Phase I trial of SU14813 in patients with advanced solid malignancies

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Background: This phase I, open-label, dose-escalation study investigated SU14813, an oral multitargeted tyrosine kinase inhibitor, in adults with solid tumors.

Patients and methods: Seventy-seven patients received once-daily SU14813, either for 4 weeks followed by 1 week off treatment (schedule 4/1) or continuously [continuous daily dosing (CDD)]. The primary end point was to determine the maximum tolerated dose (MTD). Safety, pharmacokinetics, pharmacodynamics, and efficacy were assessed.

Results: MTDs were 200 mg/day on schedule 4/1 and 100 mg/day with CDD. Adverse events included fatigue (64%), diarrhea (61%), nausea (44%), anorexia (43%), and vomiting (42%). SU14813 steady state was attained by day 8. Exposure increased in a generally dose-proportional manner and SU14813 was eliminated with a mean terminal half-life of 9–34 h. Target plasma concentrations (>100 ng/ml SU14813) were achieved and sustained over 12 h at ≥100 mg/day. Progression-free survival among the 1 complete responder and 12 partial responders was 1.4–53.2 months. Fifteen patients remained on treatment at 1 year and 3 patients at 2 years.

Conclusion: SU14813 has manageable safety and tolerability and allows once-daily continuous oral dosing. SU14813 shows dose-proportional pharmacokinetics, with target plasma concentrations achieved at doses ≥100 mg/day. Clinically meaningful activity with durable responses was observed, meriting further study.

Key words: dose-escalation, inhibition, KIT, PDGFR, SU14813, tyrosine kinase receptor, VEGFR

introduction

Antiangiogenic therapy has become an established therapeutic principle in oncology [1], and vascular endothelial growth factor (VEGF) is the key player in promoting tumor angiogenesis. A number of compounds affecting VEGF or its receptors have been approved for treatment of various types of solid tumors, including bevacizumab [2, 3], sunitinib [4], and sorafenib [5]. SU14813, an oral indolmine multitargeted tyrosine kinase inhibitor (TKI), blocks VEGF receptors (VEGFRs) 1, 2, and 3, platelet-derived growth factor receptor (PDGFR)-α and -β, stem cell factor receptor (KIT), and fms-like tyrosine kinase 3 (FLT3) at nanomolar concentrations [6]. In vitro, SU14813 inhibited VEGFR-2, PDGFR-β, and FLT3-internal tandem duplication phosphorylation, with cellular IC50 values of 0.04, 0.02, and 0.05 μmol/l, respectively, and showed antitumor efficacy in tumor xenograft models [6]. Preclinical studies in mice demonstrated a lack of major active metabolites, linear pharmacokinetics and oral bioavailability of ~40% [6]. This phase I study investigated the maximum tolerated dose (MTD), safety, pharmacokinetics, and pharmacodynamics of SU14813 in patients with advanced solid tumors.

methods

study design

This phase I, open-label, dose-escalation study in patients with solid tumors (clinicaltrials.gov: NCT00982267) was conducted at two centers in Germany and The Netherlands. The study was performed according to International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki 1996 and was approved by the independent ethics committee for each center.
inclusion and exclusion criteria
Adults aged ≥18 years with a histologically proven advanced solid tumor for which no standard therapy was available, or for which therapy had failed, were eligible. Other inclusion criteria were Eastern Cooperative Oncology Group performance status of zero or one, adequate organ and hematologic function, and informed consent.

Exclusion criteria included previous treatment with any TKI, anti-VEGF agent, or antiangiogenic agent; known brain metastases; history of cardiac abnormalities or cerebrovascular accident; severe hypertension; pulmonary embolism; or deep-vein thrombosis within the last 12 months.

study treatment and dose escalation
SU14813 was administered orally as a hard gelatine capsule once daily in the morning on an empty stomach. The starting dose was 25 mg/day for 4 weeks followed by 1-week off treatment (schedule 4/1). Dose escalation began in an accelerated process: the next dose group received a 100% increase in the dose of SU14813 if no drug-related toxicity grade ≥2 was experienced; if any patients experienced grade ≥2 toxicity, the next escalation was 40% ± 10% according to dosage-form availability. Upon emergence of toxicology data, continuous daily dosing (CDD) schedules could also be investigated. The starting dose selected for the CDD schedule was 100 mg/day, which was the highest daily dose administered on schedule 4/1 without dose-limiting toxicity (DLT); this dose was selected to avoid exposure of patients to lower potentially inefficacious doses.

