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Clinical Activity of Single-Agent Cabozantinib (XL184), a Multi-receptor Tyrosine Kinase Inhibitor, in Patients with Refractory Soft-Tissue Sarcomas

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ABSTRACT

Purpose: Soft-tissue sarcomas (STS) are a rare, heterogeneous group of mesenchymal tumors. For decades the mainstay of treatment for advanced, unresectable STS has been palliative chemotherapy. High levels of activated MET receptor have been reported in various sarcoma cell lines, together with elevated vascular endothelial growth factor (VEGF) levels in patients with STS, suggesting that dual targeting of the VEGF and MET pathways with the multi-receptor tyrosine kinase inhibitor cabozantinib would result in clinical benefit in this population.

Patients and Methods: We performed an open-label, multi-institution, single-arm phase II trial of single-agent cabozantinib in adult patients with advanced STS and progressive disease after at least 1 standard line of systemic therapy. Patients received 60 mg oral cabozantinib once daily in 28-day cycles, and dual primary endpoints of overall response rate and 6-month progression-free survival (PFS) were assessed. Changes in several circulating biomarkers were assessed as secondary endpoints.

Results: Six (11.1%; 95% CI, 4.2%–22.6%) of the 54 evaluable patients enrolled experienced objective responses (all partial responses). Six-month PFS was 49.3% (95% CI, 36.2%–67.3%), with a median time on study of 4 cycles (range, 1–99). The most common grade 3/4 adverse events were hypertension (7.4%) and neutropenia (16.7%). Patients' levels of circulating hepatocyte growth factor (HGF), soluble MET, and VEGF-A generally increased after a cycle of therapy, while soluble VEGFR2 levels decreased, regardless of clinical outcome.

Conclusions: Cabozantinib single-agent antitumor activity was observed in patients with selected STS histologic subtypes (alveolar soft-part sarcoma, undifferentiated pleomorphic sarcoma, extraskeletal myxoid chondrosarcoma, and leiomyosarcoma) highlighting the biomolecular diversity of STS.

Introduction

Soft-tissue sarcomas (STS) are a rare, heterogeneous group of nonepithelial tumors that arise predominantly from embryonic mesoderm (1). There is a wide spectrum of pathologic and clinical variability in STS, making therapeutic approaches challenging. Despite this noted diverse histologic and biological behavior of STS, the mainstay of therapy for patients with advanced disease has been palliative chemotherapy. The chemotherapy standard of an anthracycline backbone with or without ifosfamide has been used for decades, yielding response rates of less than 20% and a median overall survival of approximately 12–19 months (2–6). Incremental improvements over the past decades in overall survival for this very heterogeneous group of malignancies can be attributed to recognition of the role of multidisciplinary, centralized, and supportive care for patients in sarcoma-dedicated centers, as well as improved subtype-specific second-line therapies (7–9). Newer combination therapies, such as gemcitabine and docetaxel, have shown clinical activity but have lacked standardization (3). Certain STS subtypes have highly specific molecular aberrations with therapeutic targets [e.g., activating *KIT* mutations in gastrointestinal stromal tumors (GIST)], but for patients with less well molecularly characterized entities, therapeutic targets are lacking.

One of the targets that has emerged in this setting is the tumor-produced angiogenic vascular endothelial growth factor (VEGF), which is postulated given the characteristic hematogenous route of

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Translational Relevance

Cabozantinib is a multi-receptor tyrosine kinase (RTK) inhibitor that engages a number of targets, including VEGF and MET, two pathways considered therapeutically relevant in a number of subtypes of soft-tissue sarcomas (STS), including in facilitating resistance to more specific RTK inhibitors. The category of STS includes many molecularly heterogeneous but relatively rare subtypes; as such, molecularly targeted treatments for specific STS subtypes are the exception rather than the rule. Given its range of known targets and their importance in tumorigenesis and resistance, we investigated the possibility of clinical benefit from single-agent cabozantinib treatment for all WHO-recognized subtypes of STS in a nonrandomized, phase II trial. The trial did not meet its primary efficacy endpoint, but the varied nature of the four subtypes in which responses were observed both emphasizes the molecular diversity within the STS category and suggests such all-STS trials can be useful for signal finding.

metastatic spread in STS, as well as its purported regulator role in angiogenesis (10, 11). Elevated VEGF levels have been reported in patients with STS and have been shown to correlate with both tumor grade and size (11, 12). The VEGF-targeting monoclonal antibody bevacizumab has been studied both as a single agent and in combination with chemotherapy with modest results (13, 14), and small-molecular inhibitors of VEGF receptor tyrosine kinase (RTK), such as the multi-RTK inhibitors sunitinib and pazopanib, have shown activity in various sarcoma subtypes (7, 15). To date, pazopanib is the only FDA-approved tyrosine kinase inhibitor (TKI) for patients with nonadipocytic or GIST STS previously treated with chemotherapy.

In models of several cancer types, the hepatocyte growth factor (HGF)/MET pathway has been shown to play an important role in facilitating resistance to VEGF inhibitors (16, 17). The HGF protein is secreted by mesenchymal cells; paracrine binding of HGF to the RTK MET activates this signaling pathway, promoting cell proliferation, survival, and invasion (18–20). Various sarcoma cell lines express high levels of activated MET, suggesting that HGF/SF signaling pathway may contribute to sarcomagenesis (21), and interruption of autocrine or paracrine HGF/MET signaling in sarcoma cell lines and xenograft models has resulted in demonstrable dependence on the HGF/MET axis for invasion, chemotaxis, and survival as well as preclinical antitumor efficacy (22, 23).

