Phase II Study of Cediranib in Patients with Advanced Gastrointestinal Stromal Tumors or Soft-Tissue Sarcoma

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Abstract

**Purpose:** Cediranib is a potent VEGF signaling inhibitor with activity against all three VEGF receptors and KIT. This phase II study evaluated the antitumor activity of cediranib in patients with metastatic gastrointestinal stromal tumor (GIST) resistant/intolerant to imatinib, or metastatic soft-tissue sarcomas (STS; ClinicalTrials.gov, NCT00385203).

**Experimental Design:** Patients received cediranib 45 mg/day. Primary objective was to determine the antitumor activity of cediranib according to changes in [18F]fluoro-2-deoxy-D-glucose positron emission tomography ([18FDG-PET]) tumor uptake in patients with GIST using maximum standardized uptake values (SUVmax). Secondary objectives included objective tumor response and tolerability in patients with GIST/STS.

**Results:** Thirty-four of 36 enrolled patients were treated (GIST n = 24; STS n = 10). At day 29, five patients had confirmed decreases in SUVmax (≥10% from day 8) and two had confirmed partial metabolic responses (≥25% decrease), but arithmetic mean percentage changes in SUVmax averaged across the cohort, were not significant at day 8 [6.8%; 95% confidence interval (CI), 19.95–33.54) or day 29 (4.6%; 95% CI, 8.05–17.34). Eleven patients with GIST achieved a best objective tumor response of stable disease; eight achieved stable disease ≥16 weeks. In patients with STS, four of six with alveolar soft-part sarcoma (ASPS) achieved confirmed and durable partial responses. The commonest adverse events were diarrhea (85%), fatigue (74%), and hypertension (68%).

**Conclusions:** In patients progressing on imatinib/sunitinib, cediranib 45 mg/day demonstrated evidence of activity by [18FDG-PET, but did not reduce average SUVmax. Evidence of antitumor activity was seen in ASPS. Clin Cancer Res; 20(13); 3603–12. ©2014 AACR.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common type of sarcoma in the gastrointestinal tract, most commonly arising from the stomach; they are generally characterized by expression of the receptor tyrosine kinase KIT (1). In the majority of cases, the disease is driven by activating mutations in KIT and, less commonly, mutations in the platelet-derived growth factor receptor-α (PDGFRα) gene (2, 3).

Imatinib mesylate is a tyrosine kinase inhibitor (TKI) with activity against KIT, PDGFRα, and ABL. Imatinib is an effective treatment for unresectable and/or metastatic malignant GIST, and as adjuvant therapy following resection of high-risk cases (4, 5). However, most patients eventually experience disease progression while on treatment because of the development of secondary mutations (2, 3). Sunitinib, a multitargeted TKI with activity against PDGFRα, PDGFRβ, KIT, VEGF receptors 1–3 (VEGFR1–3), colony-stimulating factor receptor 1, fms-related tyrosine kinase 3, and other kinases, is available as second-line therapy for imatinib-refractory GIST, but is only effective in a proportion of cases as some secondary mutations confer resistance to both imatinib and sunitinib (6). A number of other TKIs have also demonstrated activity against GIST, including regorafenib, a close analogue of sorafenib and also an inhibitor of VEGFRs. In a prospective randomized trial comparing regorafenib with placebo in patients who had progressed on both imatinib and sunitinib, regorafenib produced an improvement in median progression-free survival of 3.9 months (HR 0.27, P < 0.0001; ref. 7).

Cediranib is an oral, highly potent, VEGF signaling inhibitor with activity against all three VEGFRs and additional activity versus KIT (8–10). In vitro, cediranib has been...
patients was included as an additional activity against KIT, demonstrated promising antitumor activity in early clinical studies. This phase II cediranib monotherapy study used 
[18F]fluorodeoxy-D-glucose positron emission tomography (18FDG-PET) to assess preliminary antitumor activity in imatinib-resistant/intolerant GIST patients; individual patients had sustained decreases in uptake, with two experiencing confirmed a partial metabolic response. Prolonged disease stabilization (≥16 weeks) occurred in eight patients with GIST who had previously progressed on imatinib, including patients who had also received sunitinib previously.

