Phase II study of cediranib in patients with advanced gastrointestinal stromal tumours (GIST) or soft tissue sarcoma (STS)

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Running header: Cediranib in patients with advanced GIST or STS

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I Judson has received an honorarium for participation in an advisory board; M Marotti, B Collins and H Young are employees of AstraZeneca and own stock; JM Jürgensmeier is a former employee of AstraZeneca

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**Translational Relevance**

GIST is generally driven by activating mutations in the *KIT* or *PDGFRA* 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 antitumour activity in early clinical studies. This Phase II, cediranib monotherapy study used $^{18}$FDG-PET to assess preliminary antitumour 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 ($\geq 16$ weeks) occurred in 8 GIST patients who had previously progressed on imatinib, including patients who had also received sunitinib previously.
Abstract

**Purpose:** Cediranib is a potent vascular endothelial growth factor (VEGF) signalling 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 tumour (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 antitumour activity of cediranib according to changes in $^{18}$FDG-PET tumour uptake in GIST patients using maximum standardized uptake values ($SUV_{\text{max}}$). Secondary objectives included objective tumour response and tolerability in GIST/STS patients.

**Results:** 34/36 enrolled patients were treated (GIST $n=24$; STS $n=10$). At day 29, five patients had confirmed decreases in $SUV_{\text{max}}$ ($\geq 10\%$ from day 8) and two had confirmed partial metabolic responses ($\geq 25\%$ decrease), but arithmetic mean percentage changes in $SUV_{\text{max}}$, averaged across the cohort, were not significant at day 8 (6.8%; 95% CI: $-19.95$, 33.54) or day 29 (4.6%; 95% CI: $-8.05$, 17.34). Eleven GIST patients achieved a best objective tumour response of stable disease (SD); 8 achieved SD $\geq 16$ weeks. In STS patients, 4/6 with alveolar soft part sarcoma (ASPS) achieved confirmed and durable partial responses. The commonest adverse events were diarrhoea (85%), fatigue (74%) and hypertension (68%).

**Conclusions:** In patients progressing on imatinib/sunitinib, cediranib 45 mg/day demonstrated evidence of activity by $^{18}$FDG-PET but did not reduce average $SUV_{\text{max}}$. Evidence of antitumor activity was seen in ASPS.
Introduction

Gastrointestinal stromal tumours (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 alpha (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 multi-targeted TKI with activity against PDGFRα, PDGFRβ, KIT, vascular endothelial growth factor receptors 1–3 (VEGFR-1–3), colony-stimulating factor receptor 1 (CSFR1), fms-related tyrosine kinase 3 (Flt-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 randomised trial comparing regorafenib with placebo in patients who had progressed on both imatinib and sunitinib, reforafenib produced an improvement in median progression-free survival of 3.9 months (HR 0.27, p<0.0001) (7).
Cediranib is an oral, highly potent, vascular endothelial growth factor (VEGF) signalling inhibitor with activity against all three VEGFRs and additional activity versus KIT (8-10). In vitro, cediranib has been 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 antitumour activity in patients with advanced solid tumours, both as a single agent and in combination with other anticancer strategies (11-17).

Previous studies have suggested that 2-[F-18]-fluoro-2-deoxy-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 antitumour 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 antitumour activity by objective tumour response, using Response Evaluation Criteria In Solid Tumours (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 to cediranib in a patient with this disease in a phase I trial.
Patients and Methods

Patients

Patients aged ≥18 years with histological confirmation of either GIST that was resistant/intolerant to imatinib mesylate, or metastatic STS that was refractory to standard therapies or for which no standard therapy exists, such as alveolar soft part sarcoma (ASPS), based on earlier evidence of an objective response to cediranib in a patient with this disease; a World Health Organization 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 computed tomography (CT) scan or 20 mm with conventional techniques, for RECIST assessment. An additional criterion for GIST patients was one or more measurable lesions ≥20 mm for \(^{18}\text{FDG-PET}\) 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 (ie \(^{18}\text{FDG-PET}\) scans). Specific exclusion criteria related to \(^{18}\text{FDG-PET}\) assessments were applied to GIST patients, including type I 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 \(^{18}\text{FDG-PET}\)-assessable lesion.
Study objectives