Cabozantinib (XL184, Cabometyx and Cometriq, Exelixis Inc.) inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis, with targets including MET, VEGFR2, RET, AXL, KIT, and TIE-2 (24). As a monotherapy, it has received FDA approval for the treatment of various advanced epithelial malignancies, in two different formulations and at two different dose levels. *In vitro* and *in vivo* pharmacodynamic (PD) activity against MET and VEGFR2 has been evaluated in a number of tumor types, and has been associated with tumor growth inhibition and tumor regression (24, 25). In STS, cabozantinib has been evaluated preclinically in various cell lines and animal models (26, 27) and has shown single-agent clinical efficacy in several early-phase trials (28, 29). Given the potential for a dual VEGF/MET inhibitor to minimize the resistance seen to date with antiangiogenic agents, we carried out a single-arm phase II clinical trial of cabozantinib to determine the clinical activity and evaluate the molecular PD of this agent in an advanced, unselected STS patient population.

Patients and Methods

Patient eligibility

Patients 18 years or older with histologically confirmed STS (all WHO-recognized subtypes, including GIST), metastatic or unresectable, and for whom standard treatment prolonging survival did not exist or was no longer active, were eligible. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 and adequate liver, kidney, and marrow function defined as creatinine < 1.5× the upper limit of normal (ULN), total bilirubin ≤ 1.5× ULN, aspartate aminotransferase and alanine aminotransferase ≤ 2.5× ULN, an absolute neutrophil count ≥ 1,500/μL, platelets ≥ 100,000/μL, hemoglobin ≥ 9 g/dL, and a urine protein/creatinine ratio ≤1 were required. All patients were required to have QTc < 500 msec by Fridericia correction and a blood pressure no greater than 140 mmHg (systolic) and 90 mmHg (diastolic). Pathologic confirmation of histologic subtype via archival tissue of either primary tumor tissue or known recurrence was performed centrally for first stage of this study but was not required when the study opened to other sites during the second stage.

Patients receiving anticancer therapy, including kinase inhibitors or any investigational agent, within the previous 4 weeks or five agent half-lives (6 weeks for nitrosoureas or mitomycin C) and those who had not recovered to baseline from clinically significant adverse events were not eligible for this study, nor were patients who had received prior cabozantinib or inhibitors of MET or HGF. There was no limit on the number of prior therapies and prior anthracycline therapy was not mandatory. Patients with significant intercurrent or recent illness were also excluded (see https://clinicaltrials.gov/ct2/show/study/NCT01755195 for a complete list of exclusions). Patients were required to have at least one measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (30).

Study design

This was a two-stage, single-arm phase II study where all patients received 60 mg cabozantinib oral tablets once daily in 28-day cycles, to be taken whole on an empty stomach (1 hour before or 2 hours after food). Patient compliance was tracked by Study Diary and treatment continued until disease progression, intercurrent illness preventing agent administration, unacceptable toxicity, patient refusal, noncompliance with study requirements, pregnancy or breast feeding, or death. Adverse events were assessed in all patients at baseline, every week for the first cycle, and every 4 weeks thereafter, and were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03. A maximum 2-week dosing interruption and/or sequential dose modifications to 40 or 20 mg/day cabozantinib were allowed for grade 2 or higher adverse events (grade 3 or higher for hematologic or pancreatic adverse events) considered related to cabozantinib and intolerable to the subject or deemed unacceptable by the primary investigator. Tumors were assessed at baseline and every two cycles by CT scans. Patients were followed for 30 days after the final dose of cabozantinib.

This trial was conducted under an NCI-sponsored Investigative New Drug application and designed by the study investigators with input from the sponsor (the NCI Cancer Therapy Evaluation Program). Cabozantinib was supplied by Exelixis under a Collaborative Research and Development Agreement with the NCI Division of Cancer Treatment and Diagnosis. Patients were enrolled at the NCI Developmental Therapeutics Clinic (DTC) during stage 1 and at 3 participating sites during stage 2. All patients provided written informed consent before participation and protocol design and the

study was conducted in accordance with recognized ethical guidelines (U.S. Common Rule) and approved by the NIH institutional review board (ClinicalTrials.gov Identifier: NCT01755195).

PD studies

Blood samples (mandatory for NCI-enrolled patients and optional at participating sites) were collected before treatment and 3–6 hours after agent administration on the first day of cycles 1 and 2 to determine circulating levels of HGF, soluble MET ectodomain (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2). HGF and sMET protein content in plasma were measured using a two-site electrochemiluminescent immunoassay developed for use with a Meso Scale Discovery Sector S600 plate reader as described previously (31). Antibodies for capture (MET, BAF-358; HGF, and MAB-694) and detection (MET, AF-276; HGF, and AF-294) were from R&D Systems. Detection antibodies were tagged with a ruthenium chelate (Sulfo-Tag, Meso Scale Discovery) following the manufacturer's instructions. Purified recombinant proteins [MET ectodomain-Ig fusion protein (358-MT) and HGF (294-HG), R&D Systems] were used to construct standard curves from which plasma content values were derived. Assays for VEGF-A (K151UVK) and sVEGFR2 (K151BOC) were obtained from Meso Scale Discovery and performed according to the manufacturer's instructions.

