unacceptable toxicity, patient choice or provider decision. The extent of disease was assessed using CT or MRI 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. Electrocardiogram was performed during screening and after the first month of treatment. Correction of the QT interval was made by local sites' using Bazett's formula. Safety evaluations included complete blood counts and comprehensive metabolic panel 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 Common Terminology Criteria for Adverse Events version 3.0.

The primary study endpoint was 6-month PFS rate using 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 target lesions). We chose to assess tumor response using Choi criteria instead of RECIST or WHO because improvements in the resolution of cross-sectional imaging allowed for more precise tumor measurements such that we felt a change in tumor size of more than 10% could be reliably determined and because of prior experience assessing GIST response treated with another tyrosine-kinase inhibitor, imatinib.[18] Secondary endpoints included patient safety assessment by adverse event rate, 2 and 4-month PFS rates, median time to progression, 2-year and 5-year overall survival rates. Study endpoints were assessed by participating investigators; central radiology review was not performed. Patients were censored for PFS at the date of last radiology evaluation if progression had not occurred. Patients were censored for survival at the date of last contact with survival time calculated from date of registration to death. Patients were contacted at least every 12 months for survival until 5 years from registration.

Statistical methods

Patients with one of the eligible "indolent" sarcoma sub-types were enrolled into a single cohort because of the relative rarity and uncertainty of rate of accrual of each of the sarcoma sub-types under study to justify enrollment in sub-type-specific cohorts. The study was designed to estimate the PFS and OS for the group. Post hoc analysis was performed on each sarcoma sub-type. We estimated a 6-month PFS rate of 30-40% for inactive therapies and greater than 50% for an 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 .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 and a maximum of 116 patients were to be enrolled. We anticipated an accrual rate of 1-3 patients per month.

Results

Patient demographics

One-hundred and sixteen patients were registered over 45 months starting July 2007 providing 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 ineligible sarcoma sub-type (extraskeletal myxoid chondrosarcoma) on central pathology review, 2 were ineligible because of use of prohibited concomitant medication, and 3 chose not to start therapy after registration. Characteristics for the 109 patients who started dasatinib are shown in table 1. Chordoma and CS were the commonest sub-types 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 are off treatment. A median of 4 cycles (range 1-87 months) of dasatinib were administered. Median numbers of cycles completed by patients with ASPS was 7.5, chordoma was 6, CS was 4, ES was 9 and SFT was 2. Treatment interruption was reported in 62 patients (57%) and reduction in dose was reported in 36 patients (33%). Reduction in dasatinib dose was more frequent in patients with SFT (52%) than 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). Non-hematologic adverse events occurring in more than 5% of patients included fatigue, fever, anorexia, weight loss, rash, nausea, vomiting, constipation, diarrhea, edema, pleural effusion, dyspnea, cough, headache, pain, elevated serum creatinine, 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 patients included pain in 17%, dyspnea in 11%, pleural effusion in 6% and diarrhea in 5%. Non-hematologic grade 4 adverse events included 1 episode each of cardiac infarction, intracranial hemorrhage, meningitis, pyelonephritis, dyspnea, elevated serum creatinine and hypokalemia. Six patients died during therapy; 2 deaths were from 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 pre-treatment 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 baseline and measured 429 and 427 milliseconds, respectively, in 93 patients for which data was available.

Dasatinib activity

The 6-month PFS rate was 48%. Median PFS and OS were 5.8 months 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 and 2-year and 5-year OS rates by subtype are shown in table 3. 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 objective tumor response per Choi criteria. Of the patients with response, 19 started treatment with dastinib 70 mg twice daily and 1 with 100 mg twice daily. On 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 in sub-types that usually exhibit an indolent rate of growth and for which there are very limited accepted standard chemotherapy treatments. Collectively, ASPS, ES and SFT comprise about 1% of soft tissue sarcomas and chordoma represents about 5% of bone sarcomas.[19] Because of the rarity of the different sub-types, patients were enrolled into one cohort rather than "indolent" histology sub-type-specific cohorts. This study demonstrated that SARC, as a cooperative clinical research group, was able to enroll patients with very rare sub-types at a rate

consistent with *a priori* expectations and successfully complete accrual. SARC members are predominately medical oncologists, with expertise in treatment of patients with sarcoma and commitment to sarcoma clinical research, practicing at medical centers with demonstrated multi-disciplinary 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 which likely contributed to the successful enrollment. In addition, most of the member institutions support pathologists with special expertise in diagnosis of soft tissue and bone tumors which accounted for a low rate (<2%) of discrepancy in diagnosis between local and central pathologists.

