Original Article

Phase II Trial of Continuous Once-Daily Dosing of Sunitinib as First-Line Treatment in Patients with Metastatic Renal Cell Carcinoma

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BACKGROUND: Sunitinib at 50 mg/day on the 4-weeks-on-2-weeks-off schedule is the current approved regimen for advanced/metastatic renal cell carcinoma (mRCC). Escudier et al reported that continuous, once-daily dosing with sunitinib 37.5 mg had a manageable safety profile and significant antitumor activity as second-line mRCC therapy. In this prospective, multicenter, phase II study, we evaluated the activity of continuous once-daily dosing with sunitinib 37.5 mg as first-line mRCC treatment. **METHODS:** One hundred nineteen treatment-naive patients with measurable mRCC received sunitinib. The primary endpoint was objective response; secondary endpoints included progression-free survival (PFS), safety, pharmacokinetic measurements, exploration of response biomarkers, and patient reported outcomes (PRO). **RESULTS:** Objective response rate (ORR) was 35.3%; median response duration was 10.4 months; 36% of patients had stable disease ≥12 weeks. Median PFS at 1 year was 9 months, and 1-year survival probability was 67.8%. The most common any-grade treatment-related adverse events (AEs) were diarrhea (50%) and hand-foot syndrome (43%); the most common grade 3-4 treatment-related AEs were hand-foot syndrome (13%), neutropenia (11%), and diarrhea (9%). Steady-state pharmacokinetics were reached within 3 weeks, with no disproportionate accumulation of sunitinib or its active metabolite throughout the study. No significant correlations between trough drug, active metabolite, or soluble protein levels and clinical response were observed. PRO was largely maintained, although fatigue appeared to worsen after treatment started, with improvement over time. **CONCLUSIONS:** Continuous once-daily dosing with sunitinib 37.5 mg was active with a manageable safety profile as first-line mRCC therapy, making this a feasible alternative dosing regimen. ***Cancer* 2012;118:1252–9.** © *2011 American Cancer Society.*

KEYWORDS: renal cell carcinoma, metastastic, sunitinib, continuous dosing, treatment-naive.

INTRODUCTION

Over the last few years, the clinical benefits of using targeted agents to treat patients with metastatic renal cell carcinoma (mRCC) have become increasingly clear,[1-7] leading to regulatory approval of several such agents globally. Although these targeted therapies have dramatically improved the prognosis of patients with advanced RCC, there is still much to be learnt about their optimal scheduling, sequencing, and potential for combination therapy.

Sunitinib malate (SUTENT; Pfizer Inc., New York, NY) is an orally administered receptor tyrosine kinase (RTK) inhibitor of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, and other RTKs.[8-10] In a randomized phase III trial, sunitinib, given at the recommended dose of 50 mg/day on schedule 4/2

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(4 weeks on treatment, 2 weeks off), was superior to interferon-alfa (IFN-α) as first-line therapy for mRCC.[11] Progression-free survival (PFS; the primary endpoint) was 11 months and 5 months in patients randomized to sunitinib and IFN-α, respectively ($P < .001$), and the objective response rate (ORR) was 47% and 12% ($P < 0.001$). Median overall survival was more than 2 years (26.4 months) in the sunitinib group, compared with 21.8 months in the IFN-α group.

Recently, Escudier et al[12] reported that sunitinib 37.5 mg, administered on a continuous, once-daily dosing regimen, has a manageable safety profile and significant antitumor activity as second-line mRCC therapy. The authors concluded that continuous administration of sunitinib 37.5 mg might be a useful alternative to intermittent treatment, providing flexibility in dosing, which could be explored in combination studies. Continuous dosing might also prove useful in patients who develop symptoms in the 2-week off-treatment period with the recommended schedule 4/2.

Here, we report the final results of an open-label, single-arm, multicenter, phase II trial of sunitinib given at 37.5 mg on a continuous dosing schedule as first-line therapy for mRCC (ClinicalTrials.gov: NCT00338884).