Statistical analysis

This open-label, multicenter interventional trial of single-agent cabozantinib was conducted as a dual-endpoint two-stage phase II trial with a single patient cohort. On the basis of the dual anti-VEGF and anti-MET activity of cabozantinib, we targeted an improvement in clinical response over that seen with VEGF-targeting small molecules such as pazopanib in STS. In particular, the design of this trial was based on the results of the PALETTE trial, in which 239 patients with metastatic nonadipocytic STS (who previously received anthracycline) were treated with pazopanib monotherapy (7). In that trial, a 6-month progression-free survival (PFS) rate of approximately 40% was observed in the pazopanib arm, along with an objective response rate (ORR) of 6%. Based on these results, we targeted a null 6-month PFS of 45% and a null ORR of 10%. It should be noted that the PALETTE trial required patients to have received prior anthracycline, whereas our protocol limited enrollment to patients for whom a standard treatment did not exist or was no longer effective. Given this restriction, we believed that most enrolled patients would have progressed on prior anthracycline, and thus the PALETTE trial was felt to be a reasonable basis for our design. If either at least 11 objective responses (22%) or at least 27 instances of 6-month PFS (54%) were observed among 50 evaluable patients, cabozantinib would be considered worthy of further testing in STS. An interim analysis was conducted on the initial 25 patients, requiring more than 3 objective responses (12%) or more than 12 instances of 6-month PFS (48%) to continue accrual. The design yielded at least 90% power to detect a true objective response rate of at least 30% and at least 92% power to detect a true 6-month PFS rate of at least 65% (median PFS of 9.6 months). The secondary objective was to determine and compare circulating levels of HGF, sMET, VEGF-A, and sVEGFR2 prior to and following administration of cabozantinib.

Patient demographics and adverse event frequencies were summarized with descriptive statistics. For each response rate estimate, we obtained the corresponding 95% exact binomial confidence interval (CI). We used the Kaplan–Meier method to estimate duration of response, PFS, and overall survival, and curve comparisons were made by means of the one-sided log-rank test. Comparisons of 6-month PFS were made using the two-sample test of proportions, where proportions were taken to be the Kaplan–Meier estimates at 6 months, and corresponding standard errors were obtained using Greenwood's formula. All statistical analyses were performed using R version 4.0.3.

Data availability

The data generated in this study are publicly available in the U.S. National Library of Medicine's ClinicalTrials.gov database at https://clinicaltrials.gov/ct2/show/results/NCT01755195.

Results

Patient disposition and outcomes

Between January 15, 2013 and April 25, 2018, a total of 55 patients were enrolled on study. One patient did not start therapy, resulting in a total of 54 patients evaluable for response. Baseline patient characteristics and demographics are detailed in **Table 1**. Patients enrolled on this study had a broad range of ages, between 27 and 81 years of age at enrollment. Over half of the patient population (30 patients, 55.5%)

Table 1. Baseline patient demographics.

Patient characteristics	
Number of patients evaluable/enrolled	54/55
Median age, years (range)	51 (27–81)
ECOG performance status	
0	16
1	38
Unknown	1
Sex	
Male	24
Female	31
Diagnosis	
Leiomyosarcoma, total (uterine; nonuterine)	11 (8; 3)
Alveolar soft-part sarcoma	8
Undifferentiated pleomorphic sarcoma	5
Synovial sarcoma	4
Myxofibrosarcoma, total (standard; fibrosarcoma variant)	4 (3; 1)
Clear cell sarcoma	3
Spindle cell sarcoma	3
Extraskeletal myxoid chondrosarcoma	3
Liposarcoma, total (myxoid; well differentiated/dedifferentiated)	3 (2; 1)
Endometrial spindle sarcoma	2
MPNST	2
Embryonal rhabdomyosarcoma	2
PNET	1
Myofibroblastic sarcoma	1
Malignant myoepithelioma	1
Solitary fibrous tumor	1
GIST	1
Prior lines of therapy	
None[a]	3
1	11
≥2	41
Median (range)	2 (0–8)
Doxorubicin/liposomal doxorubicin-based therapy	30
Anti-VEGF therapy/TKI therapy	19
Immunotherapy	10
Checkpoint inhibitor (single or double inhibitor)	6
Other (interferon alpha or vaccine)	4

[a]No standard therapy option available.

