First-in-Human Phase I Trial of Two Schedules of OSI-930, a Novel Multikinase Inhibitor, Incorporating Translational Proof-of-Mechanism Studies

Timothy A. Yap\textsuperscript{1,2}, Hendrik-Tobias Arkenau\textsuperscript{1}, D. Ross Camidge\textsuperscript{5}, Suzanne George\textsuperscript{6}, Natalie J. Serkova\textsuperscript{5}, Stephen J. Gwyther\textsuperscript{4}, Jennifer L. Spratlin\textsuperscript{5}, Rohit Lal\textsuperscript{1}, James Spicer\textsuperscript{1}, Nandita M. Desouza\textsuperscript{3}, Martin O. Leach\textsuperscript{3}, S. Gail Eckhardt\textsuperscript{5}, Stan B. Kaye\textsuperscript{1,2}, George Demetri\textsuperscript{6}, and Michelle Scurr\textsuperscript{1,2}

\textsuperscript{1}Drug Development Unit, Royal Marsden NHS Foundation Trust; \textsuperscript{2}Division of Clinical Studies; \textsuperscript{3}Cancer Research UK and T.A. Yap and H.-T. Arkenau are joint first authors of this article.

Abstract

**Purpose:** OSI-930 is a novel, potent, oral small-molecule receptor tyrosine kinase inhibitor, predominantly against VEGF receptors (VEGFR), c-Kit, and platelet-derived growth factor receptors. A phase I trial was undertaken to determine safety, maximum-tolerated dose (MTD), pharmacokinetics, pharmacodynamics, and antitumor activity of OSI-930 in patients with advanced solid tumors.

**Experimental Design:** OSI-930 was administered once or twice a day using a modified accelerated titration design. Pharmacokinetics and plasma soluble VEGFR2 (sVEGFR2) studies were undertaken. Dynamic contrast-enhanced MRI (DCE-MRI) and 2[18F]fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) MTD expansion cohorts were conducted.

**Results:** Fifty-eight patients received OSI-930 in 2 schedules; once a day schedule: 12 patients at doses up to 1,600 mg without reaching MTD; twice a day schedule: 46 patients at 400 mg (\(n = 7\)), 500 mg (\(n = 31\)), and 600 mg (\(n = 8\)). Dose-limiting toxicities were observed at 600 mg twice a day (\(n = 3\)): G3 rash (\(n = 2\)) and G4 \(\gamma\)-glutamyltransferase, establishing the MTD at 500 mg twice a day. Common G1–2 toxicities included fatigue, diarrhea, nausea, and rash. Antitumor responses were seen in 2 patients with advanced ovarian cancer [Response Evaluation Criteria in Solid Tumors (RECIST) partial response (PR) (\(n = 1\))]. GCGIC CA125 response (\(n = 1\)). Eleven of 19 heavily pretreated imatinib-resistant patients with gastrointestinal stromal tumors achieved RECIST stable disease (median duration: 126 days), with FDG-PET scans showing PRs in 4 of 9 patients. OSI-930 exposure increased with dose; substantial decreases in sVEGFR levels were observed with OSI-930 twice a day doses \(\geq 400\) mg, while DCE-MRI responses were shown in 4 of 6 patients.

**Conclusions:** OSI-930 is safe and well tolerated, with pharmacokinetic–pharmacodynamic data supporting proof-of-mechanism with clinically relevant antitumor activity. Clin Cancer Res; 19(4): 909–19. ©2012 AACR.

Introduction

The split kinase domain family of receptor tyrosine kinases (RTK) includes the VEGF receptors (VEGFR), c-Kit and the platelet-derived growth factor receptors (PDGFR). Aberrant activation of these receptors has been shown to play a critical role in malignant pathogenesis, including angiogenesis and uncontrolled tumor growth (1–4). The paradigm of this pathophysiologic process is gastrointestinal stromal tumor (GIST), which is driven by gain-of-function mutations of c-Kit in more than 80% of tumors (5). Clear cell renal cell carcinoma with its dependence on overexpression of VEGF is another example, but angiogenesis and neovascularization...
Translational Relevance