DLT was defined as any grade 4 hematologic toxicity; grade 3 thrombocytopenia associated with grade ≥3 hemorrhage; grade 4 hypertension; grade 2 pancreatitis; or any other grade ≥3 nonhematologic toxicity attributable to the study drug except nausea/vomiting that responded to treatment, grade 3 diarrhea controlled by medication, or grade 3 hypertension requiring use of additional antihypertensive treatment.

Each dose group initially enrolled three patients; if no DLTs were reported in the first cycle, the dose was escalated in the next three patients. If a DLT occurred in one patient in the first cycle, three additional patients were recruited to the same dose level. Dose escalation continued until two or more patients had DLTs. The MTD was defined as the highest dose of SU14813 that induced hematologic and nonhematologic DLTs in <33% of patients during cycle 1.

assessments
The primary objective was to determine the MTD of SU14813. Secondary objectives included evaluation of safety, efficacy, pharmacokinetics, and pharmacodynamics. Adverse events (AEs) and laboratory abnormalities were monitored according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Additional assessments included physical examinations, chest X-ray, vital signs, 12-lead electrocardiogram, and echocardiogram.

Assessment of efficacy used Response Evaluation Criteria in Solid Tumors [7], determining objective tumor response and long-term stable disease (224 weeks). Measurements were taken pre-study, at the end of cycle 1, and at the end of every third cycle thereafter.

Blood samples were drawn predose and at 1, 2, 3, 4, 6, 8, 10, 12, 20, and 24 h postdose on cycle 1 day 1, and on cycle 1 day 28 at the same timepoints with additional samples at hour 48 (day 30), 72 (day 31), 96 (day 32), and 144 (day 34). Samples were also taken predose and at intervals up to 96 h postdose on cycle 2 day 28. Predose trough plasma concentrations of SU14813 were measured on cycle 1 days 8 and 15, and cycle 2 days 1 and 15. For patients in CDD cohorts, predose trough plasma concentrations of SU14813 were also determined on days 1 and 28 of cycles 3 and 4. Predose plasma concentrations of SU14813 were used to determine the attainment of steady state and whether a pronounced trend for time-dependent changes in SU14813 concentrations occurred during multiple dosing.

Pharmacokinetic parameter estimates were determined from individual plasma concentration versus time data using noncompartmental analyses (WinNonLin version 4.1, Pharsight Inc., Mountain View, CA, USA). Summary statistics for SU14813 plasma concentration–time data [mean, standard deviation, percent coefficient of variation (%CV), median, minimum, and maximum] were calculated by dosing group, cycle, study day, and nominal time.

Blood-based tyrosine kinase receptor concentrations were measured to assess the biological activity of SU14813. Plasma concentrations of VEGF, soluble (s) VEGFR-2, sVEGFR-3, and sKIT were measured on cycle 1 days 1, 15, and 28; cycle 2 days 1 and 28; and upon withdrawal of dosing. Samples were analyzed using enzyme-linked immunosorbent assays [8].

results
patients and dose escalation
Seventy-seven patients were enrolled between December 2003 and February 2006 (Table 1). Treatment schedules, doses, DLTs during cycle 1, and median number of treatment cycles are presented in Table 2. On schedule 4/1, SU14813 was investigated at doses escalating between 25 and 250 mg/day. No DLT was observed on schedule 4/1 at doses up to 100 mg/day. During cycle 1, one of the seven patients receiving 150 mg/day 4/1 experienced grade 4 hypertension; this patient with pancreatic cancer subsequently died of cerebral bleeding and is discussed in more detail below. Since none of the other six patients enrolled at 150 mg/day...
Table 2. Dose-limiting toxicities (DLTs) during treatment cycle 1 and median number of treatment cycles given

<table>
<thead>
<tr>
<th>Dose (mg/day), schedule</th>
<th>Patients with DLT in cycle 1, n</th>
<th>DLT details</th>
<th>Cycles started*, median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25, 4/1</td>
<td>0/6</td>
<td>–</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>50, 4/1</td>
<td>0/6</td>
<td>–</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>100, 4/1</td>
<td>0/7</td>
<td>–</td>
<td>6 (1–54)</td>
</tr>
<tr>
<td>150, 4/1</td>
<td>1/7</td>
<td>Grade 4 hypertension</td>
<td>3 (1–13)</td>
</tr>
<tr>
<td>200, 4/1</td>
<td>1/6</td>
<td>Grade 3 fatigue</td>
<td>7 (2–17)</td>
</tr>
<tr>
<td>250, 4/1</td>
<td>2/6</td>
<td>Grade 3 fatigue (n = 2)</td>
<td>8 (1–27)</td>
</tr>
<tr>
<td>100, CDD</td>
<td>0/6</td>
<td>–</td>
<td>4 (2–16)</td>
</tr>
<tr>
<td>150, CDD</td>
<td>4/33</td>
<td>Grade 3 hypertension, grade 5 bleeding brain metastases, grade 3 stomatitis, grade 3 diarrhea</td>
<td>4 (1–26)</td>
</tr>
</tbody>
</table>

*The number of cycles started at any dose; some patients received dose modifications during the study.

