Published in final edited form as:

Curr Opin Oncol. 2013 July ; 25(4): 373–378. doi:10.1097/CCO.0b013e3283622d3a.

Pazopanib in sarcomas: expanding the PALETTE

Breelyn A. Wilky^a, Christian F. Meyer^a, and Jonathan C. Trent^b

^aDepartment of Medical Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland ^bDepartment of Medicine, Division of Hematology/Oncology, Leonard M. Miller School of Medicine University of Miami, Miami, Florida, USA

Abstract

Purpose of review—After failure of standard therapy, few effective treatment options exist for adult patients with metastatic sarcomas, and median survival remains dismal at approximately 1 year. Pazopanib, a multitargeted tyrosine kinase inhibitor, has recently been approved for nonadipocytic soft tissue sarcomas refractory to chemotherapy. In this review, we will revisit the efficacy of pazopanib in sarcomas, and present a patient case that illustrates two of many unanswered questions: which sarcoma patients are most likely to benefit from pazopanib therapy, and what criteria are best suited to accurately detect benefit in clinical trials?

Recent findings—Pazopanib has been tested in sarcoma patients in a phase II and phase III study, and was shown to prolong progression-free survival by 3 months relative to placebo. Although histology has been the primary stratification variable for subgroup analysis in large sarcoma trials, the PALETTE study did not demonstrate superior response within histologic cohorts. Ongoing trials seek to explore efficacy of pazopanib in previously excluded histologies, as well as include correlative studies to identify histologic and molecular biomarkers to predict patients likely to benefit.

Summary—Pazopanib has been proven to provide modest benefit overall to nonadipocytic soft tissue sarcoma patients, but we have yet to identify the molecular basis for those patients who derive exceptional benefit.

Keywords

biomarker; clinical trial; pazopanib; sarcoma

INTRODUCTION

Sarcomas make up only 1% of adult cancers, with over 50 histologic subtypes. Drug development has lagged behind other cancers because of the rarity and genetic heterogeneity

© 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

Correspondence to Breelyn A. Wilky, MD, 1650 Orleans Street, Bunting-Blaustein Cancer Research Building, Room 186, Baltimore, MD 21231, USA. Tel: +1 410 955 8838; fax: +1 410 955 0125; bwilky1@jhmi.edu.

Conflicts of interest

There are no conflicts of interest.

of the various subtypes. The most successful discovery in recent years has been the efficacy of imatinib in KIT-mutated and platelet-derived growth factor (PDGFR)-mutated gastrointestinal stromal tumors (GIST). Unfortunately, most adult soft tissue sarcomas are genetically complex, with few conserved mutations or pathway aberrations that lend themselves to treatment with kinase-specific inhibitors. Pazopanib is a multitargeted tyrosine kinase inhibitor that can produce impressive stabilization and occasional responses in sarcomas. In this review, we will present a representative case of a patient deriving substantial benefit from pazopanib, review the clinical data for efficacy in sarcoma patients overall, and describe ongoing efforts to expand and identify new applications for pazopanib therapy.