PATIENTS AND METHODS

Study Population

The study population comprised adults aged 18 years or older, with histologically confirmed RCC that had a component of clear cell histology, and evidence of metastases. Key eligibility criteria included no previous systemic therapy of any kind for RCC; resolution of all acute toxic effects of prior radiotherapy or surgical procedure to grade ≤1, based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0; evidence of unidimensionally measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST);[13] Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate liver, renal, and hematologic function. Patients were excluded if they had central nervous system (CNS) disease, or clinically significant cardiovascular events or disease during the preceding 12 months. All patients provided written, informed consent.

Study Design and Treatment

In this single-arm, open-label, multicenter, phase II trial, patients received oral sunitinib at a starting dose of 37.5 mg continuously once daily in the morning, without regard to meals, until disease progression or 1 year on study was completed. Patients with benefit after 1 year were offered sunitinib on a separate protocol. The protocol allowed dose interruption or reduction to 25 mg/day in the event of grade 3 or 4 treatment-related toxicity; the dose could be increased back to 37.5 mg/day in the absence of grade ≥2 hematologic or grade ≥1 nonhematologic treatment-related toxicity for 4 weeks. Discontinuation was recommended for patients with a dosing interruption of more than 4 weeks. No dose escalation (ie, to doses higher than 37.5 mg/day) was allowed. Treatment with other antitumor therapies during the trial, including chemotherapy, biological response modifiers, hormone therapy, or immunotherapy, was not permitted.

The primary endpoint was objective response, including confirmed complete response (CR) or partial response (PR) as determined using RECIST,[13] with a minor modification to accommodate standard practice in use of spiral computed tomograthy (CT) scan (ie, a reconstruction interval up to 8 mm). In the event spiral CT scan was used to assess tumors, the minimum lesion size qualifying as measurable was twice the reconstruction interval used and was at least 10 mm. Secondary endpoints included duration of response; PFS; the proportion of patients alive 1 year after starting treatment; safety; measurement of trough plasma levels of sunitinib and SU12662 (the primary active metabolite); exploration of soluble plasma biomarkers of response; and patient reported outcomes (PRO).

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and applicable local regulatory requirements and laws, and was approved by the institutional review board or independent ethics committee of each participating center.

Assessments

Tumor assessment was performed using imaging techniques (CT or magnetic resonance imaging) at baseline, at weeks 5 and 9, and then every 8 weeks thereafter until the end of treatment, as well as to confirm a response or if disease progression was suspected. Bone scans were required at baseline and if bone metastases were present or suspected at any time. Other evaluations included medical history; physical examination and assessment of ECOG performance status; hematology and blood chemistry tests; cardiac function (12-lead electrocardiogram); and adverse events (graded according to the NCI CTCAE version 3.0).

PRO was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale[14] and the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI) questionnaire, including its 9-item disease-related symptoms (FKSI-DRS) subscale.[15] In both instruments, higher scores indicate better outcomes.

Pharmacokinetic and Pharmacodynamic Methods

Blood samples for determination of trough plasma concentrations of sunitinib and SU12662, and for analysis of soluble proteins (VEGF and a soluble VEGFR-2 [sVEGFR-2]), were taken before dosing on day 1 of weeks 1, 3, 5, 7, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53.

Plasma samples were analyzed for sunitinib and SU12662 concentrations at Bioanalytical Systems, Inc. (West Lafayette, Ind) using a validated analytical assay (high-performance liquid chromatography tandem mass spectrometric method) in compliance with the sponsor's standard operating procedures. The lower limit of quantification for sunitinib and SU12662 was 1.00 ng/mL.

Sodium heparin plasma samples were assayed for VEGF and sVEGFR-2 using validated, sensitive, and specific quantitative sandwich immunoassay (ELISA) methods, at Alta Analytical Laboratory. Assay reproducibility expressed as coefficient of variation (CV)% of quality control samples ranged from 3.5% to 13.9% for VEGF and 5.3% to 7.5% for sVEGFR-2.