CDD, continuous daily dosing.

experienced DLT, dose escalation proceeded to 200 mg/day 4/1. Grade 3 fatigue was dose limiting in one of the six patients receiving this dose and in two of the six patients receiving 250 mg/day 4/1. Therefore, 200 mg/day was determined as the MTD of SU14813 for the 4/1 dosing schedule.

Following determination of the MTD for schedule 4/1, enrollment to the CDD schedule began in 4-week cycles. The first CDD cohort received 100 mg/day, at which no DLTs were observed. Of the six patients initially enrolled at 150 mg/day CDD, one experienced a DLT of grade 3 hypertension, which required temporary treatment discontinuation. The protocol was amended for expanded enrollment into the 150 mg/day CDD group to further study the safety and tolerability of SU14813 when given continuously. Thirty-three patients completed a median of four treatment cycles (range 1–26) at this dose. In the expanded group, three further DLTs occurred during cycle 1. One patient experienced grade 5 bleeding brain metastases, considered to be treatment related (the patient did not have known brain metastases at baseline); there was also one case of grade 3 stomatitis and one patient had grade 3 diarrhea, requiring temporary drug discontinuation. Investigators noted that the 150 mg/day CDD dose was not well tolerated over subsequent cycles, and dose reductions were required in 20 of the 33 patients. Further dose escalation was not performed and 100 mg/day was determined as the MTD for CDD.

safety

AEs by dose group are shown in Table 3. Among 77 patients enrolled, the most common nonhematologic AEs regardless of causality, on any schedule and in any cycle, were fatigue (64%; 17% grade 3) and diarrhea (61%; 10% grade 3). Nausea (44%), anorexia (43%), and vomiting (42%) were the next most prevalent AEs and rarely exceeded grade 1/2 severity. Hypertension occurred in 38% of patients (12% grade 3/4). Overall, 31% of patients reported abdominal pain (6% grade 3/4). Hair color changes and rash occurred in 39% and 36% of patients, respectively. The most common hematologic AE was thrombocytopenia (22%); this reached grade 3/4 severity in five patients (6%). Leukopenia and neutropenia occurred in six (8%) and five (6%) patients, respectively, and did not exceed grade 3 severity. All-cycle laboratory abnormalities are shown in supplemental Table S1 (available at *Annals of Oncology* online); low hemoglobin occurred in the majority of patients. Liver toxicity was rare, though some patients had asymptomatic increases in liver function tests.

Forty-four patients died during the study, 33 due to progressive disease. Of the 11 deaths that occurred for other reasons, 3 were considered related to study treatment, as follows. One patient with osteosarcoma in the 150 mg/day CDD dose group pretreated with anthracyclines died due to cardiac failure and myocardial infarction; this was considered to have a reasonable possibility of being related to SU14813 treatment in the presence of very high SU14813 plasma concentrations on cycle 1 day 1 [maximum plasma concentration (Cmax) 1020 ng/ml], cycle 1 day 28 (1560 ng/ml), and cycle 2 day 1 (1600 ng/ml). In two other patients, a contributory role of SU14813 could not be excluded. A patient with pancreatic cancer (150 mg/day schedule 4/1) died due to cerebral bleeding while on treatment following DLT of grade 4 hypertension. At study entry, he had asymptomatic coronary artery disease and chronic medication with 100 mg/day acetylsalicylic acid may have contributed to the bleeding. A patient with non-small-cell lung cancer (150 mg/day CDD, then 50 mg/day CDD after dose reduction) died of a pulmonary embolism, which was considered a high risk in the presence of active tumor but was considered possibly attributable to SU14813.

pharmacokinetics

On cycle 1 day 1, all patients had detectable plasma concentrations of SU14813 at the first measured time point (1 h) following oral administration. SU14813 was absorbed with median time to Cmax ranging from 1.4 to 3.8 h following single-dose administration across all dosing groups in the 4/1 and CDD schedules. Thereafter, plasma levels declined slowly over the dosing interval, with concentrations reported in plasma at 24 h postdose ranging from 13.8 to 142.9 ng/ml (24.7–255.8 nM) with %CV from 40% to 101%.