The primary objective was to determine the preliminary antitumour activity of cediranib in patients with GIST by utilizing $^{18}$FDG-PET scans to assess maximum standardized uptake ($SUV_{\text{max}}$) 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 $^{18}$FDG-PET ($SUV_{\text{max}}$) in patients with GIST following 8 days and 4 weeks (day 29) of cediranib dosing, and an evaluation of cediranib efficacy by objective tumour response (RECIST; version 1.0) in GIST and STS (ASPS), assessed every 12 weeks. A planned central review of response by RECIST in GIST patients 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 $^{18}$FDG-PET and CT parameters, including total lesion volume, were also analysed 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-centre, 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 delay permitted was 14 days. Cediranib doses were based on results achieved in a previous Phase I monotherapy trial of patients with solid tumours, 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 antitumour activity in GIST patients, $^{18}$FDG-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 $^{18}$FDG-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 370–740 MBq (10–20 mCi) $^{18}$FDG (dose was dependent on local practice and scanner type). $^{18}$FDG uptake in the primary tumour and metastatic lesions (up to a maximum of three lesions) was analysed semi-quantitatively by SUV$_{\text{max}}$ for body weight, according to the following equation:

$$SUV_{\text{max}} = \frac{[\text{Maximum radiotracer concentration in tumour (kBq/ml; } \mu\text{Ci/ml)} \times \text{Body weight (kg)}]}{\text{Injected dose (MBq; mCi)}}$$
The $^{18}$FDG-PET scans were assessed by independent central review (VirtualScopics, Rochester, USA) and by investigational site review. $^{18}$FDG uptake was classified as complete metabolic response (CMR; complete resolution of $^{18}$FDG uptake within the tumour), partial metabolic response (PMR; $\geq$25% reduction in $^{18}$FDG $\text{SUV}_{\text{max}}$), stable metabolic disease (SMD; <25% increase or decrease in $^{18}$FDG $\text{SUV}_{\text{max}}$) or progressive metabolic disease (PMD; $\geq$25% increase in $^{18}$FDG $\text{SUV}_{\text{max}}$ or visible increase in $^{18}$FDG tumour uptake) based on European Organization for Research and Treatment of Cancer (EORTC) criteria (20). A confirmed partial metabolic response was defined as PMR on both days 8 and 29 by central review.

To determine the efficacy of cediranib in GIST and STS patients, objective tumour response (according to RECIST; version 1.0) was also assessed by investigator review of CT or magnetic resonance imaging (MRI) scans (CT scan of the chest, abdomen or pelvis, or MRI if CT unavailable) at baseline (within 21 days prior to starting treatment), week 8, week 16 and then every 12 weeks thereafter until study discontinuation. Blood samples were drawn prior to 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 GIST patients. Details of the methods used to analyse the soluble markers of angiogenesis are described by Drevs et al (13).

Safety was monitored throughout the study, with the incidence and severity of adverse events (AEs) graded according to National Cancer Institute common terminology criteria for AEs (CTCAE) version 3.
Statistical methods

Sample size calculations were performed separately for GIST and STS patients. In a previous study of $^{18}$FDG-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 standard deviation 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 (CIs) of −40% to −60%. Assuming that 10% of patients would not have readable scans, approximately 25 GIST patients 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 ~10%; this was considered sufficiently low to warrant the inclusion of 10 STS (predominantly ASPS) patients.

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 $^{18}$FDG SUV$_{\text{max}}$ values from central and investigator reviews for GIST patients 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 $^{18}$FDG SUV$_{\text{max}}$ from central and investigator reviews were also conducted in GIST patients 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 tumour 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 cut-off (8 July 2009), 33 patients had discontinued due to worsening of their condition ($n = 21$, 58.3%), AEs ($n = 9$, 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 due to 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 STS patients (6 of 10). Of the other 4 STS patients 2 had uterine leiomyosarcoma, one a retroperitoneal liposarcoma and the fourth a soft tissue spindle cell sarcoma. All GIST patients received prior imatinib, as per the inclusion criteria, and 13 of 24 patients received prior sunitinib. ASPS patients may have received prior chemotherapy but none had received prior treatment with a multi-targeted TKI or other anti-angiogenesis treatment.

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

When assessed by central review, 67% and 50% of GIST patients 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 ≥10% decreases in $\text{SUV}_{\text{max}}$ 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 tumour-averaged $\text{SUV}_{\text{max}}$ and prior treatment with or without sunitinib (Fig. 2B). Overall central review of the patients assessable by $^{18}\text{FDG}$-PET indicated that only 3 of 30 on day 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 $^{18}\text{FDG}$ 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 tumour response by RECIST

Twenty-eight patients were evaluable for response by RECIST (Table 2; Fig. 3A), of whom 20 had GIST. While none of the GIST patients had an objective tumour response, 15 had a best response of stable disease (SD) when assessed according to investigator review, of whom 14 had SD for ≥16 weeks (≥112 days). At the time of data cut-off 6 patients were still on treatment with stable disease. By investigator review median progression-free survival (PFS) was 7 months. When assessed by central review 11 patients had SD as best response and although 8 of these had SD for >16 weeks, the overall median PFS was 2 months. No differences were seen between GIST patients who received prior sunitinib and those who did not (prior imatinib: SD n = 8, PD n = 2, not evaluable n = 1; prior imatinib and sunitinib: SD n = 7, PD n = 3, not evaluable n = 3). The comparison in GIST patients between investigator and central review is shown in Figs 3A and B). There was no clear relationship between PMR according to ¹⁸FDG-PET and RECIST response. The 2 patients with a confirmed PMR by central review, i.e. PMR on days 8 and 29, had SD. One discontinued because of toxicity but the other had prolonged disease control, i.e. for 358 days. Two patients with PMR on either day 8 or day 29 alone both had PD, however, time to discontinuation of treatment ranged from 64 to 213 days, hence there was deemed to be some clinical benefit in spite of objective progressive disease. The relationship between PMR and RECIST was extremely variable, see Fig 3C.