Statistical Analysis

A sample size of 120 patients was needed to detect a 37% ORR with a 95%, 2-sided confidence interval (CI) with a 9% half width. All patients receiving at least 1 dose of sunitinib were included in all analyses, with the exception of objective response and PRO, which also needed a baseline assessment of disease or a baseline PRO assessment, respectively. Time-to-event data were summarized using the Kaplan-Meier method. PFS was defined as the time from the date of first study dose to first documentation of objective tumor progression or death from any cause, whichever occurred first over 1 year of therapy. For patients who were alive and progression free, or who had received antitumor therapy other than sunitinib before progression, PFS data were censored on the day after the date of the last tumor assessment on study. For PRO, summary statistics of total scores and change from baseline scores on the FACIT-Fatigue, FKSI, and FKSI-DRS scales were calculated at each assessment time point. For all 3 measures, higher scores indicate better outcome. A mean change from baseline of 3 or more points in FACIT-Fatigue and FKSI scale scores was considered clinically meaningful.[15,16] Similarly, a mean change from baseline of 2 points was considered clinically meaningful for the FKSI-DRS scale score according to a study by Cella et al.[17] Statistical significance in the mean change from baseline was determined using the confidence interval approach: a 95% CI not containing 0 was considered statistically significant. No adjustments were made for multiple testing.

Potential relationships between plasma trough levels of sunitinib, SU12662 and total drug (sunitinib plus SU12662) and plasma soluble protein levels were explored by linear regression analysis. Correlation between trough plasma drug (sunitinib, SU12662, and total drug) levels and clinical response, and that between plasma VEGF and sVEGFR-2 levels (at baseline and for changes from baseline) and clinical response (CR, PR, stable disease [SD] $\geq$12 weeks, or progressive disease [PD]), were analyzed using a Wilcoxon rank sum test.

RESULTS

Between September 2006 and June 2009, 120 patients were enrolled from 12 sites in 6 countries. Of these 120 patients, 119 patients received treatment and were included in the safety analysis, whereas 118 patients were evaluable for efficacy (1 patient was excluded for a protocol violation after poststudy surgery determined that mRCC was not the primary tumor). The mean age was 57.5 years (range, 24-78), 76% were male and 42% Asian. Baseline patient characteristics are summarized in Table 1.

Treatment and Patient Disposition

Patients were treated with sunitinib for a median of 24.3 weeks (range, 1.0-53.7 weeks). At the time of analysis, 42 of the 119 treated patients (35%) had completed 1 year of therapy as per protocol and 77 patients (65%) had discontinued treatment (Table 2); the main reason for stopping treatment was disease progression in 44 patients (37%). A total of 44 patients (37%) had died. Fourteen patients (12%) died on study or within 28 days of their last sunitinib dose; 9 deaths were related to disease progression, 1 was considered related to sunitinib, and 3 deaths were related to other reasons; the cause of 1 death was

Table 1. Patient Characteristics at Baseline

Patient Characteristic	Sunitinib (N = 119)
Mean age (range), y	57.5 (24-78)
Male/female, n (%)	90/29 (76/24)
Race, n (%)	
White	54 (45)
Black	2 (2)
Asian	50 (42)
Other	13 (11)
ECOG performance status, n (%)	
0	63 (53)
1	56 (47)
Prior surgery, n (%)[a]	
No	6 (5)
Yes	112 (94)
Prior radiation therapy, n (%)	
No	104 (87)
Yes	15 (13)
Number of disease sites, n (%)[b]	
1	30 (25)
2	35 (29)
3	21 (18)
4	11 (9)
>4	20 (17)
Disease sites, n (%)	
Lung	84 (71)
Lymph nodes	43 (36)
Kidney	43 (36)
Liver	20 (17)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a] Data missing for one patient.
[b] Data missing for two patients.

unknown. The remaining 30 patients (25%) died during follow-up, from disease progression.

Efficacy

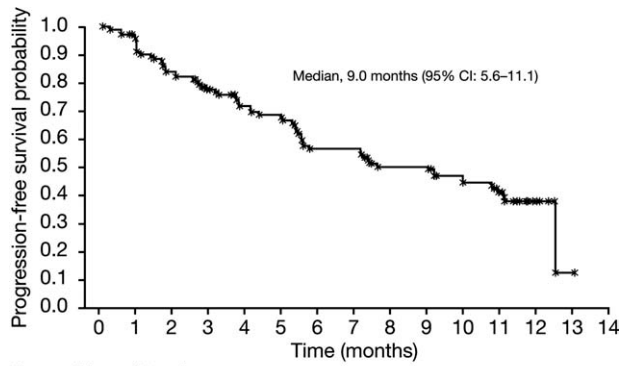
Of the 118 patients evaluable for efficacy, 2 patients were excluded due to inadequate baseline assessment, leaving 116 patients evaluable for tumor response. Forty-one patients had a confirmed PR, yielding an ORR of 35.3% (95% CI: 26.7-44.8%). The median duration of response was 10.4 months (95% CI: 7.4 months to "not reached"). Forty-two patients (36%) had SD $\geq$12 weeks, and the rate of clinical benefit (CR + PR + SD $\geq$12 weeks) was, therefore, 72%. Twenty-four patients (21%) experienced disease progression; response could not be determined in 6 patients (5%), and the remaining 3 patients died early (eg, did not have confirmed response).