The target therapeutic concentration of 100 ng/ml [6] was achieved and sustained over 12 h at doses of SU14813 ≥100 mg/day with both treatment schedules (Figure 1). Pharmacokinetic parameters for the MTDs of 200 mg/day on schedule 4/1 and 100 mg/day CDD are shown in Table 4. SU14813 exposure increased, in general, in a dose-proportional manner with Cmax and area under the plasma concentration–time curve for the dosing interval (AUCtau) increasing over the dose range of 25–250 mg on days 1 and 28 of cycle 1, and day 28 of cycle 2, although considerable variability in Cmax and AUCtau was observed across the dosing groups (supplemental Table S2, available at *Annals of Oncology* online).

Steady-state SU14813 plasma concentrations were achieved by cycle 1 day 8, as determined by visual inspection of plot trough concentrations (data not shown). Following
Table 3. Incidence of adverse events according to dose (all causalities, all cycles; N = 77)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number (%) of patients per dose group with all-causality events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 mg/day 50 mg/day 100 mg/day 150 mg/day 200 mg/day 250 mg/day 100 mg/day 150 mg/day</td>
</tr>
<tr>
<td>Nonhematologic a</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 3 (50) 0 0 1 (14) 5 (71) 0 4 (57) 0 3 (50) 1 (17) 4 (67) 2 (33) 5 (83) 4 (12) 23 (70)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (17) 4 (67) 1 (17) 5 (83) 0 5 (71) 1 (14) 2 (29) 2 (33) 4 (67) 2 (33) 6 (100) 1 (17) 4 (67) 5 (15) 19 (58)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 1 (17) 0 1 (17) 0 4 (57) 0 3 (43) 1 (17) 3 (50) 0 4 (67) 0 1 (17) 1 (3) 17 (52)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0 4 (67) 0 0 0 5 (71) 0 1 (14) 0 4 (67) 0 2 (33) 1 (17) 1 (17) 1 (3) 16 (49)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 1 (17) 0 1 (17) 0 3 (43) 0 3 (43) 0 4 (67) 0 3 (50) 0 2 (33) 0 15 (46)</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>0 0 0 0 0 3 (43) 0 2 (29) 0 4 (67) 0 4 (67) 0 5 (83) 0 12 (36)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 0 0 0 0 3 (43) 1 (14) 3 (43) 2 (33) 3 (50) 1 (17) 5 (83) 0 1 (17) 5 (15) 14 (42)</td>
</tr>
<tr>
<td>Rash</td>
<td>0 2 (33) 0 2 (33) 0 3 (43) 0 0 0 3 (50) 0 4 (67) 0 3 (50) 0 11 (33)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 0 1 (17) 1 (17) 1 (14) 4 (57) 0 2 (29) 1 (17) 3 (50) 0 3 (50) 1 (17) 1 (17) 1 (3) 10 (30)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0 1 (17) 0 0 0 2 (29) 0 3 (43) 0 3 (50) 1 (17) 3 (50) 0 4 (67) 0 8 (24)</td>
</tr>
<tr>
<td>Hematologic b</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0 0 0 0 0 1 (14) 1 (14) 2 (29) 1 (17) 3 (50) 0 0 0 0 3 (9) 11 (33)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0 0 0 0 0 1 (14) 0 1 (14) 0 0 1 (17) 1 (17) 0 1 (17) 1 (3) 2 (6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (17) 1 (17) 0 0 0 0 0 0 0 0 0 0 2 (6) 4 (12)</td>
</tr>
</tbody>
</table>

aIncidence cut-off for nonhematologic events: ≥30% of patients overall.

bIncidence cut-off for hematologic events: ≥5% of patients overall.