CLINICAL CASE

A 39-year-old woman presented with hematuria and flank pain, and computed tomography (CT) imaging revealed a large left renal mass presumed to be renal cell carcinoma. However, pathology after nephrectomy revealed a 19.5-cm high-grade synovial sarcoma with extensive necrosis. Postoperative imaging scans also detected an 8-mm lung nodule. The patient received six cycles of adjuvant doxorubicin/ifosfamide chemotherapy, and the lung nodule decreased to 2 mm in size. Six months after completion of chemotherapy, the patient developed an 8-cm recurrent mass in the surgical bed, with several small satellite nodules. The patient also developed elevated liver transaminases and bilirubin, despite the absence of apparent disease in that area. Second-line treatment was begun with two cycles of single-agent gemcitabine (due to liver dysfunction) followed by gemcitabine with docetaxel, but the patient progressed with multiple new omental implants in the abdomen and pelvis. Surgery was considered but felt to be highly morbid because of the diffuse distribution of disease, and the patient was initiated on pazopanib. Just 2 weeks after start of therapy, the patient was admitted for acute abdominal pain, nausea, and vomiting, likely related to local compressive effects from the masses. CT imaging at that time, as well as 6 weeks later, showed remarkable evolution in the tumors with decreased solid components, expansion of cystic and necrotic areas, with eventual decrease in size (Fig. 1). Clinically, the patient's abdominal pain resolved and the liver enzymes normalized. Eight months after initiation of pazopanib, she developed a new contralateral lung nodule that was successfully treated with radiofrequency ablation. After 18 months, a pelvic nodule associated with a ventral hernia began to increase in size, and pazopanib was held while she underwent surgery with removal of all visible disease in the abdomen. Imaging 8 weeks after surgery showed two new pelvic nodules, and pazopanib was reinitiated. The patient remained on pazopanib for an additional 6 months with stabilization of disease, before one nodule began to enlarge. The patient is currently enrolled on a phase I clinical trial at Johns Hopkins combining pazopanib and a MEK inhibitor, GSK1120212; the patient has been treated with pazopanib for 32 months.

PAZOPANIB MECHANISM, PHARMACOLOGY, AND CLINICAL ACTIVITY

Pazopanib is a multityrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, PDGFR- α and - β , fibroblast growth factor receptor-1 and -3, and KIT as well as other emerging targets, including B-RAF proteins [1,2]. Preclinical models of pazopanib demonstrated inhibition of ligand-induced

autophosphorylation of VEGFR-2, KIT, and PDGFR- β receptors, and impaired FGF and VEGF-mediated angiogenesis as well as xenograft growth in multiple human cancers [3]. With standard dosing of 800 mg orally, toxicities include effects common to many anti-VEGF therapies such as hypertension, bleeding and thrombosis, and proteinuria, as well as hepatotoxicity, hypothyroidism, cardiac dysfunction (prolonged QT intervals and torsades de pointes), depigmentation phenomena, and gastrointestinal disturbances. Most patients are ultimately able to tolerate the full 800-mg dose, and gradual dose escalation over 2–3 weeks with close monitoring of liver enzymes can improve patient tolerance of side-effects. Pazopanib undergoes hepatic metabolism by CYP3A4; thus, coadministration with inducers or inhibitors of CYP3A4 should be avoided.

Pazopanib was Food and Drug Administration (FDA)-approved in renal cell carcinoma after a randomized phase III study demonstrated improvement in progression-free survival (PFS) to 11.1 months in the treatment group from 2.8 months in the placebo group, for treatment-naïve patients. In cytokine-pretreated patients, PFS improved from 4.2 to 9.2 months in the treatment group. The overall tumor response rate was 30 vs. 3% [4]. Pazopanib has also shown promising activity in several other cancers, including differentiated thyroid, cervical, hepatocellular, glioblastoma, breast, urothelial, and nonsmall cell lung cancers [5–9]. Most excitingly, pazopanib is the first molecular targeted agent approved by the FDA for sarcomas since imatinib for GIST. We will now review preclinical evidence and outcomes of sarcoma-specific pazopanib clinical trials, and highlight unanswered questions and ongoing investigations.