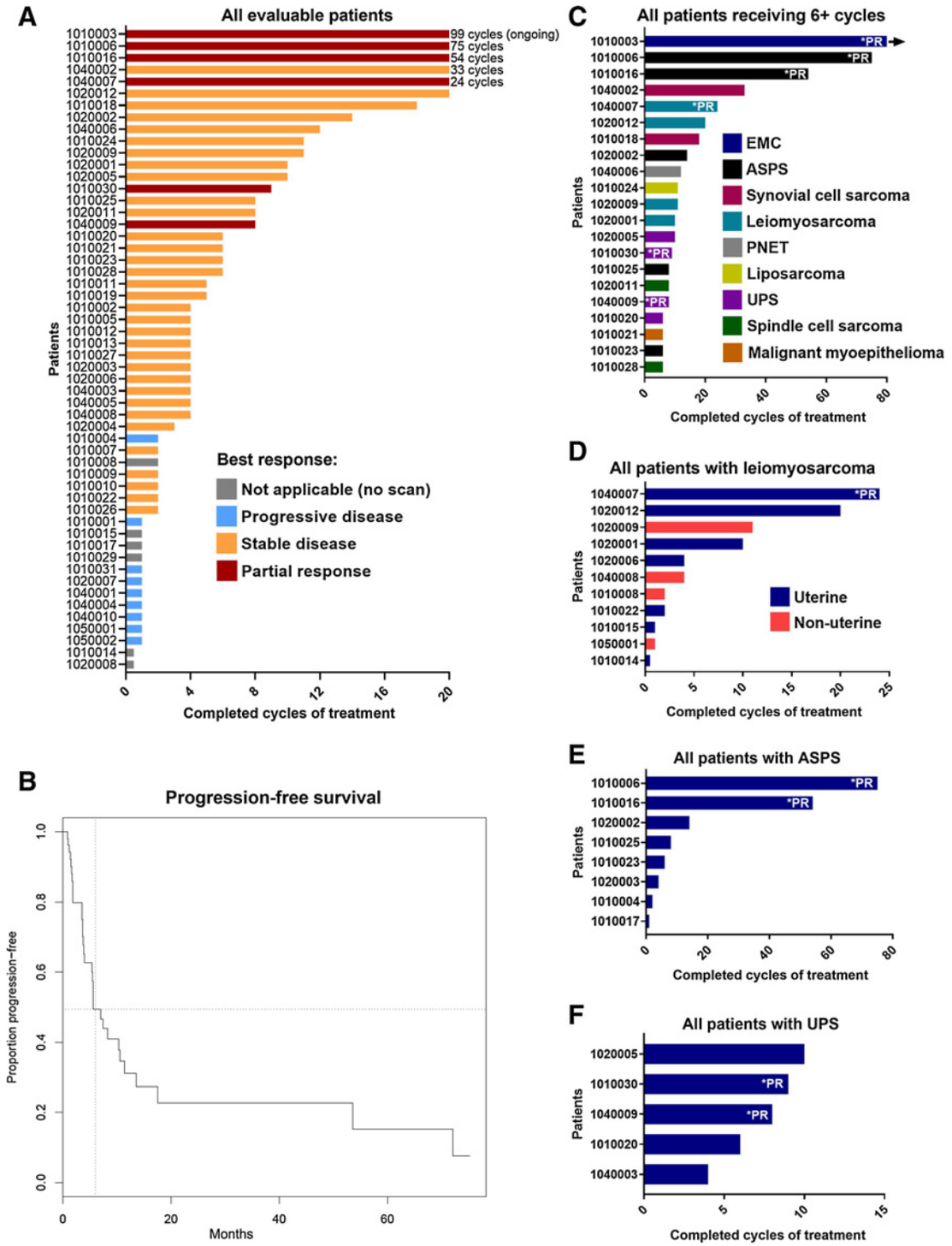

Figure 1.

Patient outcomes and time on study. **A,** Completed cycles of treatment and outcomes for all evaluable patients. 'Ongoing' indicates the patient is still receiving treatment. **B,** PFS for all evaluable patients. **C,** Completed cycles of treatment and outcomes for patients who received 6 or more cycles of treatment; colored by STS subtype. The arrow indicates the patient still receiving treatment. **D,** Completed cycles of treatment and outcomes for patients with leiomyosarcoma. **E,** Completed cycles of treatment and outcomes for patients with ASPS. **F,** Completed cycles of treatment and outcomes for patients with UPS.