Prior to 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, results of prospective clinical trials of chemotherapy in patients with ES or chondrosarcoma had not been reported. Because of a lack of objective responses observed in previous trials, we used 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 using 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 II trial. One reason for the relatively low 6-month PFS rate is the use of Choi criteria rather than RECIST; disease progression per Choi occurs when tumor growth is at least 10% and thus earlier than with RECIST that requires a 20% increase in tumor size for progression. A minority of patients met criteria for sarcoma progression per RECIST; 1 patient with ASPS, 3 with chordoma, 13 with chondrosarcoma, 1 with ES and 8 with SFT had RECIST progressive disease. This trial would likely have had a 6-month PFS rate over 50% if RECIST had been used to assess tumor response and thus been viewed as a trial with a positive primary endpoint. Differential activity of dasatinib within and/or variability in natural growth rates of sarcoma sub-types also likely impacted PFS. Patients with SFT experienced the shortest median PFS and lowest 6-month PFS rate; whereas, patients with ASPS, chordoma or epithelioid sarcoma had a 6-month PFS rate of more than 50%. If the study had been designed to enroll patients into sub-type specific cohorts, dasatinib may have been declared potentially active in ASPS, chordoma and epithelioid sarcoma. Patients with ASPS had a relatively long median PFS and OS compared to many of the other sub-types, 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 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 the tyrosine kinase Src plays a role in chondrosarcoma pathogenesis, and dasatinib had anti-tumor activity in pre-clinical chondrosarcoma models.[13, 14] In our study, patients with low or intermediate-grade CS of bone had a median PFS of 5.5 months and 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 suggesting a small subset of patients may have had some tumor control with dasatinib. Prospective trials of drug therapy in metastatic CS have infrequently been conducted to provide a basis for comparison of results. In a phase II 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 chondrosarcoma, 11% had dedifferentiated chondrosarcoma and 1 patient had clear cell chondrosarcoma in the trial of GDC-0449. The median OS in the GDC-0449 trial was 12 months compared to 27 months in our study of dasatinib. Our preliminary clinical data from dasatinib treatment of CS patients along with absence of a standard effective drug therapy for this group of patients supports further study of dasatinib in CS.

Chordomas express platelet-derived growth factor receptor-alpha and epidermal growth factor receptor and have been the subject of clinical trial research using tyrosine kinase inhibitors. Treatment of 56 patients with advanced chordoma using imatinib in a phase II trial demonstrated 1 objective partial response by RECIST, 6-month PFS rate of 64% and median PFS of 9 months.[9] Similar results were noted in a retrospective case series analysis in 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 II trial of lapatinib treatment of patients with advanced, EGFR-positive chordoma, no objective responses per RECIST were seen, but 33% of patients had partial response per Choi response criteria and the median PFS was 6 months.[23] In our trial of dasatinib using Choi response criteria, the median PFS and 6-month PFS rate in patients with chordoma were 6.3 months and 54%, respectively, which are not substantially different from results using imatinib or lapatinib. Moreover, 14% of patients treated with dasatinib were surviving without tumor progression for more than 2 years and 18% of patients were alive at 5 years highlighting 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 sub-types ranging from 71% in ES to 88% in conventional chondrosarcoma; however, the 2-year and 5-year survival rates in ES were 21% and 0%, respectively, compared with survival rates in conventional chondrosarcoma of 56% and 9%, respectively. Similar poor survival rates in 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] Response of SFT to dasatinib was worse than in previous reports of treatment with temozolomide and bevacizumab or sunitinib using Choi response criteria.[7, 8] Treatment with either regimen resulted in objective partial responses in about 50% of patients, median PFS of at least 50% and 6-month PFS rate of at least 50% compared to a median PFS of 2 months and 6-month PFS rate of 30% with dasatinib.

In summary, SARC conducted a single-arm trial of dasatinib in patients with rare sarcoma subtypes in which there is an unmet medical need for more effective chemotherapy to manage locally advanced or metastatic disease and 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 using Choi response criteria more than 50% of patients with ASPS or ES were free from disease progression more than 6 months, and 50% of the ASPS patients were alive for at least 2 years after enrollment. In addition, about 15% of patients with chordoma or CS had objective tumor response and a few had stable disease for more than 2 years on treatment. Dasatinib should not be used as standard treatment of SFT but may be worth comparative study with cediranib or sunitinib depending on results in the ongoing ASPS trial. The low rate of OS in 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 treatment of patients with locally-advanced, unresectable or metastatic CS of bone or chordoma and results discussed above, further evaluation of dasatinib in CS and chordoma should be considered in future clinical trials.

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

Figure 2. Time on treatment with dasatinib by sarcoma sub-type.

Table 1. Patient characteristics

Age at registration – median (range) in years	54 (22 – 87)
Sex – male/female	76/33
Race	N = 109
white	94 (86%)
black	8 (7%)
Asian	3 (3%)
other	4 (4%)
Sarcoma sub-type	N = 109
alveolar soft part sarcoma	12 (11%)
chondrosarcoma	33 (30%)
chordoma	32 (29%)
epithelioid sarcoma	7 (6%)
solitary fibrous tumor	25 (23%)
Prior drug therapy	
alveolar soft part sarcoma	10 (83%)
chondrosarcoma	11 (34%)
chordoma	20 (61%)
epithelioid sarcoma	6 (86%)
solitary fibrous tumor	11 (44%)

Table 2. Number of patients with hematologic toxicity 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

Table 3. Survival according to sarcoma sub-type

Sarcoma sub-type	6-month PFS	2-year OS	5-year 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%

PFS: progression-free survival; OS: overall survival

Table 4. Comparison of reported patient outcomes in selected phase II and retrospective sarcoma studies.