PRECLINICAL RATIONALE FOR PAZOPANIB EFFICACY IN SARCOMA

Areas of relative hypoxia and markers of dysfunctional angiogenesis are common features of bone and soft tissue sarcomas. Although sarcomas are heterogeneous tumors, preclinical studies have consistently described aberrant expression or function of pazopanib target kinases in many histologic subtypes. Increased expression of tumor VEGF, PDGFR, and other downstream targets has frequently been associated with worse clinical outcomes, increased metastasis, resistance to chemotherapy, and higher histologic grade in sarcomas [10,11]. Plasma levels of VEGF and basic FGF were elevated 10–13 fold in sarcoma patients compared with controls, and microarray gene expression data showed markedly elevated expression of matrix metalloproteinase 2 and PDGFR- α in sarcoma tissue compared with non-malignant tissue [12]. Angiosarcoma cells exhibit overexpression of multiple components of the VEGF pathway, including VEGFRs, hypoxia-inducible factor 1- α , TIE-1 and TIE-2 [13], but 10% of angiosarcoma patients have tumors that possess activating mutations in the gene *KDR*, leading to ligand-independent activation of VEGFR2 [14]. Several mesenchymal neoplasms notoriously resistant to traditional chemotherapy also overexpress VEGF and VEGFR, such as epithelial hemangioendothelioma and solitary fibrous tumor/hemangiopericytoma (SFT/HPC) [13]. In adult GIST patients, 90% of tumors carry mutations in KIT or PDGFR, and a small fraction possesses B-RAF mutations [15,16]. Recent investigations have also shown that PDGFR- α is a highly expressed target in dermatofibrosarcoma protuberans (DFSP), a key regulator of downstream pathways in synovial sarcomas [17], and possibly a marker for poor prognosis in many soft tissue sarcomas [18]. Finally, FGF and its receptors also appear to play key mechanistic and

prognostic roles in soft tissue sarcomas other than GIST [19,20]. Several other subtypes of sarcomas have demonstrated promising responses to antiangiogenic therapies such as bevacizumab and cediranib, though specific targets and mechanisms remain to be elucidated. In summary, the preclinical rationale in sarcomas strongly supports clinical investigation of pazopanib and other multitargeted tyrosine kinase inhibitors.

EFFICACY OF PAZOPANIB IN SARCOMA PATIENTS

In humans, pazopanib has shown clinical activity in various sarcoma subtypes. In the initial phase I study by Hurwitz *et al.* [21], 63 advanced solid tumor patients were treated with pazopanib, including nine sarcoma patients. Four of the nine sarcoma patients achieved stable disease for greater than 6 months, including two patients with chondrosarcoma, one with leiomyosarcoma, and one GIST patient. This led to the European Organisation for Research and Treatment of Cancer phase II study of pazopanib in soft tissue sarcoma patients [22]. One hundred forty-two patients with intermediate or high-grade soft tissue sarcomas were enrolled in the study, stratified into four histology-based cohorts: adipocytic, synovial, leiomyosarcoma, and 'other,' which included malignant peripheral nerve sheath tumor, rhabdomyosarcoma (RMS), vascular tumors, malignant SFT/HPC, and otherwise undifferentiated sarcomas. Excluded histologies included Ewing's sarcoma family tumors (ESFT), osteosarcoma, embryonal RMS, chondrosarcoma, GIST, DFSP, and inflammatory myofibroblastic tumor. The primary endpoint of the study was PFS rate 12 weeks after treatment, with secondary endpoints of PFS, response rate, duration of response, overall survival (OS), and safety. Twenty-six percent of adipocytic sarcomas, 49% of synovial sarcomas, 44% of leiomyosarcomas, and 39% of other sarcomas were progression-free at 12 weeks. The adipocytic cohort was closed after meeting predetermined futility standards at interim analysis; data regarding benefit in the adipocytic subtypes are not reported. Nine partial remissions were observed, including one patient with leiomyosarcoma, five with synovial sarcoma, and three from the undifferentiated cohort. The leiomyosarcoma patient and four of five synovial sarcoma patients showed long-term freedom from progression (415–812 days). The other patients with partial response progressed between 253 and 503 days after treatment. PFS and OS compared favorably with historical controls. In summary, for a few selected patients, pazopanib offered prolonged periods of stabilized disease and delayed progression, seemingly most pronounced in synovial sarcomas.