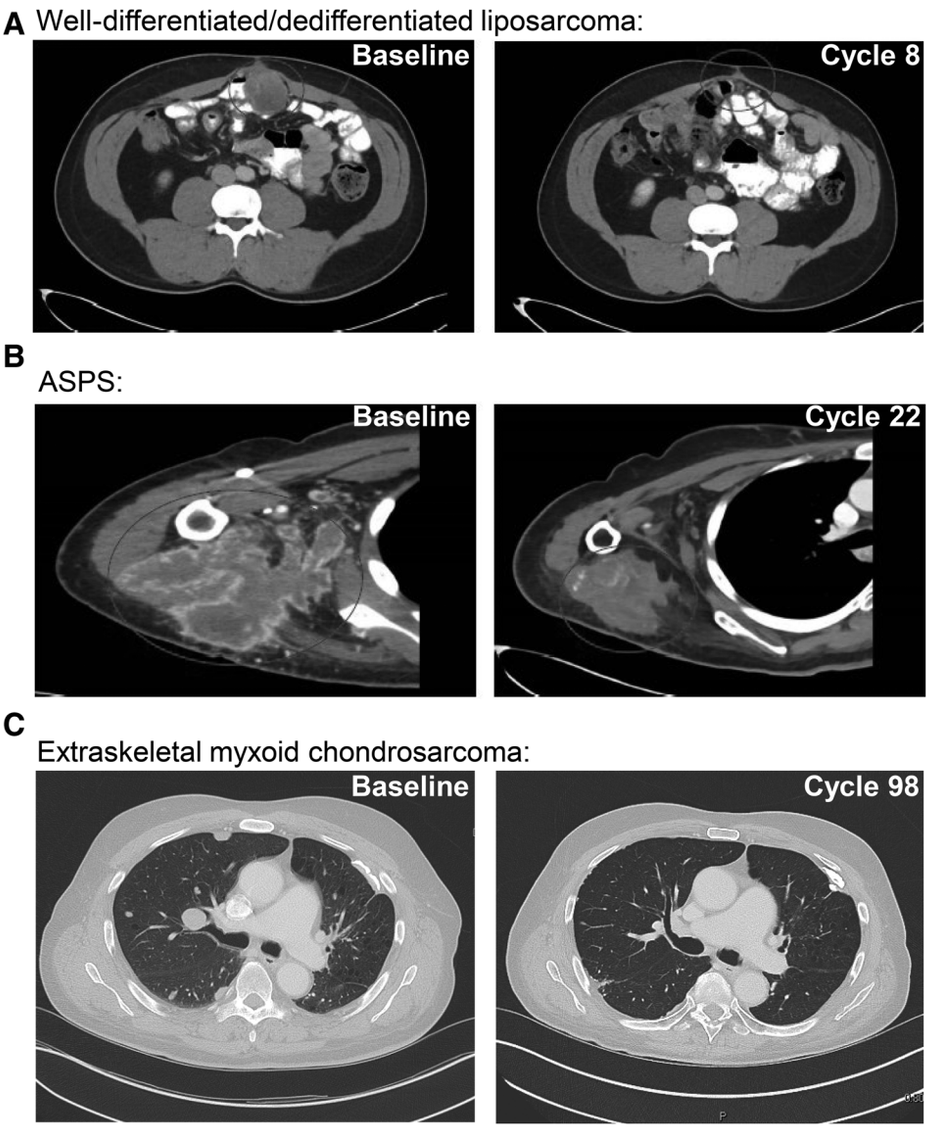

Figure 2.

Representative pre- and post-treatment images for three patients on study. **A,** CT axial images for patient 1010024, well-differentiated/dedifferentiated liposarcoma, at baseline and after 8 cycles. The patient experienced a PR, but the response was not confirmed. **B,** CT axial images, baseline and after 22 cycles, for patient 1010016. Circles denote the changes in the right shoulder ASPS primary, with marked reduction in the tumor mass posttreatment and improvement in associated pectoral girdle pain and function. **C,** CT axial images, lung windowing, for patient 1010003, EMC. Multiple bilateral lung parenchymal nodules and noncalcified pleural masses are noted at baseline, contrasting with the improvement, and durable response in the disease noted in a similar level image after 98 cycles of therapy.

had received prior doxorubicin-based therapy. Eleven patients (20.3%) had received only one prior line of palliative therapy; of these, 6 had been treated with single-agent TKI as initial therapy [4 patients with alveolar soft-part sarcoma (ASPS), 1 patient with extraskeletal myxoid chondrosarcoma, and 1 patient with solitary fibrous tumor]. Of the 54 evaluable patients, 10 eventually came off study due to adverse events, 6 refused further treatment, 2 came off due to patient noncompliance, 1 due to intercurrent illness (a small intestine obstruction), and 34 patients came off study due to radiographic or clinical evidence of disease progression; as of the data cutoff for this publication (October 1, 2020), 1 patient remained on study after 99 cycles of therapy.

Confirmed partial responses to cabozantinib were seen in 6 patients (**Fig. 1**): 2 patients with ASPS, 2 patients with undifferentiated pleomorphic sarcoma (UPS), 1 patient with extraskeletal myxoid chondrosarcoma (EMC), and 1 patient with uterine leiomyosarcoma for an ORR of 6/54 patients (11.1%; 95% CI, 4.2%–22.6%). An unconfirmed partial response was also reported in a patient with a liposarcoma, reclassified as well-differentiated/dedifferentiated liposarcoma, following central pathology review (MDM2 expression by IHC, low cellularity and mitotic rate, and lack of lipomatous differentiation), metastatic disease pattern, and clinical history (**Fig. 2A**). Among those patients who experienced a response to cabozantinib therapy, the median duration of response was 16 months (range, 4–78 months; **Table 2**). The estimated 6-month PFS (Kaplan–Meier; **Fig. 1B**) was 49.3% (95% CI,

Table 2. Patient outcomes.

Patient outcomes	
RECIST best response:	
Complete response	0/54 (0%; 95% CI, 0.0%–6.6%)
Partial response	6/54 (11.1%; 95% CI, 4.2%–22.6%)
Stable disease	33/54 (61.1%; 95% CI, 46.9%–74.1%)
Progressive disease	9/54 (16.7%; 95% CI, 7.9%–29.3%)
6-month PFS	49.3% (95% CI, 36.2%–67.3%)
Duration of response: median (range)	16 (4–78) months

36.2%–67.3%). Neither of the primary efficacy criteria (22% ORR or 54% 6-month PFS) were reached, and no significant differences were observed in the ORR or 6-month PFS for patients who had or had not previously received anthracycline therapy.

Because of the unanticipated high proportion of patients with the indolent ASPS subtype enrolled, we performed a *post hoc* analysis of their outcomes separately from the rest of those enrolled. The ORR in patients with ASPS was 25% (2/8 patients; 95% CI, 3.2%–65.0%), and the 6-month PFS was 71.4% (95% CI, 44.7%–100%). Both ASPS responders had progressed on single-agent cediranib (32) after over two (1010006) and three (1010016) years of treatment immediately before enrolling on this study. They both received cabozantinib therapy for over a year before achieving a confirmed PR. Patient 1010016 experienced a marked reduction in tumor burden (–42% by RECIST) but progressed after 40 cycles of response (**Fig. 2B**). Patient 1010003, with an EMC, presented with a deep right thigh mass that grew slowly over several years. He underwent a local resection of a 9×6 cm mass with clear margins, followed by adjuvant radiotherapy. Multiple pulmonary nodules were initially observed for 2 years prior to commencing therapy with cabozantinib. He experienced a PR after 10 cycles of therapy and remains on study after 99 cycles (**Fig. 2C**).