Median PFS at 1 year was 9.0 months (95% CI: 5.6-11.1 months; Fig. 1). A total of 54 of 118 patients (46%) evaluable for PFS analysis were censored, and 32 of these 54 patients (27% overall) were in follow-up for progression.

Table 2. Treatment and Patient Disposition

	Sunitinib (N = 119)
Median duration of treatment (range), weeks	24.3 (1.0-53.7)
Mean actual daily dose intensity (range), mg	29.1 (9.4-37.5)
Mean relative dose intensity (range), %	77.6 (25-100)
Patients completing 1 year of therapy per protocol, n (%)	42 (35)
Patients still on treatment, n (%)	0
Patients with a dose interruption, n (%)	21 (18)
Patients with a dose reduction, n (%)	39 (33)
Patients who discontinued treatment early (ie, after <1 year), n (%)	77 (65)
Reasons for discontinuation, n (%)	
Progression/relapse	44 (37)
Treatment-related adverse event	12 (10)
Death	8 (7)
Consent withdrawn (for reason other than adverse event)	3 (3)
Global deterioration of health status	3 (3)
Other[a]	5 (4)

[a] Includes 1 patient lost to follow-up.



CI = confidence interval.
*One patient was excluded from the efficacy analyses due to a protocol violation.

Figure 1. This figure shows the Kaplan-Meier estimate of progression-free survival at 1 year (n = 118*).

At the time of analysis, 72 of 118 patients evaluable for efficacy (61%) were alive at 1 year after the start of treatment (2 patients were lost to follow-up), and the 1-year survival probability was 67.8% (95% CI: 59.2-76.3%).

Safety

The most commonly reported treatment-related adverse events were diarrhea (50%) and hand-foot syndrome (43%; Table 3) with the overall incidence of treatment-

Table 3. Treatment-Related Adverse Events of Interest and Those Reported in ≥10% of All Patients by Maximum NCI CTCAE Grade (n = 119)

Adverse Event	Number of Patients (%)		
	Grade 1-2	Grade 3-4	Total[a]
Diarrhea	49 (41)	11 (9)	60 (50)
Hand-foot syndrome	35 (29)	16 (13)	51 (43)
Fatigue	34 (29)	8 (7)	42 (35)
Anorexia	37 (31)	3 (3)	40 (34)
Mucosal inflammation	32 (27)	5 (4)	37 (31)
Dysgeusia	30 (25)	2 (2)	32 (27)
Nausea	27 (23)	3 (3)	30 (25)
Hypertension	26 (22)	3 (3)	29 (24)
Skin discoloration	26 (22)	0	26 (22)
Vomiting	21 (18)	4 (3)	25 (21)
Asthenia	16 (13)	8 (7)	24 (20)
Neutropenia	9 (8)	13 (11)	22 (18)
Anemia	10 (8)	9 (8)	19 (16)
Rash	19 (16)	0	19 (16)
Thrombocytopenia	9 (8)	8 (7)	17 (14)
Dyspepsia	16 (13)	0	16 (13)
Epistaxis	14 (12)	2 (2)	16 (13)
Stomatitis	16 (13)	0	16 (13)
Weight decreased	15 (13)	1 (1)	16 (13)
Yellow skin	15 (13)	0	15 (13)
Abdominal pain, upper	12 (10)	2 (2)	14 (12)
Abdominal pain	10 (8)	3 (3)	13 (11)
Hypothyroidism	5 (4)	2 (2)	7 (6)
Cardiac failure, congestive	0	1 (1)	1 (1)

Abbreviations: NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0).
[a] In total, 2 patients died with treatment-related adverse events (1 each of intracranial hemorrhage and dyspnea; data not shown).

related adverse events of grade 1-2 and 3-4 severity occurring in 32% and 64% of patients, respectively. The most commonly reported grade 3-4 treatment-related adverse events were hand-foot syndrome (13%), neutropenia (11%), and diarrhea (9%).