Study objectives

The primary objective was to determine the preliminary antitumor activity of cediranib in patients with GIST by utilizing 18FDG-PET scans to assess maximum standardized uptake value (SUVmax) at baseline, and following 8 days and 4 weeks (day 29) of cediranib dosing, with central review of all scans. Secondary objectives included response assessment by investigator review using 18FDG-PET (SUVmax) in patients with GIST following 8 days and 4 weeks (day 29) of cediranib dosing, and an evaluation of cediranib efficacy by objective tumor response (RECIST; version 1.0) in GIST and STS (ASPS), assessed every 12 weeks. A planned central review of response by RECIST in patients with GIST was performed and central review of CT images from STS patients was included as an ad-hoc analysis. Also included was an assessment of safety and tolerability. Additional 18FDG-PET and CT parameters, including total lesion volume, were also analyzed by central review. Exploratory objectives included the effect of cediranib on soluble KIT, VEGF, and soluble VEGFR-2 (sVEGFR-2).

Study design

This was a phase II, open-label, two-center, UK-based study of cediranib monotherapy conducted between June 2006 and July 2009. Patients received once-daily oral doses of cediranib 45 mg. Patients were permitted to continue study medication indefinitely provided that they did not meet the criteria for discontinuation, were free from intolerable toxicity, and were receiving benefit from the treatment as assessed by the investigators. If toxicity occurred, a maximum of two dose reductions were allowed (to 30 mg/day and then 20 mg/day) or treatment could be stopped until resolution of symptoms. Treatment could be restarted at the discretion of the investigator; the maximum dosing

shown to inhibit two mutant forms of KIT (V654A, N822K) associated with secondary resistance to imatinib, but has not been shown to inhibit all mutants thought to be responsible for the development of resistance to imatinib and sunitinib (10). In phase I and II studies, cediranib has demonstrated evidence of antitumor activity in patients with advanced solid tumors, both as a single agent and in combination with other anticancer strategies (11–17).

Previous studies have suggested that 2[18F]fluorodeoxy-D-glucose positron emission tomography (18FDG-PET) in GIST may be a useful tool to evaluate treatment response to new therapies and may provide more information than computed tomography (CT), especially in relation to early indications of response to imatinib (18). The primary aim of this open-label, phase II study was to investigate the antitumor activity of cediranib, as measured by 18FDG-PET, in patients with metastatic GIST resistant or intolerant to imatinib mesylate (ClinicalTrials.gov number: NCT00385203). In addition, an assessment of antitumor activity by objective tumor response, using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0), was performed. A subsidiary aim was to evaluate the activity of the drug in patients with alveolar soft-part sarcoma (ASPS) following the observation of a prolonged partial response (PR) to cediranib in a patient with this disease in a phase I trial.

Patients and Methods

Patients

Patients ages ≥18 years with histologic confirmation of either GIST that was resistant/intolerant to imatinib mesylate, or metastatic soft-tissue sarcoma (STS) that was refractory to standard therapies or for which no standard therapy exists, such as ASPS, based on earlier evidence of an objective response to cediranib in a patient with this disease; a World Health Organization (WHO) performance status of 0–2; and a life expectancy >12 weeks qualified for study entry. Eligible patients were required to have one or more measurable lesions, ≥10 mm in the longest diameter by spiral CT scan or 20 mm with conventional techniques, for RECIST assessment. An additional criterion for patients with GIST was one or more measurable lesions ≥20 mm for 18FDG-PET assessment.

Exclusion criteria included untreated or unstable central nervous system metastases, radiotherapy within 4 weeks of study entry, or other concomitant anticancer therapy (except steroids). Previous treatment with sunitinib or imatinib mesylate had to be stopped at least 14 days before starting cediranib, and no TKI therapy was permitted during baseline investigations (i.e., 18FDG-PET scans). Specific exclusion criteria related to 18FDG-PET assessments were applied to patients with GIST, including type 1 insulin-dependent diabetes, poorly controlled type II insulin-independent diabetes or fasting blood glucose >10 mmol/L (200 mg/dL), and radiotherapy within the previous 4 weeks or planned radiotherapy if covering the only 18FDG-PET-assessable lesion.