These results led to the multiinstitutional, international randomized trial of pazopanib vs. placebo, PAzopanib expLorEd in SofT-Tissue Sarcoma—a phase III study (PALETTE) [23²⁴]. This study randomized 369 patients with metastatic soft tissue sarcoma, and excluded adipocytic tumors in addition to the subtypes excluded in the phase II study. Forty-three percent of patients had leiomyosarcoma, 10% had synovial sarcoma, and 47% had other subtypes. Patients were required to have received at least one line of anthracycline-based chemotherapy and to have documented progression on imaging, and were randomized in a 2 : 1 ratio to pazopanib or placebo, with no cross-over permitted. Median PFS favored the pazopanib cohort at 4.6 months compared with placebo at 1.6 months, although no statistically significant OS benefit was observed (12.5 months pazopanib vs. 10.7 months placebo). Partial response was observed in 6% of patients on pazopanib vs. 0% on placebo, and stable disease occurred in 67 vs. 38% on placebo. In Cox regression analysis, histology

(leiomyosarcoma vs. other vs. synovial sarcoma) was not significantly associated with superior PFS with pazopanib therapy. The positive results of this study led to FDA approval of pazopanib for non-adipocytic metastatic soft tissue sarcoma after failure of at least one line of chemotherapy on 26 April, 2012.

UNANSWERED QUESTIONS REGARDING PAZOPANIB TREATMENT IN SARCOMAS

The results from the phase II and phase III studies provide convincing evidence that pazopanib offers statistically significant clinical benefit with stabilization of disease and improved PFS, despite the lack of an overall survival benefit. As has been discussed in several prior commentaries, the lack of overall survival benefit is difficult to interpret [24[•], 25[•]]. Patients in the placebo group clearly had aggressive disease, based on the short PFS at 1.6 months, yet the overall survival of this group was over 10 months, suggesting that patients went on to receive additional therapies. This may have further limited the power of the study to detect an overall survival advantage in the pazopanib cohort.

The large study population enrolled to ensure statistical power created another challenge. Large patient numbers increased the heterogeneity of the population and diluted the impact of the isolated patients with superior benefit. Synovial sarcomas certainly appeared to be highly responsive to pazopanib in the phase II study, with five of the nine partial responses occurring in patients with synovial sarcoma; our case report also illustrates a striking example of prolonged clinical benefit. However, in the PALETTE study, histologic subtype (leiomyosarcoma vs. synovial sarcoma vs. other) did not correlate with PFS, although the specific histologies of the 6% of patients who achieved partial response were not reported. Case reports detail dramatic responses in rarer sarcomas that are generally lumped into ill-characterized ‘other’ categories: a patient with pericardial angiosarcoma obtained a durable partial remission with pazopanib following paclitaxel chemotherapy, with stable disease over a 10-month follow-up period [26]. Within the phase I study, sporadic responses occurred in patients with GIST and chondrosarcoma, both histologies that were excluded from phase II and III studies. Preclinical studies in pediatric cancers suggest potential benefit from pazopanib in ESFT, osteosarcoma, and RMS, yet these tumors were also excluded [27[•]]. Finally, 26% of adipocytic tumors were free from progression at 3 months, without additional data regarding outcomes in specific adipocytic subtypes available.

In addition to clarifying the role of histology, additional biomarkers worthy of investigation include expression of angiogenic factors in the patient’s serum or in tumor tissue. Signatures of cytokine changes have been shown to correlate with PFS and response with pazopanib in renal cell and nonsmall cell lung cancer [28,29]. Mouse xenograft models of pediatric cancers have shown a decrease in circulating endothelial cells and endothelial progenitors, markers of angiogenic activity, with combined pazopanib and temozolamide treatment [30]. In sarcomas, biochemical analysis of patient samples from the phase II study investigated pazopanib-induced effects on angiogenic cytokines, and showed that higher serum VEGFR2 and lower placental-derived growth factor levels at week 12 of treatment correlated with increased pazopanib toxicity (hypertension and elevated thyroid-stimulating hormone), and a better PFS rate at 12 weeks and OS [31^{••}]. Other markers such as interleukin-12p40,

MPC3, basic nerve growth factor, and hepatocyte growth factor showed associations with PFS and OS, although they lost significance when included in the multivariable analysis in this study. Inclusion of additional biomarker studies with correlation to clinical outcomes is vital in upcoming clinical trials to define measurable pharmacodynamic targets of pazopanib treatment and further explore potential predictive biomarkers.