Treatment-related hypothyroidism of any grade severity was reported in 7 patients (6%), with 2 patients (2%) reporting grade 3-4 severity (note: this included 3 patients who presented with baseline hypothyroidism). One patient, a 78-year-old male who presented with baseline hyperlipidemia and hypertension, experienced grade 3 treatment-related congestive cardiac failure for which treatment was given but which led to sunitinib discontinuation.

In total, 12 patients (10%) discontinued sunitinib because of treatment-related adverse events, which included (in 1 patient each): congestive heart failure; fatigue; vomiting; hand-foot syndrome; renal failure; dyspnea; thrombocytopenia; intracranial hemorrhage; abdominal pain, nausea, and vomiting; mucosal inflammation; and gastric ulcer hemorrhage. Two patients died with treatment-related adverse events (one each of intracranial hemorrhage and dyspnea).

Pharmacokinetic and Biomarker Studies

A total of 116 patients were evaluable for pharmacokinetic analysis, with serum biomarker data available for 113 patients. After continuous daily dosing of sunitinib, the dose-corrected (reference dose: 37.5 mg) mean trough plasma concentrations (day 1 of weeks 3-53) for sunitinib, SU12662, and total drug (sunitinib plus SU12662) were within the ranges 37.5-55.6, 16.0-23.7, and 53.4-76.2 ng/mL, respectively. Steady state was reached within the first 3 weeks. Dose-corrected trough plasma concentrations were relatively constant between weeks, with no apparent disproportionate accumulation of sunitinib or SU12662 throughout the study.

Plasma levels of VEGF and sVEGFR-2 changed in response to treatment. The first on-treatment sample analyzed was collected at week 3 and showed increased VEGF levels, with a maximum 2-fold increase observed at week 9. VEGF levels remained elevated above baseline at all time points throughout the study. In contrast, plasma levels of sVEGFR-2 decreased by week 3 and reached a maximum reduction (45%) by week 13.

Drug levels and changes in mean plasma VEGF and sVEGFR-2 levels were significantly correlated ($P < .05$) during the majority of weeks assessed. Increases in plasma sunitinib, SU12662, and total drug levels were associated with increases in plasma VEGF levels, whereas plasma sVEGFR2 decreased with increasing drug concentrations.

There were no statistically significant correlations between median trough levels of sunitinib, SU12662, and total drug and either objective response or clinical benefit (data not shown). Similarly, neither baseline nor changes from baseline levels (at any time point) of plasma VEGF or sVEGFR-2 showed a significant association with clinical response (data not shown).

Patient Reported Outcomes

At each assessment point through up to 49 weeks of treatment, at least 91% of patients available for PRO assessment completed 1 or more questions on the FACIT-Fatigue and FKSI questionnaires, and at least 81% of patients completed at least 1 question on the end-of-treatment assessment.

The baseline mean FACIT-Fatigue score was 39.29, which was lower than the general US population's average score of 43.6 and comparable with that reported for nonanemic cancer patients (40.0),[18] suggesting that subjects

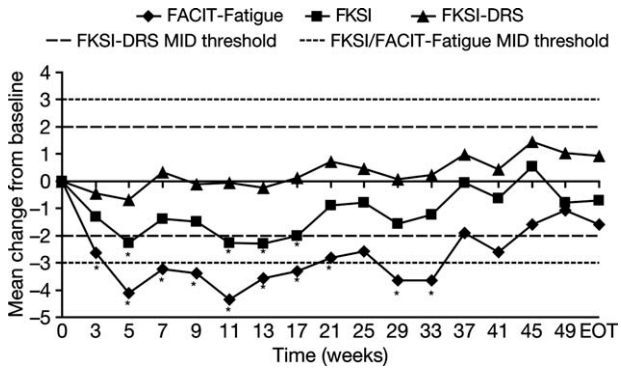


Figure 2. This figure shows mean change from baseline in FACIT-Fatigue, FKSI, and FKSI-DRS scores. *Indicates that the change from baseline was statistically significant as determined by the 95% confidence interval (CI) not containing 0. FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FKSI = Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index; FKSI-DRS = Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index disease-related symptoms; MID = minimally important difference; EOT = end of treatment (completers only).