OSI-930 is a novel, potent, oral small-molecule receptor tyrosine kinase (RTK) inhibitor, predominantly against VEGF receptors (VEGFR), c-Kit and platelet-derived growth factor receptors. OSI-930 has a pharmacokinetic–pharmacodynamic profile distinct from other RTK inhibitors, with potent antitumor activity in multiple xenograft models. OSI-930 inhibits wild-type and mutant c-Kit with equal potencies in intact cellular systems, and potentially blocks wild-type c-Kit–dependent tumor growth to a greater degree than imatinib. This first-in-human phase I study established the maximum-tolerated dose at 500 mg twice a day and confirmed that OSI-930 is well tolerated, with pharmacokinetic–pharmacodynamic data supporting proof-of-mechanism with clinically relevant antitumor activity. Substantial decreases in plasma soluble VEGFR levels were observed with OSI-930, whereas dynamic contrast-enhanced MRI studies showed multiple responses, indicating antiangiogenic activity. Heavily pretreated imatinib-resistant patients with gastrointestinal stromal tumors achieved prolonged Response Evaluation Criteria in Solid Tumors stable disease with OSI-930, with 2[18F]fluoro-2-deoxy-d-glucose-positron emission tomography studies showing partial responses in multiple patients.

We now report the clinical evaluation of OSI-930 in once a day and twice a day dosing schedules in an open-label phase I dose escalation study. The primary objective of this study was to establish the maximum-tolerated dose (MTD) and recommended phase II dose (RP2D) of OSI-930. Secondary objectives included the assessment of safety and tolerability, defining dose-limiting toxicities (DLT), evaluating the pharmacokinetic profile, correlating pharmacodynamic assays with systemic exposure, and assessing for preliminary evidence of antitumor activity.

Patients and Methods

This was an open-label, phase I dose escalation study evaluating both once a day and twice a day schedules of the oral agent, OSI-930, given continuously in 3-weekly treatment cycles. The enrollment period for this study was 23 months. It was conducted at 3 centers (Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; University of Colorado Cancer Center, Denver, CO; and Dana-Farber Cancer Institute, Boston, MA) and in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines and approved by relevant regulatory and independent ethics committees.

Patient selection

Patients with histologically confirmed advanced solid tumors that were not amenable to established forms of therapy were eligible for the study. Key inclusion criteria included the following: age 18 years or older; written informed consent; Eastern Cooperative Oncology Group Performance Status (ref. 15; ECOG PS) 0–2, predicted life expectancy of at least 12 weeks; and adequate hematopoietic, hepatic, and renal function. Exclusion criteria included the following: patients with significant comorbidities including severe cardiac disease or uncontrolled hypertension; pregnancy, breast-feeding; residual drug-related toxicities from prior TKI therapy (e.g., imatinib or sunitinib) and because of the risk of symptom flare that may occur with TKI withdrawal in patients with GIST, these patients were only required to have a minimum period of 7 days off other TKI therapy.

Study design and dosing

The study used a modified accelerated titration 2B design (16). In the initial accelerated phase of the study, patients were treated only on the once a day schedule starting at an initial dose of 50 mg once a day based on preclinical studies and a healthy volunteer study (unpublished data). Single patient cohorts with dose escalations of up to 100% were permissible if OSI-930-related toxicities seen in the first...
treatment period in the preceding cohort were limited to Common Terminology Criteria for Adverse Events v3.0 (CTCAE; ref. 17) grades 0 to 1. The accelerated phase would be terminated and a parallel twice a day schedule commenced upon either the observation of grade 2 or greater clinically significant toxicity during the first treatment period, or if review of preliminary pharmacokinetic data from 4 dose levels on the once a day schedule indicate that twice a day dosing may result in a potential improvement in drug exposure with acceptable toxicity. At this point, patient cohorts would increase to 3 to 6 patients per dose level, and both the once a day and twice a day schedules would be evaluated in parallel cohorts. The dose of the parallel twice a day cohort would start at the same total daily dose as the previous once a day dose but be divided into 2 equal oral doses. Dose escalation would be limited to a maximum of 30% and a 1-week safety observation period between the first and subsequent patients in a dose cohort would be introduced. Intrapatient dose escalation was allowed but only at 1 dose level at a time, and only if the patient had completed a treatment period with less than grade 2 clinically significant toxicity, and if the patients at the next dose level had completed a treatment period with less than grade 2 clinically significant toxicity.

Once the MTD had been established and the RP2D determined, additional patients were enrolled at the RP2D into 2 parallel expansion cohorts: (i) a cohort with appropriate tumors to undergo sequential dynamic contrast-enhanced MRI (DCE-MRI) to explore the antiangiogenic properties of OSI-930; and (ii) a cohort of patients with GIST to assess for preliminary evidence of clinical activity, and to assess for potential metabolic activity of OSI-930 using sequential 2[18]Ffluoro-2-deoxy-ß-glucose-positron emission tomography (FDG-PET) imaging in patients.