CDD, continuous daily dosing; G, grade.
multiple-dose administration, the mean SU14813 apparent volume of distribution ranged from 584 to 2995 l. SU14813 was eliminated slowly, with a mean terminal half-life ranging from 8.9 to 34.5 h across all dosing groups (both schedules), while mean apparent oral clearance following multiple-dose administration ranged from 27.3 to 133 l/h. SU14813 minimally accumulated in plasma, with the accumulation ratio ranging from 1- to 1.7-fold across all dosing groups (excluding two outliers in the 200 mg/day 4/1 group).

pharmacodynamics

Levels of pharmacodynamic plasma markers for the MTD of 100 mg/day CDD are shown in supplemental Table S3 (available at Annals of Oncology online). SU14813 decreased plasma concentrations of both sVEGFR-2 and sVEGFR-3 in a schedule-dependent manner (supplemental Figure S1, available at Annals of Oncology online).

clinical activity

Of 77 patients enrolled, 65 were assessable for tumor response (Table 5). Thirteen patients achieved a tumor response (1 complete response and 12 partial responses; 20.0% objective response rate). Responses were observed at all SU14813 doses and schedules except the lowest dose of 25 mg/day 4/1. Tumor stabilization was the best confirmed response in 24 patients and occurred with all SU14813 doses and schedules, except the lowest dose of 25 mg/day 4/1; of these, 13 patients had stable disease for $\geq 24$ weeks at dose levels $\geq 100$ mg/day CDD or $\geq 100$ mg/day 4/1. Tumor progression was the observed response during the study for 28 patients.

The pathologically verified complete response occurred in a 60-year-old patient with renal cell carcinoma (RCC) receiving SU14813 50 mg/day 4/1. The response lasted for 2.6 months, at which time he died of aortic rupture. The 12 partial responses in this study occurred in several tumor types. In a number of cases, the response was preceded by a period of stable disease. The longest recorded partial response was in a patient with RCC [response duration 23.5 months; progression-free survival (PFS) 53.2 months]. Another notable response occurred in a patient with hereditary von Hippel-Lindau disease, who had a partial response of 12.9 months of duration (PFS 15.8 months) in a pancreatic neuroendocrine tumor and liver metastases. A patient with cholangiocellular carcinoma achieved a partial

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Table 4. Pharmacokinetic parameters at the maximum tolerated dose with schedule 4/1 and continuous daily dosing, at cycle 1 day 1 and cycle 1 day 28

<table>
<thead>
<tr>
<th>Parameter</th>
<th>200 mg/day, schedule 4/1</th>
<th>100 mg/day, continuous daily dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$, ng/ml, mean (%CV)</td>
<td>253 (87)</td>
<td>171 (42)</td>
</tr>
<tr>
<td>$C_{\text{24h}}$, ng/ml, mean (%CV)</td>
<td>75 (81)</td>
<td>34 (67)</td>
</tr>
<tr>
<td>$C_{\text{early}}$, nM, mean</td>
<td>134.3</td>
<td>60.9</td>
</tr>
<tr>
<td>$\tau_{0.5}$, h, mean (%CV)</td>
<td>19.1 (59.2)</td>
<td>13.2 (53.4)</td>
</tr>
<tr>
<td>Clearance, l/h, mean (%CV)</td>
<td>132.6 (122.5)</td>
<td>50.2 (48.3)</td>
</tr>
<tr>
<td>Volume of distribution, l, mean (%CV)</td>
<td>2996 (119)</td>
<td>821 (34)</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$, maximum plasma concentration; CV, coefficient of variation; $AUC_{\text{tau}}$, area under the plasma concentration–time curve for the dosing interval; $T_{\text{max}}$, time to $C_{\text{max}}$; $C_{\text{24h}}$, plasma concentration at 24 h; $\tau_{0.5}$, terminal half-life.
response lasting 4.8 months (PFS 10.3 months). Other durable partial responses occurred in two further patients with RCC (PFS 12.4 and 10.7 months), two patients with lung cancer (PFS 14.0 and 3.0 months), two patients with malignant thymoma (PFS 15.3 and 9.0 months), and one patient with alveolar soft tissue sarcoma (PFS 22.6 months).

Five of the 24 patients with a best response of stable disease experienced PFS for >12 months. These were a patient with leiomyosarcoma (PFS 18.0 months), a carcinoid lung tumor (PFS 14.2 months), osteosarcoma (PFS 21.6 months), and two patients with colon cancer (PFS 12.0 and 13.5 months).

**Discussion**

SU14813 is a novel multitargeted TKI that is generally well tolerated. With SU14813 on schedule 4/1, DLTs of fatigue and hypertension were observed; the most common AEs were constitutional or gastrointestinal, including fatigue and diarrhea. A similar profile of AEs was also experienced with sunitinib, pazopanib, and motesanib in phase I trials, suggesting class effects of tyrosine kinase inhibition [9–14]. Hematologic AEs occurred most commonly in the higher dose groups but were rarely of grade 3/4 severity. Hair depigmentation was observed with SU14813 at doses of ≥100 mg/day in both schedules, which is a recognized consequence of KIT inhibition, consistent with target inhibition in vivo [6, 15]. The small numbers of patients in each dose group make it difficult to establish clear relationships between dose of study drug and incidence of the most common AEs. However, some events such as hypertension, rash, hair color change, and dysgeusia tended to be more frequently reported at doses ≥100 mg/day. The MTD of the 4/1 schedule was 200 mg/day.