included in the study were already experiencing clinically relevant fatigue before the initiation of sunitinib treatment. The mean fatigue level among patients receiving sunitinib treatment increased during treatment, as reflected by declining scores on the FACIT-Fatigue Scale (Fig. 2). The change from baseline was, at times, both statistically significant (95% CI not containing 0) and clinically meaningful ($\geq$3 points). However, there was a trend toward alleviation of fatigue during later treatment cycles for subjects who continued sunitinib for a longer period of time.

Kidney-related symptoms (as measured by FKSI; Fig. 2) deteriorated slightly during sunitinib treatment compared with baseline, although these changes from baseline did not exceed the clinically meaningful decline difference of 3 points. For patients treated longer with sunitinib, symptoms returned to baseline levels.

The mean FKSI-DRS domain score did not fluctuate greatly during sunitinib treatment compared with baseline, and showed an upward trend (symptom alleviation; Fig. 2). However, none of the changes was statistically or clinically significant.

DISCUSSION

In this study, continuous once-daily dosing with sunitinib 37.5 mg showed activity with a manageable safety profile in first-line mRCC therapy. The entry criteria for this study were very similar to those used in the pivotal, phase III, first-line trial in which sunitinib 50 mg was administered on an intermittent dosing schedule,[5,11] suggesting that the populations treated in the 2 trials may have been similar with respect to prognosis. The median PFS of 9.0 months in our study was shorter than that in the pivotal trial (11 months).[5,11] This shorter median PFS may have been the result of censoring progression data in 54 patients after only 1 year of assessment in this trial, which is a weakness of this study (as is lack of independent review of tumor scans) and introduces a bias toward early disease progression (eg, 27% of patients were in follow-up for progression). Comparable data on patients censored were not reported for the pivotal study, but the follow-up was clearly longer, as recently reported in the final analysis by Motzer et al,[11] where median duration of treatment with sunitinib was 11 months, and ranged from $<$1 to 41 months, compared with a median treatment duration of approximately 5.6 months (range, $<$1 to approximately 12.4 months) in the current study.

The efficacy results reported in this study are very similar to those reported by Escudier et al[12] with continuous sunitinib as second-line treatment of mRCC, after failure of cytokine therapy, with the median PFS similar (8.2 months; 95% CI, 6.4-8.4), as was the 1-year survival probability (72%; 95% CI, 62.1-79.3%). The prognosis of patients enrolled in the second-line study was relatively good, with only 7% categorized as poor based on MSKCC risk factors, and the distribution of ECOG performance status was similar to that in the present study. Although all patients started treatment at sunitinib 37.5 mg/day, dose escalation to 50 mg/day was permitted in the Escudier et al[12] trial. This resulted in a higher median daily dose intensity than that achieved in the study reported here (37.5 mg, range, 25.4-48.8, vs 29.1 mg, range, 9.4-37.5, respectively), and it is possible that the higher drug exposure contributed to the relatively good efficacy for a population receiving second-line treatment.

In the present study, sunitinib given on a continuous dosing schedule as first-line therapy for mRCC was generally well tolerated with manageable toxicity, and the majority of patients did not need dose reduction or a delay in treatment. Compared with the initial report of the pivotal phase III trial, and after a similar median duration of treatment (5.6 months vs 6 months in the phase III trial), dosing delays were less frequent in the present study (18% vs 38%) but a similar proportion of patients required a dose reduction (33% vs 32%).[5] The proportion of patients discontinuing treatment because of an adverse event was comparable (10% vs 8% in the phase III trial). The safety

profile was broadly similar to that reported by Escudier et al[12] in the second-line setting, as well as in sunitinib studies of mRCC using the intermittent schedule 4/2.[11,19,20] However, the 13% incidence of grade 3 hand-foot syndrome (there were no grade 4 cases) was notably higher than that reported in the phase III study (5%),[5] and was also higher than using continuous daily dosing in the second-line setting (9%).[12] Several studies of sunitinib in Asian patients with mRCC have reported a relatively high incidence of grade 3/4 hand-foot syndrome (13-16%),[21-23] and it is plausible that the comparable rate in the present study may be related to the ethnicity of the study population, of whom 42% were Asian.