DLT was defined as grade 4 neutropenia for ≥7 days, ≥ grade 3 febrile neutropenia, grade 4 thrombocytopenia, or ≥ grade 3 nonhematologic toxicity of any duration with the exception of fatigue (unless an increase of ≥2 grades from baseline) or grade 3 γ-glutamyltransferase (GGT) occurring in the first treatment period. Grade 3 hypertension, nausea, vomiting, and diarrhea were only considered as DLTs if they occurred despite optimal medical management. Interruption of dosing for 5 continuous days within the first treatment period, or an inability to begin a second treatment period by day 36 were also considered to be DLTs if due to study drug-related toxicity. The MTD was defined as the highest dose at which ≤ 1 of 6 patients experienced a DLT. In the absence of DLT in 2 or more patients, the maximum dose could be declared on the basis of the maximum number of capsules that could be acceptably ingested per dose.

OSI-930 formulation

OSI-930 was administered orally as 25 or 100 mg capsules. All dose escalations were calculated to the nearest dose feasible with these 2 capsule doses. The capsules were taken with food. Midway through the study, the manufacturing method of active OSI-930 drug product changed from screened material to micronized material. To evaluate potential pharmacokinetic differences between the 2 formulations, 3 patients in the 400 mg twice a day cohort received capsules containing sieved (screened) OSI-930 and 4 patients received capsules containing micronized OSI-930. As the rate and extent of absorption of OSI-930 from the 2 drug formulations was similar (data not shown) all other patients in the twice a day regimen received the capsules containing micronized OSI-930.

Safety and efficacy assessments

Safety was assessed via clinical assessment (including symptom review, physical examination, and vital signs), clinical laboratory tests (complete blood count, clinical chemistry, and urinalysis), and electrocardiogram (ECG). All adverse events were graded using CTCAE v3.0. All assessments were conducted at baseline. Clinical assessments were conducted on day 1 of every treatment period and on the last study visit. Laboratory tests were conducted weekly for the first 2 treatment periods and subsequently every 3 weeks. ECGs were conducted on days 1, 8, 22, and on the last study visit.

Radiologic assessment of disease status was conducted at baseline and every 6 to 8 weeks, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 (17) with an independent review of radiology carried out for patients achieving stable disease or better. As appropriate, additional disease evaluations including serum cancer antigen 125 (CA125) were assessed according to Gynecologic Cancer Intergroup (GCIG) criteria (18).

Pharmacokinetics

Blood samples were collected predose and at 1, 2, 3, 4, 6, 8, 10 or 12, and 24 (for once a day dosing only) hours after oral administration of OSI-930 on days 1 and 22. In addition, predose plasma samples were also collected on days 8 and 15. The plasma samples were stored at −80°C. Plasma concentrations of OSI-930 were determined using a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method. The calibration range of the assay was 1 to 400 ng/mL. Non-compartmental analysis using WinNonlin 5.2 (Pharsight Corporation) was used to calculate the peak concentration (Cmax), time to peak concentration (Tmax), area under concentration versus time curve within dosing interval (AUC0-τ), and terminal half-life (T1/2).

Pharmacodynamic studies

sVEGFR2 biomarker studies. Blood samples were collected into EDTA tubes on days 1 (predose), 8, 15, and 22 to assess the concentration of soluble VEGFR2 (sVEGFR2) in plasma samples. Plasma sVEGFR2 concentrations were measured with the Human sVEGF R2/KDR Quantikine ELISA Kit (R&D Systems) according to the manufacturer’s protocol. As there is considerable interpatient variability in predose sVEGFR2 concentrations, the results were reported as a percentage of the predose value (%predose) to allow interpatient comparisons. Potential pharmacokinetic-
pharmacodynamic relationships were sought through the assessment of associations between pharmacokinetic parameters of patients treated at the RP2D and the magnitude of change in sVEGFR levels at the end of the first 21 days. In addition, a comparison between the best objective response achieved by patients [partial response (PR), SD, or progressive disease] in the expansion cohort and the magnitude of change in sVEGFR levels at the end of the first 21 days was conducted.

Functional imaging studies

DCE-MRI. DCE-MRI was conducted on day 1 predose, and on days 2 and 22 in suitable patients during the expansion phase. Each patient was required to have pelvic or hepatic lesions measuring 2 to 8 cm. Contrast media (gadolinium-based) was administered as a bolus injection during dynamic MRI scan using a power injection. The parameters determined for each lesion were AUC for total contrast uptake, initial AUC (IAUC) for the first 30 seconds of contrast uptake, the volume transfer constant (Ktrans) between the blood pool and the extravascular-extracellular space (EES) reporting on perfusion and microvascular permeability, and the volume of EES (Vve; refs. 19, 20), using MRI workbench (MRIWl; ref. 21; The Institute of Cancer Research, Sutton, United Kingdom) and Analysis Application for Medical Imaging (AAMI) software (University of Colorado, Denver, CO; Supplementary Methods).