Prior VEGF-targeting therapy was documented to explore its potential role in patient response. Eighteen patients had previously received a VEGFR-targeting TKI and 1 had received bevacizumab (**Table 1**). PFS was compared between patients with prior VEGF-targeting therapy and those without such prior therapy in two distinct ways: 6-month PFS was compared using a two-sample test of proportions, and the entire PFS curves (i.e., not just at 6 months) were compared using a log-rank test. Six-month PFS among patients with prior VEGF-targeting therapy was higher than that among patients with no such prior therapy (71.3% vs. 39.9%; one-sided $P = 0.021$); however, the comparison of the entire PFS curves found no significant differences for patients with versus without prior VEGF-targeting therapy (median 8.3 vs. 5.5 months; one-sided $P = 0.13$; Supplementary Fig. S1). In addition, there were no significant differences in ORR between these two groups (15.8% vs. 8.6%; one-sided $P = 0.35$).

Ten patients had received prior immunotherapy (10/54, 18.5%), including 2 of the 6 patients with confirmed PRs (**Table 1**). Six of these 10 had previously received a checkpoint inhibitor, including a patient with UPS who achieved a confirmed PR on cabozantinib (1040009). The remaining 4 patients with prior immunotherapy had received therapy on a clinical trial either for a single-agent vaccine ($n = 3$) or interferon alpha ($n = 1$; patient 1010016 with ASPS).

Table 3. Grade 2 and higher adverse events occurring in >3% of patients. Worst grade that is at least possibly related to study drugs is shown for each patient ($N = 54$ total patients).

	Number of patients		
Adverse event	**Grade 2**	**Grade 3**	**Grade 4**
Endocrine disorders			
Hypothyroidism	11		
Gastrointestinal disorders			
Abdominal pain	2	2	
Constipation	2		
Diarrhea	7	3	
Dyspepsia	3		
Mucositis oral	3	2	
Nausea	1	1	
Oral pain	2		
Vomiting	1	1	
General disorders and administration site conditions			
Fatigue	11	2	
Investigations			
Alanine aminotransferase increased	4	2	
Aspartate aminotransferase increased	3		
Lipase increased	1	2	1
Lymphocyte count decreased	2		
Neutrophil count decreased	7	4	
Platelet count decreased	2		
Serum amylase increased	1	1	
Weight loss	7	1	
White blood cell decreased	6	1	
Metabolism and nutrition disorders			
Anorexia	5		
Dehydration	1	2	
Hypoalbuminemia	2		
Hypophosphatemia	7	1	
Musculoskeletal and connective tissue disorders			
Myalgia	3		
Nervous system disorders			
Dysgeusia	3		
Renal and urinary disorders			
Proteinuria	7		
Skin and subcutaneous tissue disorders			
Palmar–plantar erythrodysesthesia syndrome	11	3	
Skin hypopigmentation	5		
Vascular disorders			
Hypertension	21	9	
Thromboembolic event		3	1

Adverse events

The most common adverse events attributed to cabozantinib (**Table 3**) were hypertension (30 patients, 55.5%), palmar–plantar erythrodysesthesia (14 patients, 29.5%), fatigue (13 patients, 24%), hypothyroidism (11 patients, 20.3%), neutropenia (11 patients, 20.3%), and diarrhea (10 patients, 18.5%). The most common grade 3 events were hypertension (9 patients, 11.1%) and neutropenia (4 patients, 7.4%), and two grade 4 events, a thromboembolic event (1 patient, 1.8%) and elevated lipase (1 patient, 1.8%), occurred. The incidence of hypertension was evenly distributed among patients of all clinical outcomes, and not linked to time on study (Supplementary Fig. S2). The majority of adverse events were grade 2, including one patient (1.8%) who experienced a wound dehiscence at a prior skin graft site attributed to cabozantinib. No treatment-related events of perforation or fistula were reported on study; however, the possibility of these events was anticipated given prior safety reports for cabozantinib (33) and addressed in our study with exclusion criteria to minimize risk, which may explain their low incidence here. Causes of treatment discontinuation due to adverse events were thromboembolic event (4 patients), proteinuria/nephrotic syndrome (2 patients), HTN (1 patient), elevated AST (1 patient), neutropenia (1 patient), and left ventricular ejection dysfunction (1 patient). No deaths were reported on study.

Over half of the patients (29/54; 53.7%) were dose reduced to 40 mg/day, usually in their second or third cycle of treatment (20/29, 69.0%). Over a quarter of patients (14/54; 25.9%) were further reduced to 20 mg/day, most often in the first or second cycle after their initial dose reduction (10/14; 71.4%). The most common AE associated with dose reductions was palmar–plantar erythrodysesthesia syndrome. Of the 6 patients with confirmed partial responses, all but 1 had a reduction to 40 mg/day and half had to further reduce to 20 mg/day. PRs occurred in these patients both before and after dose reductions were made.