Translational Relevance

Gastrointestinal stromal tumor (GIST) is generally driven by activating mutations in the KIT or PDGFRα genes. The tyrosine kinase inhibitor imatinib mesylate is an effective treatment for unresectable/metastatic GIST, but is associated with acquired treatment resistance owing to development of secondary mutations. Cediranib, a potent inhibitor of all three VEGF receptors with additional activity against KIT, demonstrated promising antitumor activity in early clinical studies. This phase II cediranib monotherapy study used 2[18F]fluorodeoxy-D-glucose positron emission tomography (18FDG-PET) to assess preliminary antitumor activity in imatinib-resistant/intolerant GIST patients; individual patients had sustained decreases in uptake, with two experiencing confirmed a partial metabolic response. Prolonged disease stabilization (≥16 weeks) occurred in eight patients with GIST who had previously progressed on imatinib, including patients who had also received sunitinib previously.

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delay permitted was 14 days. Cediranib doses were based on results achieved in a previous phase I monotherapy trial of patients with solid tumors, which identified 20 mg/day as biologically active, and 45 mg/day as the maximum tolerated dose (13).

The study was approved by the relevant Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on Bioethics (19). All patients provided written informed consent.

Assessments

To assess antitumor activity in patients with GIST, 18FDG-PET scans were performed at baseline (up to 14 days before study treatment), on day 8 (week 1) and on day 29 (week 4). Acquisition guidance provided to the investigational sites included a request for attenuation-corrected 18FDG-PET scans (axial extent base of skull to mid-femur) after a fasting period of 6 hours and approximately 1 hour following intravenous administration of 370 to 740 MBq (10–20 mCi) 18FDG (dose was dependent on local practice and scanner type). 18FDG uptake in the primary tumor and metastatic lesions (up to a maximum of three lesions) was analyzed semiquantitatively by SUVmax for body weight, according to the following equation:

\[ \text{SUV}_{\text{max}} = \frac{\text{maximum radiotracer concentration in tumor (kBq/mL; } \mu\text{Ci/mL}) \times \text{body weight (kg)}}{\text{injected dose (MBq; mCi)}} \]

The 18FDG-PET scans were assessed by independent central review (VirtualScopics) and by investigational site review. 18FDG uptake was classified as complete metabolic response (CMR; complete resolution of 18FDG uptake within the tumor), partial metabolic response (PMR; ≥25% reduction in 18FDG SUV\text{max}), stable metabolic disease (SMD; <25% increase or decrease in 18FDG SUV\text{max}), or progressive metabolic disease (PMD; ≥25% increase in 18FDG SUV\text{max} or visible increase in 18FDG tumor uptake) based on European Organization for Research and Treatment of Cancer (EORTC) criteria (20). A confirmed PMR was defined as PMR on both days 8 and 29 by central review.

To determine the efficacy of cediranib in patients with GIST and STS, objective tumor response (according to RECIST; version 1.0) was also assessed by investigator review of CT or MRI scans (CT scan of the chest, abdomen or pelvis, or MRI if CT unavailable) at baseline (within 21 days before starting treatment), week 8, week 16, and then every 12 weeks thereafter until study discontinuation. Blood samples were drawn before dosing on days 1, 8, 29, 57, and 113, and at the discontinuation visit, for analysis of soluble markers of angiogenesis (VEGF, sVEGFR-2, and soluble KIT) in patients with GIST. Details of the methods used to analyze the soluble markers of angiogenesis are described by Drevs and colleagues (13).

Safety was monitored throughout the study, with the incidence and severity of adverse events (AE) graded according to National Cancer Institute (Bethesda, MD) common toxicity criteria (CTC) for adverse events version 3.

Statistical analysis

Sample size calculations were performed separately for patients with GIST and STS. In a previous study of 18FDG-PET uptake in patients with imatinib-resistant GIST (21), a 52% reduction in mean SUV\text{max} was observed following 7 days of therapy with sunitinib. The intra-patient SD of SUV\text{max} on the natural log scale was calculated to be approximately 0.31; based on this variability, a 50% reduction in SUV\text{max} would require 22 patients to provide associated 95% confidence intervals (CI) of −40% to −60%. Assuming that 10% of patients would not have readable scans, approximately 25 patients with GIST would need to be recruited. Assuming an underlying response rate of 20% in the STS patient population, the probability of observing no RECIST responses in 10 patients is approximately 10%; this was considered sufficiently low to warrant the inclusion of 10 patients with STS (predominantly ASPS).