FDG-PET imaging. FDG-PET imaging studies were undertaken in consenting patients with GIST enrolled in the expansion cohort predose on day 1 and 22. Depending upon the center, imaging was either conducted using a combined PET-CT scanner or a standard dedicated PET scanner followed by a low-dose noncontrast enhanced computed tomography (CT) scan. The patient was fasted for at least 4 hours before FDG administration (dose range, 370–555 MBq), which was injected 60 minutes before image acquisition. The PET scans were assessed qualitatively and the appropriate response was assigned on the basis of standardized uptake value (SUV) changes. The PET and CT scans were assessed both by the center and also by an independent board-certified radiologist (S.J. Gwyther) experienced in PET and CT imaging.

Results

Patient characteristics

Sixty patients from the 3 investigational sites were enrolled and 58 treated in 4 once a day cohorts and 3 twice a day cohorts (see Table 1). Two patients in the 500 mg twice a day cohort were found to be ineligible for study at baseline and did not receive OSI-930. As expected, GIST represented the most common tumor type (31.7%), followed by ovarian cancer (13.3%). All patients had received at least 1 prior systemic antineoplastic treatment, with the majority having received at least 3 prior treatments. All patients with GIST had received imatinib, predominantly in the metastatic setting. One patient had received only imatinib, with the rest having received second-line sunitinib and 14 of 19 had other TKIs.

Dose escalation and MTD

Twelve patients were enrolled and received OSI-930 dosing in the once a day cohorts: 50 mg (n = 1), 100 mg (n = 1), 200 mg (n = 2), 400 mg (n = 2), 800 mg (n = 2), 1,200 mg (n = 1), and 1,600 mg (n = 3). There were no DLTs observed with the once a day dosing schedule and adverse events were generally mild in nature, including fatigue, anorexia, and nausea. However, the number of capsules per dose (16 capsules) at the 1,600 mg dose level precluded further dose escalation, and so 1,600 mg daily was defined

### Table 1. Patient demographics—all treated patients (n = 60a)

<table>
<thead>
<tr>
<th>Sex</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21 (35)</td>
</tr>
<tr>
<td>Female</td>
<td>39 (65)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>57 (19–83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Cervix</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>GIST</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Otherb</td>
<td>9 (15.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG PS at screening</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>1</td>
<td>36 (60.0)</td>
</tr>
<tr>
<td>2</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior chemotherapy</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1–2</td>
<td>17 (28.3)</td>
</tr>
<tr>
<td>≥3</td>
<td>43 (71.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior other therapyc</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>No</td>
<td>50 (83.3)</td>
</tr>
</tbody>
</table>

aSixty patients were registered, but only 58 patients received OSI-930 treatment.

bOthers include 1 patient of each tumor type of renal, desmoplastic small round cell, neuroendocrine, frontal-parietal hemangiopericytoma, unresectable duodenal adenocarcinoma, germ cell carcinoma, diffuse type giant cell, cholangiocarcinoma, and gastric adenocarcinoma.

cIncludes hormone therapy, immunotherapy, or cytostatic therapy.
as the MTD for this schedule, and a decision was made not to investigate this schedule further. Intrapatient dose escalation occurred in 3 patients, with 1 patient dose escalating stepwise from the baseline dose of 100 to 1,200 mg once a day without significant drug-related toxicity. This patient, who had low-grade sarcoma with multiple liver and renal metastases and ascites prior to starting OSI-930, achieved durable RECIST stabilization of her disease lasting 33 months and improvement in her symptoms.

Forty-eight patients were enrolled to receive OSI-930 in twice a day cohorts: 400 mg twice a day ($n = 7$), 600 mg twice a day ($n = 8$), and 500 mg twice a day cohort ($n = 33$). Two patients in the 500 mg twice a day cohort were found to be ineligible for study at baseline and did not receive OSI-930, resulting in 46 patients being included in the safety analyses for the twice a day cohorts. Three of the 8 patients treated at 600 mg twice a day had a total of 5 DLTs (1 patient had grade 4 elevation in GGT, 1 patient developed grade 3 pruritis and grade 3 papular rash, and 1 patient had grade 3 pruritis and grade 3 macular rash). As no DLTs had been noted at the 400 mg twice a day dose level, an intermediate dose of 500 mg twice a day was explored with 1 DLT (grade 3 myalgia) observed in the initial 8 patients. This level was therefore defined as the MTD and RP2D, and this cohort expanded to comprise a total of 16 patients with GIST and 17 patients with non-GIST tumors. Three patients in this expanded cohort each had a DLT: grade 3 fatigue, grade 3 nausea, and grade 3 lipase elevation, respectively.

