

# We Can Study Ultrarare Tumors Effectively in This Day and Age, It Just Takes a Cooperative Approach: The Role of Dasatinib in Assorted Indolent Sarcomas

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Sarcomas are mesenchymal malignancies with more than 60 different malignant subtypes.<sup>1</sup> Drug development has long been hampered in this group of tumors by their rarity and by the difficulty in organizing large-scale clinical trials. However, rigorous science performed by sarcoma researchers worldwide has identified novel pathways and molecular drivers in these subtypes. As our understanding of sarcoma biology accelerates with advancements in molecular and genetic techniques coupled with access to annotated tissue banks and databases, we are now beginning to decipher drivers of the disease and to develop new trials with the ever-growing armamentarium of targeted agents in development. The clinical sarcoma community has organized worldwide to breathe new life into drug development with the support of the Sarcoma Alliance Through Research and Collaboration (SARC) consortium, the National Clinical Trials Network (NCTN), and the National Institutes of Health. We have demonstrated that well-conducted, high-quality clinical translational trials can be performed efficiently for these rare diseases. Patients with rare sarcoma subtypes no longer need to be relegated to all-comer trials where the hope of drug activity is low. It is also clear that the study of these very rare subtypes of cancer has become even more important because often these tumors can elucidate previously unknown oncogenic pathways, and this may further the development of treatments of more common and perhaps more complex tumors.

In this issue of *Cancer*, Schuetze et al<sup>2</sup> present data on the activity of dasatinib in ultrarare subtypes of indolent sarcomas. This study was developed as part of a larger clinical trial (SARC009), which also included gastrointestinal stromal tumors (GISTs) as well as several cohorts of high-grade sarcomas and was developed and managed through the SARC consortium. Unfortunately, other than a possible signal in undifferentiated pleomorphic sarcoma, SARC009 failed to show appreciable activity with dasatinib for high-grade sarcomas.<sup>3</sup> The indolent sarcoma cohort was composed of 5 ultrarare sarcoma subtypes: alveolar soft part sarcoma (ASPS), low/intermediate-grade conventional chondrosarcoma, epithelioid sarcoma, solitary fibrous tumor, and chordoma. Interestingly, all 5 tumor types harbor different defining genetic aberrations.<sup>4-8</sup> The study included patients older than 13 years with an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients initially received dasatinib at 100 mg twice daily, although this dose was reduced to 70 mg twice daily because of toxicities from dasatinib apparent from other trials. The primary study endpoint was to evaluate progression-free survival at 6 months (PFS-6) with the Choi criteria.<sup>9</sup> A PFS-6 rate of 50% or higher was required for dasatinib to be considered an active agent. These tumor subtypes were grouped into 1 cohort because of uncertainty about whether accrual would be sufficient for such rare sarcoma subtypes if they were separated. The authors successfully enrolled 116 patients over the course of 45 months with an average of 2.6 new patients per month.

The final results of the study were somewhat disappointing because the primary endpoint for the entire cohort was not met with a PFS-6 rate of 48%. The median progression-free survival (mPFS) and overall survival were 5.8 and 21.6 months, respectively. The authors examined the individual tumor subtypes and suggested that dasatinib may demonstrate activity in ASPS, chondrosarcoma, and epithelioid sarcoma, but this would require confirmatory studies.