The primary analysis was performed after all patients had received 16 weeks of treatment and had either undergone a week 16 scan for RECIST assessment or been withdrawn from the study. The statistical analysis was conducted on 18FDG SUV\text{max} values from central and investigator reviews for patients with GIST who had scans with readable results at baseline and at day 8 or day 29. A paired t test was applied to compare readable results at day 8 and day 29 versus baseline. Sensitivity analyses of 18FDG SUV\text{max} from central and investigator reviews were also conducted in patients with GIST who received consecutive once-daily doses for the first 7 days of treatment and then 75% of the planned consecutive daily doses for the following 3 weeks of treatment. Objective tumor response, biomarker variables, and safety data were summarized descriptively.

Results

Patients

A total of 36 patients were enrolled in the study, of whom 34 (24 and 10 patients with GIST and STS, respectively) received treatment with cediranib 45 mg/day (Fig. 1). At the primary data cutoff (July 8, 2009), 33 patients had discontinued because of worsening of their condition (n = 21, 58.3%), adverse events (n = 9, 25%), death (n = 1, 2.8%), or incorrect enrolment (n = 2, 5.6%). Of the three patients (all with STS) who remained in the study, all subsequently discontinued because of worsening condition (n = 1), death (n = 1), or voluntary discontinuation (n = 1).

Patient demographic and baseline characteristics are summarized in Table 1. Baseline characteristics were generally representative of the study populations, with the exception of the deliberate selection of ASPS among the patients with STS (6 of 10). Of the other 4 patients with STS, 2 had uterine leiomyosarcoma, one a retroperitoneal liposarcoma, and the fourth had a soft-tissue spindle-cell...
sarcoma. All patients with GIST received prior imatinib, as per the inclusion criteria, and 13 of 24 patients received prior sunitinib. Patients with ASPS may have received prior chemotherapy but none had received prior treatment with a multitargeted TKI or other antiangiogenesis treatment.

$^{18}$FDG-PET SUV$_{\text{max}}$

When assessed by central review, 67% and 50% of patients with GIST had a best $^{18}$FDG-PET response of SMD at day 8 and day 29, respectively (Table 2; Fig. 2A); two PMRs ($\geq$25% decrease) were observed on day 8 that were confirmed on day 29, an additional PMR was observed on day 8 but not confirmed on day 29, and a further two patients achieved a PMR at day 29. In addition, five patients had $\geq$10% decreases in SUV$_{\text{max}}$ at day 8 that were confirmed on day 29. In general, patients with decreases by central review had decreases at investigator review, but these were not consistent across all patients in terms of magnitude, and one patient had a PMD by investigator review and PMR by central review. There was no relationship between best percentage change in tumor-averaged SUV$_{\text{max}}$ and prior treatment with or without sunitinib (Fig. 2B). Overall central review of the patients assessable by $^{18}$FDG-PET indicated that only 3 of 30 on days 8 and 4 of 26 on day 29, respectively, had PMD.

Because the statistical model for the study included an assessment of arithmetic mean percentage change in $^{18}$FDG SUV$_{\text{max}}$, this was calculated for the whole GIST cohort (central review) and found to be 6.8% (95% CI, −19.95–33.54) at day 8 and 4.6% (95% CI, −8.05–17.34) at day 29. These changes were not statistically significant.