Another consideration as we design endpoints for future clinical trials with pazopanib is how to best assess response and clinical benefit. As with other targeted therapies, traditional Response Evaluation Criteria in Solid Tumors (RECIST) definitions of response and progression may not adequately capture the biological effects within the tumor, or the clinical benefit to the patient. In the patient case presented, the implants initially increased in size, which could be mistaken for progression with traditional criteria. Similarly to GIST patients treated with imatinib, solid components of sarcomas responding to pazopanib can evolve to a more cystic or necrotic appearance (Fig. 1) [22]. MRI or PET/CT may be a more sensitive tool to capture this evolution, with adapted response criteria such as PET Response Criteria in Solid Tumors, or exploration of novel tracers that can quantify tumor blood flow and hypoxia may provide a superior measure of in-vivo antiangiogenic activity.

Fortunately, the exciting findings from the phase II and PALETTE studies of pazopanib have inspired many new studies in sarcoma to address these questions. Phase II trials are ongoing in several neglected histologic sarcoma subtypes including imatinib/sunitinib refractory GIST (NCT01524848), well differentiated/dedifferentiated and myxoid/round cell liposarcomas (NCT01692496, NCT01506596), uterine sarcomas (NCT01247571), angiosarcomas (NCT01462630), DFSP (NCT01059656), and bone sarcomas (NCT0179303, NCT01330966). A phase I study of pazopanib in relapsed pediatric tumors including sarcomas is also ongoing (NCT00929903). Several sarcoma-specific trials are incorporating pazopanib in the neoadjuvant and metastatic setting either alone or in combination with chemotherapy such as gemcitabine, docetaxel, and ixabepilone (NCT01446809, NCT01418001, NCT01543802, NCT01719302, NCT01012362). Other interesting options for refractory sarcoma patients include ongoing phase I studies combining pazopanib with other targeted therapies inhibiting mammalian target of rapamycin (NCT01072890), MEK (NCT0148554), and c-MET (NCT01468922). Some studies are incorporating PET imaging as a biomarker of response in addition to RECIST (NCT01446809), including one study in Israel focused on detection of early efficacy (NCT01594203). Most studies are collecting patient blood and tumor samples for exploratory biomarker analyses.

CONCLUSION

Sarcomas are rare, heterogeneous malignancies with limited treatment options in the metastatic setting. Pazopanib has generated tremendous excitement with significant impact on PFS for soft tissue sarcoma patients. Future studies are focused on identifying predictive biomarkers, exploring combination therapies, and expanding imaging criteria to assess response from pazopanib and similar molecularly targeted agents. Improving our understanding of pazopanib's actions within the patient, particularly in correlation with clinical response, will guide future rounds of drug development and optimal use of these novel agents.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 437–438).