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TABLE 1. Response Chart

Sarcoma Subtype	Source	Drug	No.	6-mo PFS Rate, %		PFS Time, mo		Best Response: RECIST, No. (%)				Best Response: Choi, No. (%)			
				RECIST	Choi	RECIST	Choi	CR/PR	SD	PD	CR/PR	SD	PD	CR/PR	SD
SFT	Stacchiotti 2012 <sup>10</sup>	Sunitinib	31	45	-	-	7	PR: 2 (6.5)	17 (54)	12 (39.5)	PR: 14 (48)	5 (17)	10 (35)		
	Park 2011 <sup>11</sup>	Temozolomide, bevacizumab	14	93	10.8	9.67	PR: 2 (14)	12 (86)	0	PR: 11 (79)	2 (14)	1 (7)			
	Park 2013 <sup>12</sup>	Conventional chemotherapy	25	-	4.6	-	0	21 (84)	4 (16)	-	-	-			
	Schuetz 2016 <sup>2</sup>	Dasatinib	25	-	30	2	0	-	-	PR: 5 (20)	-	-			
	Bompas 2015 <sup>23</sup>	Sorafenib	27	85	-	NR	-	PR: 1 (8)	12 (84)	1 (8)	PR: 7 (54)	5 (38)	1 (8)		
Chordoma	Stacchiotti 2013 <sup>21</sup>	Lapatinib	18	-	8	6	0	PR: 1 (2)	15 (83)	3 (17)	PR: 6 (33)	7 (39)	5 (28)		
	Stacchiotti 2012 <sup>20</sup>	Imatinib	56	64 (CBF)	9.2	-	-	PR: 1 (2)	35 (70)	14 (28)	-	-	-		
	Hindi 2015 <sup>22</sup>	Imatinib	50	65	9.9	-	0	34 (74)	12 (26)	-	-	-			
	Schuetz 2016 <sup>2</sup>	Dasatinib	32	-	54	6.3	0	-	-	6 (19)	-	-			
	Kumar 2013 <sup>13</sup>	Cediranib	43	84	-	-	PR: 15 (35)	26 (50)	2 (15)	-	-	-			
ASPS	Wagner 2012 <sup>15</sup>	Tivantinib	27	-	5.5	-	0	21 (78)*	5 (19)	-	-	-			
	Stacchiotti 2012 <sup>14</sup>	Sunitinib	9	88	17	-	5 (55)	3 (33)	1 (11)	-	-	-			
	Schuetz 2016 <sup>2</sup>	Dasatinib	12	-	62	11	0	-	-	PR: 1 (8)	-	-			
	Italiano 2013 <sup>16</sup>	GDC-0449 (hedgehog)	39	25.6 (CBR)	3.5	-	0	10 (26)	29 (74)	-	-	-			
	Fox 2012 <sup>18</sup>	Gemcitabine plus docetaxel	25	-	-	-	2 (8)	14 (56)	9 (36)	-	-	-			
Chondrosarcoma	Grignani 2010 <sup>17</sup>	Imatinib	26	31 4-mo PFS	3	-	0	8 (31)	18 (69)	-	-	-			
	Italiano 2014 <sup>19</sup>	Assortment of drug combinations	180	44	4.7	-	CR: 2 (1)	PR: 22 (14)	67 (41)	72 (45)	-	-			
	Schuetz 2016 <sup>2</sup>	Dasatinib	33	-	47	5.5	0	-	-	PR: 5 (15)	-	-			
	Pink 2014 <sup>25</sup>	Gemcitabine plus docetaxel	12	-	8	-	CR: 1 (8)	PR: 6 (50)	3 (25)	2 (17)	-	-			
	Jones 2012 <sup>24</sup>	Conventional chemotherapy	20	53	6.7	-	PR: 3 (15)	12 (60)	5 (25)	-	-	-			
Epithelioid sarcoma	Schuetz 2016 <sup>2</sup>	Dasatinib	7	-	57	7.9	0	-	-	PR: 2 (29)	-	-			

Abbreviations: ASPS, alveolar soft part sarcoma; CBR, Clinical Benefit Rate (CR+PR+SD); CR, complete response; N/A, not available; NR, not reported; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SFT, solitary fibrous tumor. \* For Wagner et al, 1 patient was inevaluable.

In hindsight, this trial may have been more useful had the benchmarks for success been adapted to each tumor type on the basis of outcomes generated by prior trials (Table 1). Dasatinib appears not to exhibit activity in solitary fibrous tumors in comparison with historical trials of temozolomide plus bevacizumab, conventional chemotherapy, and sunitinib.<sup>10-12</sup> Although ASPS patients appeared to have the highest PFS-6 rate at 62%, the results fall short of the activity noted in studies of sunitinib (88%) and cediranib (84%).<sup>13,14</sup> However, dasatinib (mPFS, 11 months) seemingly outperforms tivantinib (mPFS, 5.5 months), and this suggests that there may be some activity over the baseline.<sup>15</sup> The chondrosarcoma cohort achieved a PFS-6 rate of 47%. If taken in isolation, this also would not have met the primary endpoint of 50%. However, this result compares favorably with other studies: a hedgehog inhibitor achieved a PFS-6 rate of only 28%, and imatinib achieved a 4-month progression-free survival rate of only 31%.<sup>16,17</sup> A study using different combinations of conventional chemotherapy achieved a 44% PFS-6 rate, although that trial also included dedifferentiated and mesenchymal chondrosarcoma subtypes, many of which were high-grade.<sup>18,19</sup> In chordoma, dasatinib exhibited a 54% PFS-6 rate; this was similar to rates achieved with other targeted agents considered active such as lapatinib (60%) and imatinib (64%-65%).<sup>20-22</sup> However, sorafenib has recently emerged as an active agent in chordoma with an 85% PFS-6 rate and an mPFS time that has not yet been reached.<sup>23</sup> Lastly, dasatinib (PFS-6 according to the Choi criteria, 57%) performed similarly to first-line conventional chemotherapies (PFS-6 according to the Response Evaluation Criteria in Solid Tumors [RECIST], 53%) in a retrospective analysis of epithelioid sarcoma.<sup>24</sup> Dasatinib (mPFS, 7.9 months) performed comparably to gemcitabine and docetaxel (mPFS, 8 months).<sup>25</sup>

In addition, the use of the Choi criteria for responses factored most heavily in influencing our interpretation of the outcomes described in this study. The Choi criteria were established for the treatment of GISTs, which frequently undergo myxomatous changes as a response to treatment without a significant decrease in size. These criteria have been validated in several different publications and correlate closely with long-term outcomes for GIST patients.<sup>9,26</sup> The definition of a tumor response requires only a 10% decrease in the tumor size or a 15% decrease in the Hounsfield unit density for the Choi criteria, whereas RECIST 1.1 requires a 30% decrease. Tumor progression requires only a 10% increase in a 1-dimensional measurement for the Choi criteria, whereas

RECIST uses a 20% threshold. One can imagine that if the authors had applied RECIST 1.1, the extra 10% leeway in determining progression may have pushed the PFS-6 rate higher than 50% for slowly growing tumors.