**Objective tumor response by RECIST**

Twenty-eight patients were evaluable for response by RECIST (Table 2; Fig. 3A), of whom 20 had GIST. Although none of the patients with GIST had an objective tumor response, 15 had a best response of stable disease when assessed according to investigator review, of whom 14 had stable disease for $\geq$16 weeks ($\geq$112 days). At the time of data cutoff, 6 patients were still on treatment with stable disease. By investigator review, median PFS was 7 months. When assessed by central review, 11 patients had stable disease as best response and although 8 of these had stable disease for $>16$ weeks, the overall median PFS was 2 months. No differences were seen between patients with GIST who received prior sunitinib and those who did not (prior imatinib: stable disease $n = 8$, progressive disease (PD) $n = 2$, not evaluable $n = 1$; prior imatinib and sunitinib: stable disease $n = 7$, PD $n = 3$, not evaluable $n = 3$). The comparison in patients with GIST between investigator and central review is shown in Fig 3A and B). There was no clear relationship between PMR according to $^{18}$FDG-PET and RECIST response. The 2 patients with a confirmed PMR by central review, that is, PMR on days 8 and 29, had stable disease. One discontinued because of toxicity but the other had prolonged disease control, that is, for 358 days. Two patients with PMR on either day 8 or 29 alone both had

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**Figure 1. Patient disposition.** At the time of primary data cutoff.
progressive disease; however, time to discontinuation of treatment ranged from 64 to 213 days, hence there was deemed to be some clinical benefit despite objective progressive disease. The relationship between PMR and RECIST was extremely variable, see Fig 3C.

In STS, investigator-confirmed PRs were reported in 4 of the 6 patients with ASPS (duration of response: 241, 247, 365, and 633 days), whereas three other patients, including the remaining two with ASPS, achieved stable disease for 57 (\(n = 2\)) and 449 days (\(n = 1\)) by investigator review (Fig. 3D).

### Table 1. Patient demographics and baseline characteristics (full analysis set)

<table>
<thead>
<tr>
<th></th>
<th>GIST ((n = 25^a))</th>
<th>STS ((n = 10))</th>
<th>Total ((n = 35^a))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>56 (37–73)</td>
<td>45 (27–57)</td>
<td>53 (27–73)</td>
</tr>
<tr>
<td>Male/female, n (%)</td>
<td>17/8 (68/32)</td>
<td>4/6 (40/60)</td>
<td>21/14 (60/40)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>21 (84)</td>
<td>8 (80)</td>
<td>29 (83)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (12)</td>
<td>0</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Oriental</td>
<td>0</td>
<td>2 (20)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>WHO performance status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (28)</td>
<td>2 (20)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>1</td>
<td>16 (64)</td>
<td>8 (80)</td>
<td>24 (69)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td>Location of primary tumor, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>2 (8)</td>
<td>7 (70)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>9 (36)</td>
<td>0</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Stomach</td>
<td>8 (32)</td>
<td>0</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Uterus</td>
<td>0</td>
<td>2 (20)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Colon</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Muscle</td>
<td>0</td>
<td>1 (10)</td>
<td>1 (3)</td>
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<tr>
<td>Other</td>
<td>4 (16)</td>
<td>0</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Prior chemotherapy, n (%)</td>
<td>0</td>
<td>4 (40)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Prior radiotherapy, n (%)</td>
<td>1 (4)</td>
<td>6 (60)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Prior surgery, n (%)</td>
<td>19 (76)</td>
<td>10 (100)</td>
<td>29 (83)</td>
</tr>
</tbody>
</table>

\(^a\)One enrolled patient did not receive treatment; although no data are available, this patient was given a patient number so is included in the overall population.

### Table 2. \(^{18}\)FDG-PET response (SUV\(_{max}\); patients with GIST; central review) and objective tumor response (patients with GIST and STS; investigator review)

<table>
<thead>
<tr>
<th>Metabolic response category, n (%)</th>
<th>GIST ((n = 24))</th>
<th>STS ((n = 10))</th>
<th>Total ((n = 34))</th>
</tr>
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<tbody>
<tr>
<td>CMR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PMR</td>
<td>3 (13)(^a)</td>
<td>4 (17)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>SMD</td>
<td>16 (67)</td>
<td>12 (50)</td>
<td>28 (82)</td>
</tr>
<tr>
<td>PMD</td>
<td>3 (13)</td>
<td>4 (17)</td>
<td>7 (21)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objective tumor response (patients with GIST and STS; investigator review)</th>
<th>GIST ((n = 24))</th>
<th>STS ((n = 10))</th>
<th>Total ((n = 34))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor response category, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>4 (40)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>SD</td>
<td>15 (63)</td>
<td>3 (30)</td>
<td>18 (53)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (21)</td>
<td>1 (10)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>NE</td>
<td>4 (17)</td>
<td>2 (20)</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; NE, nonevaluable; SD, stable disease
\(^a\)One PMR was not confirmed at day 29; see text for further details.
and E). Of the three patients with ASPS remaining in the study at primary data cutoff, further follow-up showed that the duration of response increased for one patient from 633 to 801 days. Central review determined that 2 of 6 patients with ASPS achieved a PR and 4 of 6 patients had stable disease.