1. GlaxoSmithKline Votrient Prescribing Information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022465lbl.pdf. 2009
2. Gril B, Palmieri D, Qian Y, et al. The B-Raf status of tumor cells may be a significant determinant of both antitumor and antiangiogenic effects of pazopanib in xenograft tumor models. *PLoS One*. 2011; 6:e25625. [PubMed: 21998674]
3. Kumar R, Knock V, Rudolph S, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther*. 2007; 6:2012–2021. [PubMed: 17620431]
4. Sternberg C, Davis I, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010; 28:1061–1068. [PubMed: 20100962]
5. Bible K, Suman V, Molina J, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol*. 2010; 11:962–972. [PubMed: 20851682]
6. Schutz F, Choueiri T, Sternberg C. Pazopanib: clinical development of a potent antiangiogenic drug. *Crit Rev Oncol Hematol*. 2011; 77:163–171. [PubMed: 20456972]
7. Iwamoto F, Lamborn K, Robins H, et al. Phase II trial of pazopanib: an oral multitargeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study). *Neuro Oncol*. 2010; 12:855–861. [PubMed: 20200024]
8. Taylor S, Chia S, Dent S, et al. A phase II study of pazopanib in patients with recurrent or metastatic invasive breast carcinoma: a trial of the Princess Margaret Hospital phase II consortium. *Oncologist*. 2010; 15:810–818. [PubMed: 20682606]
9. Altorki N, Lane M, Bauer T, et al. Phase II proof of concept study of pazopanib monotherapy in treatment-naïve patients with stage I/II resectable nonsmall cell lung cancer. *J Clin Oncol*. 2010; 28:3131–3137. [PubMed: 20516450]
10. DuBois S, Demetri G. Markers of angiogenesis and clinical features in patients with sarcoma. *Cancer*. 2007; 109:813–819. [PubMed: 17265525]
11. Zhang L, Hannay J, Liu J, et al. Vascular endothelial growth factor over-expression by soft tissue sarcoma cells: implications for tumor growth, metastasis, and chemoresistance. *Cancer Res*. 2006; 66:8770–8778. [PubMed: 16951193]
12. Yoon S, Segal M, Park P, et al. Angiogenic profile of soft tissue sarcomas based on analysis of circulating factors and microarray gene expression. *J Surg Res*. 2006; 135:282–290. [PubMed: 16603191]
13. Park M, Ravi V, Araujo D. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma, and hemangiopericytoma/solitary fibrous tumor. *Curr Opin Oncol*. 2010; 22:351–355. [PubMed: 20485168]
14. Antonescu C, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. *Cancer Res*. 2009; 69:7175–7179. [PubMed: 19723655]
15. Agaram N, Wong G, Guo T, et al. Novel V600E BRAF mutations in imatinib-naïve and imatinib-resistant gastrointestinal stromal tumors. *Genes Chromosomes Cancer*. 2008; 47:853–859. [PubMed: 18615679]
16. Heinrich M, Corless C, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science*. 2003; 299:708–710. [PubMed: 12522257]