### Safety and tolerability

**Once a day cohorts.** Although all patients on study experienced at least 1 adverse event, OSI-930 was generally well tolerated. The most frequently reported adverse events in the once a day cohorts were fatigue ($n = 8$), anorexia ($n = 6$), and nausea ($n = 5$), and no treatment-related adverse events greater than grade 2 were reported. Seven patients (58%) experienced adverse events that were considered to be related to OSI-930, including all 3 patients in the 1,600 mg once a day cohort (Table 2). These grade 1 to 2 drug-related adverse events included skin and subcutaneous disorders (3 patients), fatigue (3 patients), and nausea and anorexia (2 patients).

**Twice a day cohorts.** Within the twice a day cohorts, the most commonly reported adverse events, regardless of

<table>
<thead>
<tr>
<th>Gastrointestinal AEs</th>
<th>50–400 mg once a day ($n = 5$)</th>
<th>800 mg once a day ($n = 2$)</th>
<th>1,200 mg once a day ($n = 2$)</th>
<th>1,600 mg once a day ($n = 3$)</th>
<th>400 mg twice a day ($n = 7$)</th>
<th>500 mg twice a day ($n = 31$)</th>
<th>600 mg twice a day ($n = 8$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar-plantar erythema</td>
</tr>
<tr>
<td>Hair color changes</td>
</tr>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site condition AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nervous system AEs</td>
</tr>
<tr>
<td>Metabolism and nutrition AEs</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Muscle spasms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Table 2. Treatment-related adverse events (AE). All values shown represent the number of adverse events during treatment period.

NOTE: No CTCAE grade 4 to 5 adverse events were observed during this study except 1 patient in 600 mg twice a day cohort had grade 4 elevated GGT. Adverse events were shown if observed in more than 5% of patients.
causality, were fatigue (33 patients; 72%), nausea (26 patients; 57%), and diarrhea (23 patients; 50%). Treatment-related adverse events were seen in 40 patients (87%), the most common being fatigue (23 patients, 50%), nausea, and diarrhea (n = 18 each, 39%; Table 2). Overall, 23 patients (50%) experienced at least 1 grade 3 adverse event of any cause; however, they were felt to be treatment-related in only half of these events, mainly fatigue (6%), hypertension (6%), nausea (6%), and skin toxicity (6%). There was only one observed isolated grade 4 adverse event of elevated GGT in 1 patient (grade 3 at baseline), and no treatment-related deaths. There is a recognized spectrum of toxicities associated with TKIs targeting VEGFR, including hypertension, palmar-planter erythema (PPE), hypothyroidism, and proteinuria, which can lead to the need for drug holidays or even dose reduction with agents such as sunitinib. In this study, hypertension was uncommon (11%) and mild (only 1 grade 3), PPE occurred in 15% of patients with only 1 patient having grade 3 toxicity, and only 1 case of grade 2 proteinuria was observed.

Overall, 33 patients required a dose modification. Ten patients (20%) in the twice a day cohorts required dose reductions due to drug related toxicity; 1 in 400 mg twice a day, 4 in 600 mg twice a day and 5 of 31 patients (16%) treated on 500 mg twice a day. Treatment was discontinued for toxicity in only 1 patient (1 patient with grade 4 GGT elevation). There was good compliance with drug taking, and most of the cases of drug withholding were for short durations only. Two patients died on treatment, 1 of progressive disease and 1 of uncertain causes, not felt by the investigator to be related to the study treatment.

Pharmacokinetic analysis
OSI-930 was well absorbed in patients after oral administration, with time to peak plasma concentrations of 2 to 10 hours for both the once a day and twice a day cohorts (Fig. 1). Within the once a day cohorts, it is difficult to make conclusions based on single patient cohorts, but there seemed to be linearity in Cmax and AUC in the dose range 50 to 1,200 mg, but not at 1,600 mg. In the twice a day cohorts, the exposure of OSI-930 at 400 and 500 mg twice a day was dose proportional, but was greater than dose proportional at doses between 500 and 600 mg twice a day. The terminal half-life in the twice a day cohort ranged from 2.3 to 7.1 hours. The predose plasma concentrations of OSI-930 on days 8, 15, and 22 indicate that steady state plasma concentrations were achieved by day 8 after twice a day oral administration of OSI-930. Approximately, 2-fold accumulation of OSI-930 in plasma was observed at steady state after twice a day oral administration. The summary pharmacokinetic parameters of OSI-930 are listed in Table 3 and Fig. 1.