As the intermittent schedule was well tolerated, the study also explored continuous dosing. Continued dosing may be clinically relevant to prevent tumor rebounds in fast-growing malignancies. Few DLTs were seen at 150 mg/day CDD during cycle 1, but many patients were unable to tolerate long-term treatment at this dose and required reduction to 100 mg/day CDD. The MTD and recommended phase II dose was established as 100 mg/day CDD, with the possibility of increasing to 150 mg/day CDD in patients who had not experienced grade ≥2 toxicity after two cycles.

Overall, the incidence of hypertension reported in the study appeared higher than that observed for similar targeted agents, suggesting the use of stricter cardiovascular inclusion criteria in future trials with SU14813. Caution should also be exercised in such studies when including patients with either a history of cardiovascular disease or prior/concurrent treatment with potentially cardiotoxic agents.

SU14813 median time to peak concentration ranged from ~1.4 to 4 h after single-dose administration and attained steady state by day 8. The exposure (AUCmax and Cmax) increased, in general, in a dose-proportional manner. The volume of distribution was significantly greater than total body water (42 l), indicating extensive penetration into peripheral tissues. SU14813 was eliminated slowly, with a mean terminal half-life ranging from ~9 to 34 h. However, further studies are required to fully define SU14813 pharmacokinetics in patients. Preclinical studies of SU14813 in mice determined a target plasma concentration of 100–200 ng/ml [6]. In this study, doses of SU14813 of ≥100 mg/day either in a 4/1 schedule or with CDD achieved plasma concentrations of SU14813 >100 ng/ml during the first 12 h after dosing. Continued dosing may be clinically relevant to prevent tumor rebounds in fast-growing malignancies.

Pharmacokinetics of SU14813 are different from those of sunitinib. Sunitinib is absorbed more slowly from the gastrointestinal tract than SU14813, with Cmax observed between 6 and 12 h after dosing [16]. Both sunitinib and SU14813 display dose-proportional pharmacokinetics with comparable clearance (34–62 l/h versus 27.3–110 l/h, respectively) and apparent volume of distribution values (2230 l versus 584–2046 l, respectively). Sunitinib and its active metabolite SU012662 have a terminal half-life of ~40–60 h and 80–110 h, respectively [16], whereas SU14813 is more rapidly eliminated (~9–34 h). Consequently, steady-state conditions for sunitinib and SU012662 are reached in 2 weeks [16], while SU14813 attains steady state after 8 days of administration.

Pharmacodynamic data in our study were based on small patient numbers and had high standard deviations. However, modulation of plasma sVEGFR-2 and sVEGFR-3 by SU14813 was consistent with effects reported for other class V/III TKIs targeting these receptors [8, 17, 18]. Although efficacy was not the primary end point of this study, SU14813 showed considerable clinical activity with
durable tumor responses and disease stabilization across a range of tumor types. These included renal cell and colorectal carcinoma and difficult-to-treat entities, such as refractory thymus carcinoma, soft tissue sarcoma, thyroid carcinoma, or cholangiocarcinoma. Of 65 patients in this typical phase I population who received doses ≥100 mg/day, 24 were on treatment after 6 months, of which 15 were on study after 1 year, 3 after 2 years, and 1 at 4 years. Most of these patients led active lives and many were working in their profession.

In summary, SU14813 demonstrated a manageable safety and tolerability profile. SU14813 showed encouraging single-agent activity with durable responses seen in a variety of tumor types. Two further trials with SU14813 are ongoing: a phase I trial in patients with solid tumors in combination with docetaxel, and a phase II single-agent trial in patients with metastatic breast carcinoma (clinicaltrials.gov: NCT00322517).

funding
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disclosure
WF has received research funding from Pfizer and has participated in advisory boards. NB holds stock as a Pfizer employee. RC holds stock in Pfizer and is an employee of Pfizer, the maker of SU14813, and is currently conducting research sponsored by the company. AA holds stock in Pfizer, the maker of SU14813, and is currently employed by Pfizer. DRS holds stock and options of Pfizer Inc. and is an employee of Pfizer Inc. GG, PL, IvDH, CB, and EB have declared no conflicts of interest.

references