The utility of RECIST versus the CHOI criteria for non-GIST soft tissue sarcomas remains questionable, although there are good data for solitary fibrous tumors and chordomas.<sup>10,21</sup> Depending on the primary outcome, the Choi criteria simultaneously underestimate and overestimate the efficacy of a drug. The Choi criteria may significantly underestimate the relative progression-free survival because only 10% growth is needed for progression, whereas a 20% change is required by RECIST 1.1. A 10% increment may be confounded by measurement inaccuracies due to the multilobulated nature of many of these tumors (especially chordomas). At the same time, the response rates with the Choi criteria may be amplified by the lower threshold for changes in the tumor size and density. These considerations also make the comparison of response rates in this trial difficult to assess. This study could in fact help us to decide whether the Choi criteria are a proper tool for non-GIST sarcomas because we now have a set of more than 300 patients who may have both measurements.

Another factor in this study design to consider is the fact that had the trial met its primary endpoint, this would have necessitated the assumption that dasatinib is considered active in all 5 of these sarcoma subtypes when, in reality, the activity was heterogeneous and based on the tumor subtype. Perhaps the biggest strength of this article is the demonstration that we can indeed perform high-quality clinical trials in the setting of ultrarare cancers. We applaud the investigators for completing such a complex study design for a group of ultrarare sarcomas that have thus far proven exceedingly challenging to study appropriately. This opens up more opportunities for developing more selectively designed cohort studies, which may lead us to better data on whether certain therapies are more clearly active. The ability of the authors to enroll patients with relative rapidity into a trial for extremely rare cancers shows that these types of trials are in fact possible and feasible. For example, in the case of ASPS, according to data from the Surveillance, Epidemiology, and End Results program from 1973 to 2006, 72,972 individuals with soft tissue sarcoma were identified.<sup>27</sup> Among those individuals, 164 had an ASPS diagnosis, and this means that approximately 0.2% of all sarcomas are ASPS. If we assume that there are 12,000 to 15,000 new soft tissue sarcomas every year, this suggests that there are only 24 to 30 new ASPS diagnoses every year. Under the auspices of a larger

study, Schuetze et al enrolled 12 ASPS patients over the course of nearly 4 years: they effectively enrolled more than 12% of all nationwide ASPS diagnoses in that time period! This is actually quite remarkable.

The authors initiated this trial design when they were not confident that accrual for such a rare group of tumors would be achievable. Now that we are confident of our ability to enroll patients into these types of trials, there should be more opportunities to study these exceedingly rare tumors. Although overall survival is the gold standard for assessing activity in cancer, trials in this group of disease types would suffer greatly from a randomized, placebo-controlled design without crossover because most of these patients have so few treatment options available to them and so few minimally active drugs to use as comparators. In addition, using an active comparator would make accrual only that much more difficult because then one would have to essentially enroll patients who had received no prior therapies. Progression-free survival as an endpoint is feasible, but the difficulty associated with this endpoint in a single-arm study is compounded by the fact that these tumors exhibit great heterogeneity in behavior and growth rates. An ideal trial including all of these subgroups would best have been achieved with a randomized, double-blinded basket design with crossover and stratification by disease subtype so we could properly control for tumor growth characteristics.

SARC has been leading the development of these types of trials in the United States for the past decade and a half and has galvanized the international community in advocating for novel and high-impact sarcoma studies. However, the reorganization of the cooperative groups has opened other avenues for pursuing clinical trials for rare tumors. The NCTN now has consolidated the former 10 cooperative groups into 5 different groups: Alliance for Clinical Trials in Oncology (ALLIANCE), Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN), SWOG, NRG Oncology, and Children's Oncology Group (COG). The most important aspect of this reorganization has been the development of the NCTN as an umbrella for all the cooperative groups; this now allows the opening of relevant and interesting clinical trials at any of the currently 30 lead academic performing sites, and nearly every major sarcoma center is a part of this. Investigators at community hospitals can also participate in NCTN trials through the National Cancer Institute's Community Oncology Research Program. In addition, there are other programs such as the UM1 program that are facilitating the development of clinical trials at large collaborating comprehen-

sive cancer centers. We need to take advantage of these new resources.

Although this trial did not achieve its primary endpoint, there appears to be considerable activity in several subtypes of indolent sarcomas (particularly chondrosarcoma, chordoma, and epithelioid sarcoma). Perhaps through SARC or one of the cooperative groups, more stringent clinical trials with the intent of registration for indications in chondrosarcoma, chordoma, and/or epithelioid sarcomas may be developed because these appear to be the most susceptible to dasatinib.

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