			Choi response criteria			RECIST		
Sarcoma	Drug	# PTS	ORR	6-mo PFS	mPFS	ORR	6-mo PFS	mPFS
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; SFT, solitary fibrous tumor; PTS, patients; ORR, objective response rate; mo, month; PFS, progression-free survival; ND, not done; NR, not reported; TMZ/BEV, temozolomide and bevacizumab.

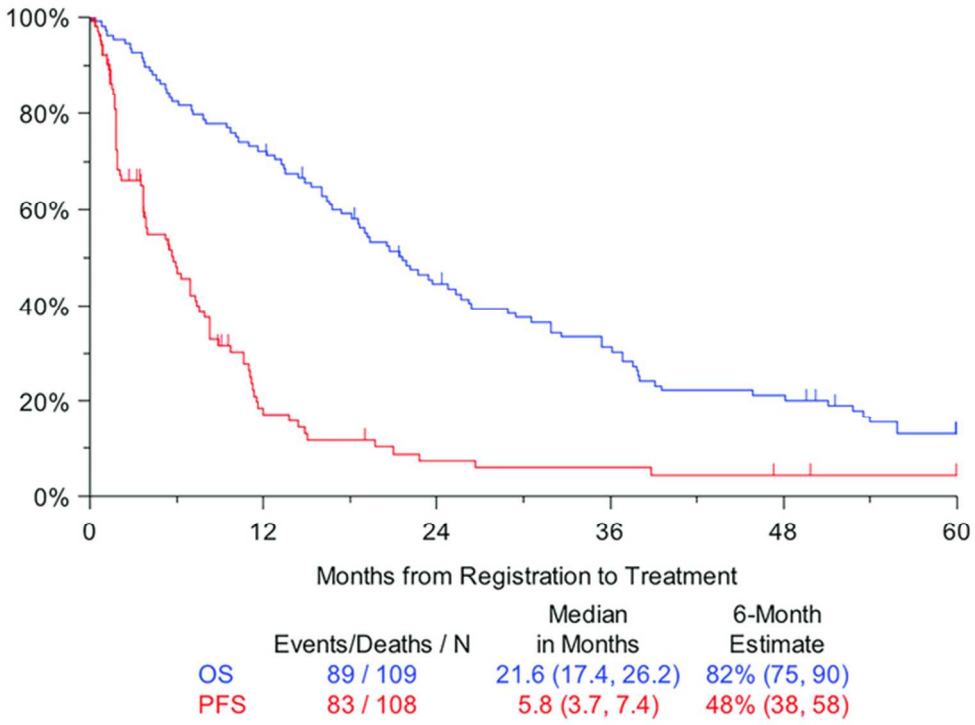

Figure 1. Kaplan-Meier progression-free and overall survival curves.

30x22mm (600 x 600 DPI)

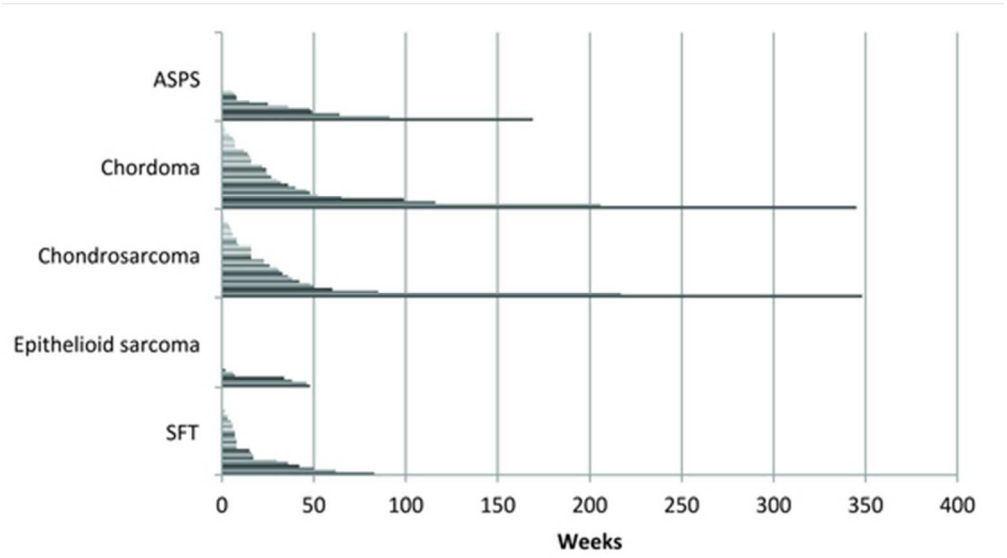

Figure 2. Time on treatment with dasatinib by sarcoma sub-type.

23x13mm (600 x 600 DPI)