There were no clinically significant changes for the overall FKSI measure or the disease-specific measure (FKSI-DRS), indicating that patient-reported disease-related symptoms were largely maintained during sunitinib treatment. Although fatigue symptoms, as measured by the FACIT-Fatigue Scale, appeared to worsen after the start of sunitinib treatment, the symptoms did not deteriorate further and remained stable over time, and only 1 patient discontinued therapy due to fatigue. For subjects who remained on sunitinib treatment for a longer period of time, fatigue tended to be no worse than at initiation of treatment.

Pharmacokinetic analyses showed that after continuous once-daily dosing with sunitinib, steady-state drug levels were reached within the first 3 weeks of treatment, with no disproportionate accumulation of either sunitinib or its active metabolite, SU12662, throughout the study. This is consistent with pharmacokinetic findings from prior studies with sunitinib continuous daily dosing.[24,25]

Our data indicated the absence of a correlation between plasma drug concentrations and VEGF or sVEGFR-2 with clinical response. Although previous studies have shown similar changes in plasma levels of both soluble proteins on treatment of mRCC with sunitinib,[26,27] conclusions about their behavior as biomarkers of pharmacodynamic activity have varied. For example, DePrimo et al[26] found significantly larger changes in VEGF and sVEGFR-2 (as well as sVEGFR-3) in patients with mRCC who achieved an objective tumor response to intermittent dosing with sunitinib 50 mg compared with those who had stable or progressive disease. However, Kontovinis et al[27] found that sVEGFR-2 had no predictive value and, furthermore, observed that the increase in plasma VEGF was significantly lower in patients with clinical benefit compared with that in patients with progressive disease—exactly the opposite effect to that reported by DePrimo et al,[26] although the analysis was based on a different grouping of patients (clinical benefit vs progressive disease as opposed to objective response vs stable plus progressive disease). Our analysis was based on the same grouping of patients as that used by Kontovinis et al,[27] and also found no predictive value for VEGFR-2. Unlike Kontovinis et al,[27] we, in addition, failed to observe a predictive effect for VEGF. The inconsistency in results between the 3 studies may in part be related to this difference in grouping. However, another plausible explanation is the limited power of analysis of these relatively small studies; in our study, only 16 patients had progressive disease at baseline, dwindling to 2 patients by week 13, while the study of Kontovinis et al[27] had just 9 patients with progressive disease. These findings emphasize the need for additional, larger studies to elucidate the potential role of VEGF and sVEGFR-2 as biomarkers for response to sunitinib.

In our study, we showed that continuous once-daily dosing with sunitinib 37.5 mg is a feasible alternative dosing regimen to 50 mg intermittent dosing in the first-line treatment of mRCC. However, only a randomized trial comparing the 2 schedules can provide a rigorous comparison of their relative efficacy and safety, such as the recently reported randomized, phase II study of 292 treatment-naive mRCC patients by Motzer et al.[28] In that trial, there was no statistically significant difference in time to tumor progression (TTP), the primary endpoint ($P = .090$); in addition, tumor response, overall survival, and the adverse event and PRO profiles were similar between the 2 schedules, supporting the results of our study. Nonetheless, the authors concluded that the goal of treatment should be adherence to the approved 50 mg on schedule 4/2, based on the trend toward superior TTP (and PFS) with intermittent dosing and its statistically superior time to deterioration ($P = .034$), a composite endpoint of death, progression, and patient-reported, disease-related symptoms.

Based on the findings of the randomized trial and our study, we can conclude that, although sunitinib 50 mg on schedule 4/2 may be the optimum regimen, daily dosing may still, in fact, be a viable and/or preferred option in select circumstances, for example, when patients experience tumor regrowth or symptom flare during the 2-week off-treatment period with schedule 4/2.

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CONFLICT OF INTEREST DISCLOSURES

C.H. Barrios reported receiving advisory board fees from Pfizer. S.-H. Lee reported receiving honoraria and expert testimony fees from Pfizer. S. Hariharan, B.A. Martell, J. Yuan, A. Bello, Z. Wang, and R. Mundayat are full-time employees of Pfizer. No other authors reported any financial disclosures.

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