**Biomarker variables**

Increases in VEGF levels were observed at day 8 in all but one patient with GIST, with a mean increase of 253.3% versus baseline. Mean levels of VEGF remained elevated in comparison with baseline for the rest of the treatment period (Supplementary Fig. S1A). Mean decreases of −25.7% at day 8 and −41.0% at day 29 versus baseline were recorded for sVEGFR-2. Mean sVEGFR-2 levels stayed low until the end of the treatment period (Supplementary Fig. S1B). Mean serum soluble KIT levels did not change appreciably at day 8 and day 29 versus baseline; however, a late increase in mean soluble KIT levels was observed from day 57 onwards (24.1% and 21.3% at days 57 and 113, respectively; Supplementary Fig. S1C).

**Safety and tolerability**

The mean daily dose of cediranib received was 34.4 mg for patients with GIST and 31.4 mg for patients with STS. Overall, patients received treatment with cediranib for a mean duration of 164 days (GIST, 126 days; STS, 257 days). In total, 21 of 24 (87.5%) patients with GIST and 7 of 10 (70%) patients with STS required a cediranib dose reduction or pause in dosing. Fifty percent of all patients had a dose reduction or pause within the first 40 days of treatment; 4 patients in each population (GIST or STS) required two dose reductions. Adverse events were the principal reason for a reduction or pause in cediranib dosing. The most commonly experienced adverse events were diarrhea (85%), fatigue (74%), and hypertension (68%; Table 3). Adverse events of CTC grade ≥3 with a total frequency ≥10% were fatigue (29%), all patients with...
GIST patients), hypertension (24%; GIST n = 7; STS n = 1), and diarrhea (18%; GIST n = 5; STS n = 1). One CTC grade 4 case of hypertensive crisis occurred in a patient with GIST.

Two patients died during the study: one patient with STS because of disease progression and one patient with GIST from hemorrhage in a hepatic metastasis. Serious adverse events (SAE) occurred in 13 patients (10 GIST and 3 STS); the most frequently observed SAE, and the only one reported by more than one patient, was abdominal pain (one patient each in the GIST and STS population). Eleven patients discontinued because of an adverse event (GIST, n = 7; STS, n = 4), most commonly due to fatigue (4 patients with GIST) and hypertension (2 patients; 1 GIST, 1 STS). Of the three patients with STS remaining in the study at primary data cutoff, one subsequently died because of myocardial infarction and one patient had convulsions leading to hospitalization; neither was considered to be due to study treatment. The third patient discontinued the study owing to progressive disease.

Discussion

This phase II study used 18FDG-PET uptake as the primary endpoint to assess the antitumor activity of cediranib as second- or third-line therapy in patients with GIST who had progressed on prior therapy with imatinib or imatinib and sunitinib. A cohort of patients with STS was studied owing to prior demonstration of prolonged remission in a patient with ASPS who received cediranib, as an opportunity to investigate further the activity of the drug in this disease.