Response evaluation
Once a day cohorts. No RECIST partial or complete responses were observed in the once a day cohorts. Stable disease was the best response in 4 of 12 patients at dose levels ranging from 50 to 1,600 mg once a day, with 1 patient with anthracycline-resistant low-grade sarcoma achieving durable disease stabilization for 139 weeks.

Twice a day cohorts. There was 1 confirmed PR in a patient with heavily pretreated metastatic ovarian cancer treated in the 400 mg twice a day cohort, based on both RECIST criteria and CA125 levels. The patient achieved a GCIG CA125 response after 15 weeks of treatment with a significant improvement in disease-related symptoms and a confirmed RECIST PR at 24 weeks until the development of disease progression at 65 weeks. A second patient with advanced ovarian cancer receiving 500 mg twice a day OSI-930 achieved a GCIG CA125 response at 12 weeks that lasted for a further 12 weeks before developing disease progression; her best response by RECIST criteria was stable disease. There were 22 patients (48%) who achieved stable disease in the twice a day cohort.

In the subgroup of 19 evaluable patients with GIST, there were no RECIST PRs seen. However, 11 patients (57.9%) had stable disease as the best response and in some cases these were prolonged, with an overall median duration of 126 days (range, 21–693 days). Although the number of patients is small, these results are encouraging in this group of patients with heavy previous exposure to TKIs.

Pharmacodynamic analyses
sVEGFR biomarker studies. Substantial decreases in the levels of plasma sVEGFR2 (range, 0%–57%) were observed by the end of the first treatment period in the majority of patients treated with doses ≥400 mg once a day and ≥400 mg twice a day (Fig. 2A). The magnitude of these changes increased in a time-dependent manner over the 21 days.
(Supplementary Fig. S1). Preliminary evidence of a relationship between OSI-930 exposure at the RP2D and a targeted pharmacodynamic effect was seen with linear regression analysis showing a modest association between steady state drug concentrations and the magnitude of change in sVEGFR (Supplementary Fig. S2). Interestingly, an association between the pharmacodynamic parameters of changes in sVEGFR and objective responses was also seen in 17 patients treated in the expansion cohort, with a significantly greater reduction in sVEGFR levels in those patients achieving RECIST stable disease compared with those who progressed (P = 0.003; two-tailed unpaired t test; Supplementary Fig. S3).

### Functional imaging

**DCE-MRI.** Seven patients enrolled and treated in the 500 mg once a day non-GIST tumor expansion cohort had DCE-MRI scans, 6 of whom had baseline, day 2 and 22 scans. A single pelvic lesion was analyzed in 3 patients, whereas multiple liver lesions were studied in the other 3 patients (Supplementary Table S2). Of these, 4 patients (2 with liver lesions and 2 with pelvic lesions) had a significant vascular response based on decreased enhancement in targeted lesions following treatment (Fig. 2B), with changes observed in K_trans and V_e parametric images (Fig. 2C and D). The semiquantitative assessment of tumor perfusion (IAUC values) and overall tumor vascularity (AUC values) confirmed positive responses from multicompartmental modeling for the 4 patients (Supplementary Table S1) with decreases of IAUC and AUC in the range of −4% to −78% from baseline values.

**FDG-PET imaging.** Eight patients with GIST and 1 patient with diffuse type giant cell tumor had both baseline and day 22 FDG-PET scans (Supplementary Table S1). Of the 9 patients with evaluable PET and CT scans on both day 1 and 22, 4 achieved a qualitative functional PR on PET scan (Fig. 3), while the remainder showed stable disease (22–24). These FDG-PET scan results were determined by the site radiologist and an independent reviewer. The corresponding CT scans showed no significant change in size of the lesions, although 1 patient who achieved a functional PR had more cystic liver lesions on the corresponding CT scan, suggestive of tumor necrosis. Overall, however, functional response by PET imaging did not correlate with RECIST response (Supplementary Table S1); 2 of 4 patients who achieved a functional PR by PET scan developed RECIST disease progression at the first formal tumor assessment, whereas of the 5 patients who had stable FDG-PET functional responses, 4 had evidence of RECIST disease progression.