In STS, investigator-confirmed partial responses (PRs) were reported in four of the six patients with ASPS (duration of response: 241, 247, 365 and 633 days) while three other patients, including the remaining two with ASPS, achieved SD for 57 (n =
2) and 449 days ($n = 1$) by investigator review (Fig. 3D and 3E). Of the three ASPS patients remaining in the study at primary data cut-off, further follow-up showed that the duration of response increased for one patient from 633 to 801 days. Central review determined that 2/6 ASPS patients achieved a PR and 4/6 patients had SD.
Biomarker variables

Increases in VEGF levels were observed at day 8 in all but one GIST patient, 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 GIST patients and 31.4 mg for STS patients. 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%) GIST patients and seven of 10 (70%) STS patients 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; four patients in each population (GIST or STS) required two dose reductions. AEs were the principal reason for a reduction or pause in cediranib dosing. The most commonly experienced AEs were diarrhoea (85%), fatigue (74%) and hypertension (68%; Table 3). AEs of CTC grade ≥3 with a total frequency ≥10% were fatigue (29%, all GIST patients), hypertension (24%; GIST n = 7; STS n = 1) and diarrhoea (18%; GIST n = 5; STS n = 1). One CTC grade 4 case of hypertensive crisis occurred in a GIST patient.
Two patients died during the study: one STS patient because of disease progression and one GIST patient from haemorrhage in a hepatic metastasis. Serious AEs occurred in 13 patients (10 GIST and three 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 due to an AE (GIST, n = 7; STS, n = 4), most commonly due to fatigue (four GIST patients) and hypertension (two patients; one GIST, one STS). Of the three patients with STS remaining in the study at primary data cut-off, one subsequently died due to 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 $^{18}$FDG-PET uptake as the primary endpoint to assess the antitumour 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 $^{18}$FDG-PET (central review), with confirmed decreases in \( \text{SUV}_{\text{max}} \) of \( \geq 10\% \) in five patients at day 29 and two confirmed PMRs (\( \geq 25\% \) decrease). However, there was no statistically significant percentage change in arithmetic mean $^{18}$FDG-PET \( \text{SUV}_{\text{max}} \) from baseline, across the whole cohort, at day 8 or day 29 (central review). There were no RECIST-confirmed objective tumour responses in GIST, but SD was achieved in 62.5% of patients by investigator review, with 14 of 20 evaluable patients achieving disease stabilization for \( \geq 16 \) weeks. However, by central review only 9 patients had SD as best response and PFS was only 2 months, as opposed to 7 months according to investigator review. Reduction in tumour $^{18}$FDG uptake may provide an early and sensitive pharmacodynamic marker of antitumour activity, and has led to the development of EORTC guidelines (20); a number of additional guidance approaches have been proposed that are currently undergoing wider evaluation, including PET Response Criteria in Solid Tumours (PERCIST) (22). Further validity of $^{18}$FDG-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 $^{18}$FDG-PET decreases in \( \text{SUV}_{\text{max}} \) and prolonged (\( \geq 16 \) weeks) radiological stable disease. Two
patients with a confirmed PMR had SD by RECIST. However, the relationship between changes in $^6$FDG uptake and duration of SD was variable, although it is worth noting that some patients with PD by RECIST continued on treatment for up to 213 days because of perceived clinical benefit. In individual patients $^{18}$FDG-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 $^{18}$FDG-PET changes seen in response to first-line imatinib. There is known to be considerable heterogeneity in refractory tumours, with the likelihood that some cells are sensitive to treatment while others are not. Similarly, there may be considerable heterogeneity of $^{18}$FDG-PET response within the tumour, with cells possessing a resistance mutation being uninhibited and taking up $^{18}$FDG, while other cells respond and do not, resulting in stable $^{18}$FDG uptake overall; however, currently this remains speculation.

There was no difference in treatment outcome for the GIST patients who had received prior therapy with sunitinib, a multi-targeted 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 ($V654A$, $N822K$) (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) (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 a tendency to metastasise 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 six 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 lead 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 USA (NCT00942877) (30). A randomized Phase II study is currently being performed in which cediranib is compared with placebo in order 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 alveolar soft part sarcoma; 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 to 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 STS patients since the numbers were very small and certain analyses, such as soluble KIT, may not be relevant in this patient population.