In patients with GIST, there was some evidence of activity according to 18FDG-PET (central review), with confirmed decreases in SUV_{max} of ≥10% in 5 patients at day 29 and 2 confirmed PMRs (≥25% decrease). However, there was no statistically significant percentage change in arithmetic mean 18FDG-PET SUV_{max} from baseline, across the whole cohort, at day 8 or day 29 (central review). There were no RECIST-confirmed objective tumor responses in GIST, but stable disease was achieved in 62.5% of patients by investigator review, with 14 of 20 evaluable patients achieving disease stabilization for ≥16 weeks. However, by central review, only 9 patients had stable disease as best response and PFS was only 2 months, as opposed to 7 months according to investigator review. Reduction in tumor 18FDG uptake may provide an early and sensitive pharmacodynamic marker of antitumor activity, and has led to the development of EORTC guidelines (20); a number of

Figure 3. Best percentage change from baseline in tumor size (RECIST 1.1) for patients with GIST and STS by investigator review (A) and central review (B). C, best percentage change from baseline in SUV_{max} response (central review) and tumor size (investigator review) for patients with GIST. Patients are presented in the same order for both plots. Only patients with available data for both analyses are presented. D, best percentage change from baseline in tumor size for patients with ASPS by investigator review. E, percentage change from baseline in tumor size over time for patients with ASPS by investigator review.
additional guidance approaches have been proposed that are currently undergoing wider evaluation, including PET Response Criteria in Solid Tumors (22). Further validity of 18FDG-PET as a primary endpoint is underscored by increasing reports of its use in determining early response to TKIs in patients with GIST (18, 23–25).

However, in this study there was no clear relationship between 18FDG-PET decreases in SUVmax and prolonged (>21 weeks) radiological stable disease. Two patients with a confirmed PMR had stable disease by RECIST. However, the relationship between changes in 18FDG uptake and duration of stable disease was variable, although it is worth noting that some patients with progressive disease by RECIST continued on treatment for up to 213 days because of perceived clinical benefit. In individual patients, 18FDG-PET seemed to be a poor predictor of disease behavior. It may be that, in the third-line setting, one should not expect the dramatic 18FDG-PET changes seen in response to first-line imatinib. There is known to be considerable heterogeneity in refractory tumors, with the likelihood that some cells are sensitive to treatment while others are not. Similarly, there may be considerable heterogeneity of 18FDG-PET response within the tumor, with cells possessing a resistance mutation being uninhibited and taking up 18FDG, while other cells respond and do not, resulting in stable 18FDG uptake overall; however, currently this remains speculation.

There was no difference in treatment outcome for the patients with GIST who had received prior therapy with sunitinib, a multitargeted TKI with activity against the receptors that are also targeted by cediranib (VEGFR1–3, KIT), compared with those who had not. The patients included in our study were not screened for secondary mutations in KIT or PDGFRα as part of the trial, so no conclusions can be drawn as to which mutations known to confer resistance to imatinib and sunitinib were present, and whether these also confer resistance to cediranib. Preclinical data suggest that cediranib has activity against a range of primary KIT-mutant forms found in GIST (V560G, V559D, W557R Del557-558), including two of the mutations that are thought to play a role in resistance to imatinib (V654A, N822K; ref. 10). However, similar to imatinib, cediranib was not active against the T670I KIT gatekeeper mutation (ATP-binding region of KIT) or the D816V/D816Y KIT mutations (10). We do know that VEGFR was inhibited by cediranib, as shown by the common side effect of hypertension and the impact on circulating VEGF and sVEGFR-2. Similarly, in a phase I/II study in imatinib-resistant/intolerant GIST patients receiving sunitinib (in on- and off-treatment cycles), increases in VEGF levels and decreases in sVEGFR-2 levels observed during treatment returned to near-baseline levels during the off-treatment periods (26). However, all the evidence to date suggests that KIT remains the key driver in the majority of imatinib-resistant GISTs and that inhibition of VEGFR does not play a significant role in the treatment of this disease, with the possible exception of wild-type or syndromic GISTs that are not driven by kinase mutations, often associated with loss of succinate dehydrogenase complex subunits and upregulation of hypoxia-inducible factor.