### Discussion

This phase I study of OSI-930 established the MTD and RP2D as 500 mg twice a day. At this dose, OSI-930 was well tolerated with mainly low-grade toxicities, a satisfactory pharmacokinetic profile, and preliminary evidence of clinical activity. Interestingly pharmacodynamic results suggesting antiangiogenic activity were also noted. Although the number of capsules per dose of OSI-930 (16 capsules) at 1,600 mg once a day precluded further dose escalation in the once a day schedule, further investigation of this schedule may be warranted if a suitable formulation can be achieved in the future.

There are several split domain TKIs already approved, such as imatinib, sunitinib, and sorafenib, and many more undergoing clinical development. This raises the question about OSI-930 and the rationale for developing this compound. The first factor to consider is the toxicity profile of such as imatinib, sunitinib, and sorafenib, and many more undergoing clinical development. This raises the question about OSI-930 and the rationale for developing this compound. The first factor to consider is the toxicity profile of OSI-930. At the RP2D, the principal toxicities were low-grade fatigue, nausea, and diarrhea. These represent common toxicities seen with similar TKIs. There are certain toxicities associated with VEGFR inhibitors such as hypertension, PPE, mucositis, proteinuria, and hypothyroidism that can impact both compliance and the ability to maintain efficacious chronic dosing. In this study, there were no reports of mucositis and just one episode of low-grade proteinuria, while only 15% of patients developed grade 1 to 2 PPE and 11% experienced grade 1 to 2 hypertension. In contrast, sunitinib has significantly higher incidences reported for both mucositis (12%–20%) and PPE (up to 20%; refs. 8, 25). Pazopanib, with potent VEGFR and PDGFR inhibition, has a similar toxicity profile to OSI-...
however, 51% of patients had proteinuria on pazopanib (26). The potent pan-VEGFR inhibitor cediranib is associated with a significantly increased incidence of grade 3 hypertension (19%) and grade 3 fatigue (18%), whereas more than 80% of patients had grade 1 to 2 diarrhea (27). The results of this study therefore suggest that OSI-930 is well tolerated and perhaps better tolerable than other agents with similar mechanisms of action. Given the potential chronicity of administration of these agents, the tolerability and limited range of toxicities are important in maintaining quality of life and ensuring compliance. There are also now increasing drug development efforts to combine such TKIs with other targeted therapeutics, and thus each agent needs to be tolerable as a single agent for such a strategy to be feasible. A clinical trial investigating the combination of OSI-930 with erlotinib has recently been published (28, 29). Evidence for antitumor efficacy is important in defining a role for OSI-930. Although there was only 1 objective PR seen in a patient with ovarian cancer, these data are encouraging. There was further preliminary evidence for activity in ovarian cancer with a second patient showing prolonged CA-125 tumor marker reduction. Almost half of all patients treated with OSI-930 achieved RECIST stable disease, in some cases for considerable durations. There was certainly

Figure 2. A, changes in plasma sVEGFR2 at the end of the first 21-day dosing cycle. B, representative liver DCE-MRI scans from a 52-year-old male with castration-resistant prostate cancer with multiple liver metastases before and 22 days after cycle 1 of OSI-930 treatment shows a decrease in the enhancement and the size of the enhancing mass in targeted liver lesions. C, representative computer generated $K_{\text{trans}}$ parametric maps of a pelvic lesion from a 37-year-old female with cervical carcinoma. Parametric maps were calculated from individual pixel enhancement curves in region of interests (ROI) and displayed as color overlays on the anatomic images using MRW software (21). A reduction in mean $K_{\text{trans}}$ in the lesion was seen after cycle 1 at day 22 of OSI-930 treatment. D, changes in 2 modeled parameters, $K_{\text{trans}}$ and $V_e$, for individual patients (3 patients had multiple liver lesions) at baseline (day 1), and cycle 1 day 2 and day 22 of OSI-930 treatment. Reduction in the volume transfer constant $K_{\text{trans}}$ (min$^{-1}$) and the volume of EES is seen after treatment. N.R., nonresponders. OD, once a day; BID, twice a day.
some evidence for activity seen in GIST, with 58% of patients achieving stable disease with a median duration of 126 days. The rate of disease stabilization is the same as that reported for sunitinib (8) and better than those reported for other agents currently under investigation, such as the second-generation TKI nilotinib, which showed disease stabilization in 38% of patients for a median duration of 12 weeks (30). In addition, there is now a real impetus to develop potent c-Kit inhibitors. For example, although the clinical benefit rate of first-line imatinib is about 80%, the median duration of response is about 2 years. Furthermore, the median time to progression reported for the standard second-line therapy sunitinib, is 27 weeks (8), and there are currently no other agents as yet approved for the third line setting.