Pharmacodynamics

Blood sampling for evaluation of sMET, HGF, VEGF-A, and sVEGFR2 was obtained on 42 patients in total: 31 patients at NCI-DTC and 11 patients at external sites. Compared with baseline (**Fig. 3**), we observed a small but significant shift lower in the paired mean sMET values after treatment on the first day of cycle 1 (C1D1; −6.1 ng/mL; 95% CI, −12.0 to −0.3), and a significant shift higher on the first day of cycle 2 (C2D1; +16.4 ng/mL; 95% CI, 3.4–29.4). Significant increases in paired mean HGF (+344.8 pg/mL; 95% CI, 4.1–685.6) and VEGF-A (+32.5 pg/mL; 95% CI, 6.5–58.5) changes from baseline were also observed at C2D1, whereas paired mean sVEGFR2 changes from baseline underwent a significant decrease (−10.9 ng/mL; 95% CI, −13.5 to −8.4). The low level of C2D1 sample collections from patients who progressed at the first restaging (only 25% as many as the C1D1 sample collections from the same group) may have contributed to the observed reversal of the sMET trajectory between C1D1 and C2D1; however, the general trends were observed regardless of clinical outcome (Supplementary Fig. S3) or STS subtype. No meaningful correlations were found between baseline soluble biomarker levels and clinical outcomes.

Discussion

There are a number of ongoing clinical trials of cabozantinib for STS, both as a single agent and in combination therapy (34), and the clinical activity of single-agent cabozantinib was recently evaluated in EORTC 1317, a GIST-specific study that met its primary endpoint of PFS at 12 weeks (29). To the best of our knowledge, however, this is the first completed subtype-inclusive and multi-site phase II study to evaluate the clinical activity of single-agent cabozantinib in adult patients with advanced STS. On the basis of the dual VEGF and MET activity of cabozantinib, we targeted an improvement in clinical response from that seen with VEGF-targeting small molecules such as pazopanib in STS (7). Although the study did not meet the defined endpoints of 22% ORR or a 6-month PFS rate of 54%, the majority of patients on this study experience stabilization of their disease, with 21/54 (38.9%) patients completing 6 or more cycles of treatment. Additionally, the 6/54 (11.1%) patients who responded to single-agent cabozantinib experienced notably durable responses (median, 16 months).

The toxicity profile of cabozantinib has been well characterized. Patient study series in both GIST and osteosarcoma/Ewing sarcoma have reported between 60% and 80% of patients experiencing a grade 3 or greater adverse event or a serious adverse event (29, 35), in keeping with the findings of our study. Indeed, multiple trials to date have shown the necessity of considering dose reduction and treatment interruption to support ongoing therapy with cabozantinib (29, 35, 36). In the current trial, dose reduction occurred early in therapy, and we did not find a correlation between dose reduction and outcome. The number of patients who discontinued therapy in our study due to an adverse event (10/54, 18.5%) is higher than reported with cabozantinib in GIST (8.7%; ref. 29), but our study findings remain within the range of the reported rates in clinical trials of single-agent cabozantinib at a similar dose level in non-STS malignancies (13%-33%; refs. 29, 35–38). Our results add to the recommendation for both prophylactic and prompt supportive management algorithms as a strategy to minimize the impact of adverse events for patients.

At the time this study was conceived, the plethora of postulated targets identified for cabozantinib in preclinical studies suggested that multiple STS subtypes could potentially benefit clinically from this agent and formed part of the rationale for opening the study to all WHO-recognized STS subtypes. We observed single-agent cabozantinib activity in histologies including the more frequently occurring subtypes of liposarcoma, leiomyosarcoma, and UPS (1).

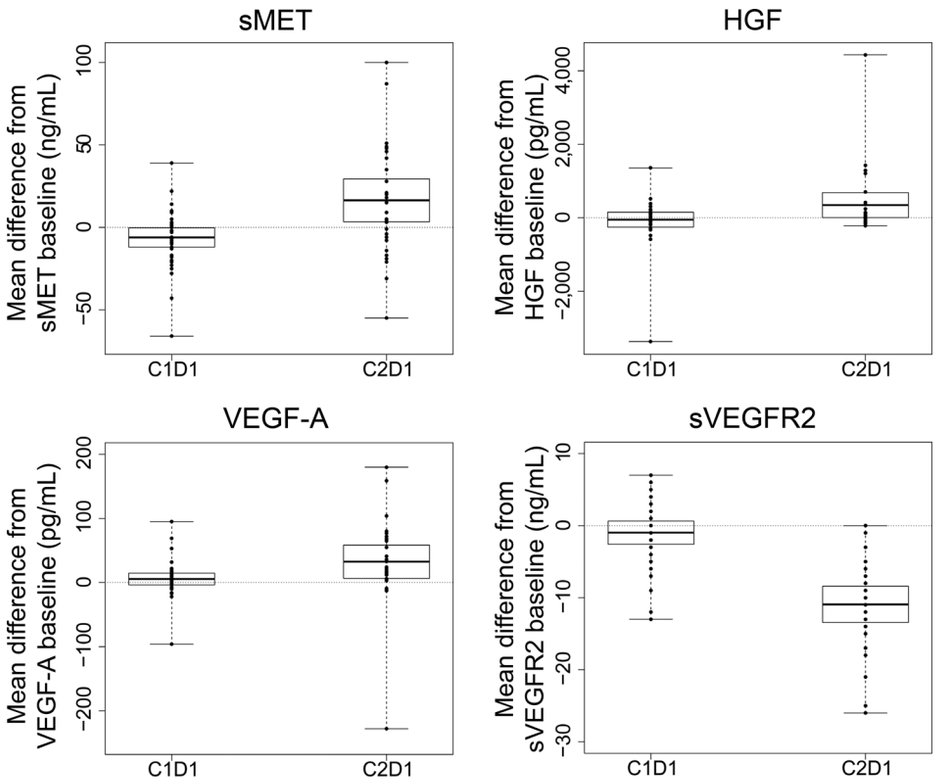

Figure 3.