17. Ho A, Vasudeva S, Lae M, et al. PDGF receptor alpha is an alternative mediator of rapamycin-induced Akt activation: implications for combination targeted therapy of synovial sarcoma. *Cancer Res.* 2012; 72:4515–4525. Novel preclinical data for mechanism of action of PDGFR in synovial sarcoma support combined therapy approach for future clinical studies. [PubMed: 22787122]
18. Kilvaer T, Valkov A, Sorbye S, et al. Platelet-derived growth factors in non-GIST soft-tissue sarcomas identify a subgroup of patients with wide resection margins and poor disease-specific survival. *Sarcoma.* 2010; 2010:751304. [PubMed: 21331156]
19. Ishibe T, Nakayama T, Okamoto T, et al. Disruption of fibroblast growth factor signal pathway inhibits the growth of synovial sarcomas: potential application of signal inhibitors to molecular target therapy. *Clin Cancer Res.* 2005; 11:2702–2712. [PubMed: 15814652]
20. Kilvaer T, Valkov A, Sorbye S, et al. Fibroblast growth factor 2 orchestrates angiogenic networking in non-GIST STS patients. *J Transl Med.* 2011; 6:104. [PubMed: 21733164]
21. Hurwitz H, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res.* 2009; 15:4220–4227. [PubMed: 19509175]
22. Sleijfer S, Ray-Coquard I, Papi Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol.* 2009; 27:3126–3132. [PubMed: 19451427]
23. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012; 379:1879–1886. Pivotal phase III study of pazopanib in sarcomas leading to FDA approval. [PubMed: 22595799]
24. Bramwell V. Pazopanib and the treatment palette for soft-tissue sarcoma. *Lancet.* 2012; 379:1854–1856. Commentary on PALETTE study. [PubMed: 22595798]
25. Ray-Coquard I, Thomas D. Targeted therapies: pazopanib for soft-tissue sarcoma: a PALETTE of data emerges. *Nat Rev Clin Oncol.* 2012; 9:431–432. Commentary on PALETTE study. [PubMed: 22751280]
26. Ong P, Greulich S, Schumm J, et al. Favorable course of pericardial angiosarcoma under paclitaxel followed by pazopanib treatment documented by cardiovascular magnetic resonance imaging. *Circulation.* 2012; 126:279–281.
27. Keir S, Morton C, Wu J, et al. Initial testing of the multitargeted kinase inhibitor pazopanib by the Pediatric Preclinical Testing Program. *Pediatr Blood Cancer.* 2012; 59:586–588. This is initial preclinical evidence of activity of pazopanib in childhood sarcomas. [PubMed: 22190407]
28. Tran H, Liu Y, Zurita A, et al. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. *Lancet Oncol.* 2012; 13:827–837. [PubMed: 22759480]
29. Nikolidakos P, Altorki N, Yankelevitz D, et al. Plasma cytokine and angiogenic factor profiling identifies markers associated with tumor shrinkage in early-stage nonsmall cell lung cancer patients treated with pazopanib. *Cancer Res.* 2010; 70:2171–2179. [PubMed: 20215520]
30. Kumar S, Mokhtari R, Sheikh R, et al. Metronomic oral topotecan with pazopanib is an active antiangiogenic regimen in mouse models of aggressive pediatric solid tumor. *Clin Cancer Res.* 2011; 17:5656–5667. [PubMed: 21788355]
31. Sleijfer S, Gorlia T, Lamers C, et al. Cytokine and angiogenic factors associated with efficacy and toxicity of pazopanib in advanced soft-tissue sarcoma: an EORTC-STBSG study. *Br J Cancer.* 2012; 107:639–645. This is the first report investigating in-vivo alterations in cytokine milieu as an effect of pazopanib therapy in sarcomas. [PubMed: 22805326]

KEY POINTS

- Pazopanib is a multitargeted tyrosine kinase inhibitor that prolonged PFS by 3 months compared with placebo in heavily pretreated nonadipocytic metastatic soft tissue sarcoma patients.
- Aberrations in expression of key pazopanib targets, such as VEGFR and PDGFR, are frequently encountered in preclinical studies of sarcomas.
- A minority of patients achieve long-term stabilization or partial response with pazopanib therapy; identifying these patients requires development of predictive biomarkers other than histologic subtype.
- Upcoming studies with pazopanib address three main clinical questions: determine efficacy in subtypes excluded from prior trials, determine efficacy in combination with traditional chemotherapy and other targeted therapies, and identify novel molecular and imaging biomarkers in patients predictive of response to pazopanib.

FIGURE 1.

Serial contrast-enhanced computed tomography (CT) imaging of a 39-year-old woman with multiple abdominal synovial sarcoma implants shows response to pazopanib treatment. At baseline, lesions showed enhancing solid components, particularly at the periphery of the lesions. Over the next 6 weeks, these lesions enlarged, but the solid component diminished, and the central necrotic/cystic component increased. Eighteen months after treatment, the lesions ultimately had decreased in size. (Lesion dimensions: top panel, left to right: 13.8 × 10.2 cm, 13.6 × 11 cm, 14.5 × 11.6 cm, 10.4 × 8.0 cm; bottom panel, left to right: 5.8 × 3.7 cm, 6.3 × 4.0 cm, 3.8 × 3.0 cm, 3.6 × 2.1 cm.)