Following a previous observation of a prolonged PR in a patient with locally advanced and metastatic ASPS who was treated in a separate study (NCT00264004; ref. 27), there was a conscious decision to recruit additional patients with this disease. ASPS is an extremely rare STS mainly affecting young people. It has a relatively indolent clinical course and

### Table 3. Adverse events (any cause; all grades; >20% in any group)

<table>
<thead>
<tr>
<th>Any AE, n (%)</th>
<th>GIST (n = 24)</th>
<th>STS (n = 10)</th>
<th>Total (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>21 (88)</td>
<td>8 (80)</td>
<td>29 (85)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (75)</td>
<td>7 (70)</td>
<td>25 (74)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (79)</td>
<td>4 (40)</td>
<td>23 (68)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (54)</td>
<td>4 (40)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>12 (50)</td>
<td>4 (40)</td>
<td>16 (47)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (42)</td>
<td>2 (20)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (33)</td>
<td>3 (30)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>6 (25)</td>
<td>4 (40)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (29)</td>
<td>2 (20)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (21)</td>
<td>4 (40)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (17)</td>
<td>4 (40)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>6 (25)</td>
<td>2 (20)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Oral pain</td>
<td>5 (21)</td>
<td>2 (20)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5 (21)</td>
<td>2 (20)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>5 (21)</td>
<td>1 (10)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (4.2)</td>
<td>4 (40)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0 (0)</td>
<td>3 (30)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>
a tendency to metastasize to lungs, brain, and bones. Conventional chemotherapy is ineffective (28). One of the curious characteristics is that metastases can be present but stable for long periods, raising speculation about the role played by neoangiogenesis in controlling its rate of growth.

In the 6 patients with ASPS treated in this study, there was clear evidence of activity, as assessed by RECIST (investigator review). Activity has also been reported with sunitinib (29) and the activity reported here has led to further trials of cediranib in the management of ASPS. The activity of cediranib has been confirmed in a single-arm phase II trial conducted by the National Cancer Institute of the United States (NCT00942877; ref. 30). A randomized phase II study is currently being performed in which cediranib is compared with placebo to quantify the rate of disease stabilization (CASPS; NCT01337401) and a separate randomized phase II study is comparing cediranib with sunitinib monotherapy (sunitinib or cediranib for ASPS; NCT01391962).

Biomarker analyses in this study revealed increases in VEGF and decreases in sVEGFR-2, which are in line with other cediranib monotherapy studies (11, 31). KIT had not previously been measured as a soluble biomarker. In contrast with the more immediate effects on the angiogenesis pathway, as measured by VEGF and sVEGFR-2, the effects on soluble KIT appeared at a later stage during long-term treatment with cediranib. Unfortunately, biomarker samples were not collected for the patients with STS because the numbers were very small and certain analyses, such as soluble KIT, may not be relevant in this patient population.

The adverse event profile of cediranib 45 mg in this study was consistent with the expected pharmacologic effects of a VEGF signaling inhibitor and with results observed in previous cediranib studies, in which the most commonly experienced adverse events were diarrhea, hypertension, and fatigue (11, 17, 31). Importantly, no new safety concerns were identified during this study. The majority of both GIST and STS patients required a cediranib dose reduction or pause in dosing, suggesting that the 45 mg/day dose was not well tolerated in this study.

In conclusion, treatment with cediranib resulted in disease stabilization for >16 weeks in 40% of patients with GIST, but median PFS was only 2 months, hence there was insufficient evidence of activity to justify further studies in this disease. As far as the primary goal of the study was concerned, which was to use $^{18}$FDG-PET to evaluate the efficacy of cediranib in the treatment of GIST, the study was also disappointing. Although a significant percentage of patients had both stable disease and stabilization of $^{18}$FDG uptake, direct correlation in individual patients was generally not observed. In the STS population, strong evidence of activity by objective response was seen in patients with ASPS, a disease that does not respond to conventional chemotherapy; this subsequently led to a phase II trial, which has confirmed these observations. In view of the high incidence of dose reductions required in this study, further trials with cediranib are being conducted using a cediranib dose of 30 mg/day, which seems to be reasonably well tolerated. Although there are no plans for further development of cediranib in GIST, two trials are ongoing with cediranib in the treatment of ASPS, a rare but refractory sarcoma, and it remains to be seen whether the drug has a particular role in the management of this disease.

Disclosure of Potential Conflicts of Interest

M. Marotti has an ownership interest (including patents) in and is an employee of AstraZeneca shares. J. Jurgensmeier was an employee of AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

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Study supervision: I.R. Judson, M. Marotti

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Phase II Study of Cediranib in Patients with Advanced Gastrointestinal Stromal Tumors or Soft-Tissue Sarcoma

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