Changes in soluble biomarkers from baseline. Paired measurements of soluble MET ectodomain (sMET), HGF, VEGF-A, and soluble VEGFR2 (sVEGFR2) in patient blood at cycle 1 day 1 (C1D1) and cycle 2 day 1 (C2D1) compared with baseline. Differences between the posttreatment and baseline values are summarized using box and whisker plots. The boundaries of the boxes represent the lower and upper bounds of the 95% CI for the change from baseline, with the midline denoting the mean change. The upper and lower whiskers denote the most extreme (i.e., highest and lowest) observed patient-specific differences. The overlaid points represent the patient-specific differences, with the dotted line at zero representing no change from the baseline value and points above and below zero representing an increase or decrease, respectively, from the baseline value.

The heterogeneous nature of the enrolled patient population brings a number of limitations, including small numbers of patients with similar STS subtypes that precludes histology-specific statistical analysis, and multiple single-patient histology cohorts that could have failed to identify a clinical impact, as well as grouping patients with varying degrees of known biological aggressiveness (e.g., malignant peripheral nerve sheath tumor, MPNST, and ASPS) that could have diluted the impact of cabozantinib on PFS. However, the design of this trial did facilitate the enrollment of rare STS subtypes (e.g., EMC) where the limited number of relevant preclinical models (39) or low incidence can be a barrier to trial participation. In the case of EMC, characterized by genomic *NR4A3* rearrangements, poor response to cytotoxic chemotherapy has been recognized going back to the 1970s (40). Data supporting better clinical activity of TKIs over chemotherapy are limited (41, 42), but does suggest activity of sunitinib in this rare and indolent subtype. The longest response in this trial (now over 99 cycles) was observed in a patient with EMC.

Our study unexpectedly traced some of the contemporary changes in the treatment paradigm for STS. None of the patients in stage 1 of the study received olaratumab combination therapy (6) or immune-checkpoint inhibitor (ICI) therapy; however, a number of stage 2 patients received either one or both of these drug classes prior to enrollment. Indeed, the majority of patients enrolled on stage 2 were more heavily pretreated. Additionally, patients who received prior ICI therapy only did so after 2016, but this population did not include patients with a diagnosis of ASPS, where anti–PD-1 therapy has shown activity (43). Anthracycline-based therapy was not mandated on our study prior to enrollment, which reflected the subtype-inclusive nature of our study and the recognition that a sarcoma subtype will determine anthracycline exposure; however, the majority of patients on our study had received prior anthracycline therapy (55%), including all patients with a recognized anthracycline-sensitive histology.

Management of STS has steadily moved toward histology subtype-specific therapy in the last decade, as evidenced by the recent FDA approvals for new anticancer therapies in two different types of STS: avapritinib for GIST patients with PDGFRA exon 18 mutations (44), and tazemetostat for patients with advanced epithelioid sarcomas (45). Next-generation sequencing (NGS) plays a significant role in the typification of STS for an accurate diagnosis, such as the identification of genomic aberrations characteristic to a specific sarcoma that can modify a therapeutic approach (46, 47), but the impact of NGS in identifying a genomic drive or actionable mutation remains under study (48). Dysregulation of the HGF/MET pathway in STS has been reported, although it is not ubiquitous across STS subtypes (49), and clinical correlation with response to MET inhibitor therapy is yet to be established. Treatment with crizotinib in two separate fusion-driven sarcomas with MET upregulation or overexpression (EWSR1/ATF1 fusion in clear cell sarcoma and the ASPL–TFE3 chimeric fusion protein in ASPS) resulted in different clinical outcomes, and neither study met its primary endpoint (50, 51). For ASPS, the ASPL–TFE3 fusion has been reported to affect angiogenesis, metastasis, and immune targets (52, 53), providing a rationale for the mechanism of action of cabozantinib in this very vascular disease; however, the reported clinical activity of single-agent checkpoint inhibitors in this disease in the last few years is changing the treatment landscape for ASPS (54), and determining incremental response rates with combination strategies such as ICI plus TKIs will need to be considered in the setting of added toxicity (43, 55). Future clinical trials in STS can be expected to include molecularly defined subgroups; angiogenesis correlatives, including our present study, have had an unsatisfactory track record as predictive biomarkers, making the molecular information provided by NGS a potential source of biological determinants of response.

Various ongoing trials are exploring the use of cabozantinib in several advanced STS settings including newly diagnosed and younger patients (NCT02867592), as a maintenance strategy following response to chemotherapy (NCT01979393), in histology-specific settings (NCT04339738), and in combination with double checkpoint inhibition (NCT04551430). These results are eagerly awaited. The recently reported clinical activity of cabozantinib (40 mg) in combination with nivolumab compared with single-agent sunitinib represents a proof-of-concept of the immunomodulatory potential of cabozantinib (56), which may be relevant in malignancies beyond advanced renal cell carcinoma. In our study, cabozantinib had marked and durable activity in several patients, raising the possibility of histology-specific responses driven by molecular susceptibilities. Though our study was a single-cohort study that included several different sarcoma subtypes with consequent limitations, our results suggest cabozantinib may represent a therapeutic option for patients with specific histologic subtypes of STS and should be further evaluated. Recognizing the heterogeneity and low incidence overall of STS, studies of sufficient patient numbers and statistical power to further develop newer treatment strategies will require large-scale collaboration on both national and international levels.

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