There was interesting evidence in this trial for the suppression of angiogenesis observed in both sVEGFR biomarker studies and DCE-MRI results. The time-dependent decreases in the levels of sVEGFR, and the association between decreased sVEGFR levels and drug exposure at MTD support a relationship between drug and pharmacodynamic modulation. In addition, the association showed between patient responses and changes in sVEGFR levels supports angiogenesis modulation as a potential mechanism of action of OSI-930 (31).

DCE-MRI has been shown to be a sensitive pharmacodynamic marker of VEGFR2 inhibitors, but has not been shown to be a surrogate marker of efficacy (32, 33). In the present study, 4 of 6 patients with non-GIST tumors had considerable reductions in DCE-MRI T1-enhancement at day 22, with significantly decreased $K_{trans}$ and $V_e$ (>40%), as well as IAUC values, indicating an antiangiogenic response to OSI-930 due to VEGFR2 inhibition. Reproducibility data have shown that $K_{trans}$ has a coefficient of variability of approximately 14%, and IAUC of approximately 15%, whereas changes seen in treated patients in this study were more than twice those values (34). Together, these DCE-MRI data indicate that pharmacologically relevant concentrations of OSI-930 were achieved and confirmed the antiangiogenic mechanism of action of OSI-930.

FDG-PET has been shown to be an important early marker of efficacy in patients with GIST being treated with imatinib or sunitinib (35, 36). In the current study of 9 patients with evaluable PET and CT scans on both day 1 and 22, 4 patients achieved a qualitative functional PR by PET scan. However, there was no correlation seen between the functional response on FDG-PET scan and the best objective response by RECIST criteria for each patient. This discrepancy in results may be due to a disconnect between glucose turnover and size, or an increase in size because of cystic change, or be because the overall SUV_{max} may not increase in a tumor that is enlarging, as it is merely a maximum measurement and does not take into account the number of pixels with that value. These findings suggest that FDG-PET is a good indicator of pharmacodynamic modulation of the tumor, but a poor means for assessing antitumor response, as defined by RECIST criteria.
Overall, this study has indicated that OSI-930 is a well-tolerated and clinically active agent, which targets the split kinase domain RTKs, especially VEGFR-2, c-Kit, and PDGFR-β. We have confirmed the antiangiogenic effects of OSI-930 in the clinic with both biochemical and radiologic pharmacodynamic studies. We have shown that the agent may offer advantages over existing members of this class, particularly for the treatment of GIST, in which resistance to the established drug, imatinib, continues to be a key issue.

Disclosure of Potential Conflicts of Interest

D.R. Camidge is a consultant/advisory board member of OSI Pharmaceuticals and a consultant/advisory board member of AstraZeneca and Genentech. D. B. Gray has received grants from Bayer, GSK, and Pfizer. A. Stephens has ownership interest (including patents) in OSI Pharmaceuticals. S. B. Kaye is a consultant/advisory board member of Astellas Advisory Board. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.A. Yap, H.-T. Arkenau, S.G. Eckhardt, G. Demetri, M. Scurr

Grant Support

This study was supported by OSI Pharmaceuticals LLC, a wholly owned subsidiary of Astellas US LLC. The Drug Development Unit of the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research is supported in part by a program grant from Cancer Research UK. The Cancer Imaging Centre at the Institute of Cancer Research is supported by Cancer Research UK Engineering and Physical Sciences Research Council. Support was also provided by the Experimental Cancer Medicine Centre (to The Institute of Cancer Research) and the NIHR Research Biomedical Research Centre (jointly to The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 7, 2012; revised November 10, 2012; accepted November 27, 2012; published OnlineFirst February 12, 2013.

References

7. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, et al. OSI-930: a novel selective inhibitor of Kit and kinase insert domain RTKs, especially VEGFR-2, c-Kit, and PDGFR-β. We have confirmed the antiangiogenic effects of OSI-930 in the clinic with both biochemical and radiologic pharmacodynamic studies. We have shown that the agent may offer advantages over existing members of this class, particularly for the treatment of GIST, in which resistance to the established drug, imatinib, continues to be a key issue.
First-in-Human Phase I Trial of Two Schedules of OSI-930, a Novel Multikinase Inhibitor, Incorporating Translational Proof-of-Mechanism Studies


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-2258

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2012/12/31/1078-0432.CCR-12-2258.DC1

Cited articles
This article cites 33 articles, 16 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/19/4/909.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.