The AE profile of cediranib 45 mg in this study was consistent with the expected pharmacological effects of a VEGF signalling inhibitor and with results observed in previous cediranib studies, in which the most commonly experienced AEs were diarrhoea, 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 18FDG-PET to evaluate the efficacy of cediranib in the treatment of GIST, the study was also disappointing. Although a significant percentage of patients both had stable disease and stabilization of 18FDG 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 appears 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.

Acknowledgments

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

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<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>
</tr>
<tr>
<td>Location of primary tumour, 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>
</tr>
<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>

GIST, gastrointestinal stromal tumours; STS, soft tissue sarcomas; WHO, World Health Organization.

*aOne 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$_{\text{max}}$) (GIST patients; central review) and objective tumour response (GIST and STS patients; investigator review)

<table>
<thead>
<tr>
<th>Metabolic response category, n (%)</th>
<th>Day 8 (n = 24)</th>
<th>Day 29 (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PMR</td>
<td>3 (13)$^a$</td>
<td>4 (17)</td>
</tr>
<tr>
<td>SMD</td>
<td>16 (67)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>PMD</td>
<td>3 (13)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

Objective tumour response (GIST and STS patients; investigator review)

<table>
<thead>
<tr>
<th>Tumour response category, n (%)</th>
<th>GIST (n = 24)</th>
<th>STS (n = 10)</th>
<th>Total (n = 34)</th>
</tr>
</thead>
<tbody>
<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>

CMR, complete metabolic response; CR, complete response; $^{18}$FDG-PET, 2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography response; GIST, gastrointestinal stromal tumours; NE, non-evaluable; PD, progressive disease; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; SMD, stable metabolic disease; SD, stable disease; STS, soft tissue sarcomas; SUV$_{\text{max}}$, maximum standardized uptake values.

$^a$One PMR was not confirmed at day 29; see text for further details.
Table 3. Adverse events (any cause; all grades; >20% in any group)

<table>
<thead>
<tr>
<th></th>
<th>GIST (n = 24)</th>
<th>STS (n = 10)</th>
<th>Total (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, n (%)</td>
<td>24 (100)</td>
<td>10 (100)</td>
<td>34 (100)</td>
</tr>
<tr>
<td>AE, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</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>

AE, adverse event; GIST, gastrointestinal stromal tumours; STS, soft tissue sarcomas.
Figure Legends

Figure 1. Patient disposition. *At the time of primary data cut-off. AE, adverse event; GIST, gastrointestinal stromal tumours; STS, soft tissue sarcomas.

Figure 2. (A) Best percentage change from baseline in SUV$_{\text{max}}$ response at days 8 and 29 (GIST, central review). Patients are presented in the same order for both study days. Only patients with available data at both time points are presented. (B) Best percentage change from baseline in SUV$_{\text{max}}$ response by prior treatment (GIST, central review). Only patients with at least one measurement of change in SUV$_{\text{max}}$ from baseline are presented. GIST, gastrointestinal stromal tumours; SUV$_{\text{max}}$, maximum standardized uptake values.

Figure 3. Best percentage change from baseline in tumour 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$_{\text{max}}$ response (central review) and tumour 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 tumour size for patients with ASPS by investigator review. (E) Percentage change from baseline in tumour size over time for patients with ASPS by investigator review. ASPS, alveolar soft part sarcoma; GIST, gastrointestinal stromal tumours; RECIST, Response Evaluation Criteria In Solid Tumours; STS, soft tissue sarcomas.
Enrolled: 36
  GIST: 26
  STS: 10

Entered: 35
  GIST: 25
  STS: 10

Treated: 34

GIST: 24

Discontinued: 26
  AE: 5
  Condition worse: 18
  Death: 1
  Incorrect enrolment: 2

STS: 10

Discontinued: 7
  AE: 4
  Condition worse: 3
  Death: 0
  Incorrect enrolment: 0

Not entered: 1
  AE (GIST): 1

Not treated: 1
  Incorrect enrolment (GIST): 1

Ongoing*: 0

Ongoing*: 3
Figure 2

A

Day 8
(N=19)

Day 29
(N=19)

Best change (%) in SUV\textsubscript{max}

+25%
–15%
–25%

B

Imatinib + sunitinib
(N=13)

Imatinib only
(N=10)

Best change (%) in SUV\textsubscript{max}

+25%
–15%
–25%
Figure 3
Phase II study of cediranib in patients with advanced gastrointestinal stromal tumours (GIST) or soft tissue sarcoma (STS)

Ian R. Judson, Michelle Scurr, Kate Gardner, et al.

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