

Sunitinib in Patients With Metastatic Renal Cell Carcinoma

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THERE IS AN URGENT NEED FOR more active agents for the treatment of metastatic renal cell carcinoma (RCC).¹ The 5-year survival rate for metastatic RCC is estimated to be less than 10%.² RCC is highly resistant to chemotherapy² and only a limited subset of patients ($\leq 20\%$) benefit from cytokine therapy (high-dose interleukin 2 [IL-2] and/or interferon- α)³⁻⁶ (TABLE 1). Overall median survival following progression after cytokine therapy is approximately 10 to 13 months,⁷ and no effective treatment is available for patients whose disease progresses after an initial response or who do not respond to cytokine therapy. Second-line treatment with the alternative cytokine produces responses in less than 5% of patients.⁸

For editorial comment see p 2537.

Context Current treatment options for metastatic renal cell carcinoma (RCC) are limited and there is a need to identify novel and effective therapies. Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor, which has shown activity in an initial study of cytokine-refractory metastatic RCC patients.

Objective To confirm the antitumor efficacy of sunitinib as second-line treatment in patients with metastatic clear-cell RCC, the predominant cell type of this malignancy.

Design, Setting, and Patients Open-label, single-arm, multicenter clinical trial. Patients were enrolled between February and November 2004, with follow-up continuing until disease progression, unacceptable toxicity, or withdrawal of consent. The reported data apply through August 2005. Patients (N=106) had metastatic clear-cell RCC, which had progressed despite previous cytokine therapy.

Intervention Repeated 6-week cycles of sunitinib, 50 mg per day given orally for 4 consecutive weeks followed by 2 weeks off per treatment cycle.

Main Outcome Measures Assessment of clinical response, degree of tumor regression on imaging studies using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Primary end point was overall objective response rate (complete plus partial). Secondary end points were progression-free survival and safety. Response was evaluated by independent third-party core imaging laboratory and by treating physicians (investigator assessment).

Results All 106 patients received sunitinib and were included in the intent-to-treat population for safety analyses. Of these, 105 patients were evaluable for efficacy analyses. The objective response rate according to an independent third-party assessment resulted in 36 patients with partial response (34%; 95% confidence interval, 25%-44%), and a median progression-free survival of 8.3 months (95% confidence interval, 7.8-14.5 months). The most common adverse events experienced by patients were fatigue in 30 (28%) and diarrhea 21 (20%). Neutropenia, elevation of lipase, and anemia were the most common laboratory abnormalities observed in 45 (42%), 30 (28%), and 27 (26%) patients, respectively.

Conclusion The results of this trial demonstrate the efficacy and manageable adverse-event profile of sunitinib as a single agent in second-line therapy for patients with cytokine-refractory metastatic clear-cell RCC.

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There are several subtypes of RCC, but over 80% of all tumors contain clear-cell carcinoma histology. A better understanding of the genetic abnormalities associated with clear-cell RCC has helped identify new targets for therapy. Studies have demonstrated that sporadic (nonhereditary) clear-cell RCC has similar genetics to von Hippel-

Lindau syndrome (an inherited disorder that carries an increased risk for vascular tumors including RCC). In both sporadic clear-cell RCC tumors and patients with the von Hippel-Lindau syn-

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drome, genetic deletions, mutations, or chemical modifications result in non-functional or reduced levels of von Hippel-Lindau gene product.^{9,10} Loss of von Hippel-Lindau protein function leads to elevated levels of hypoxia-inducible factor α and consequent overexpression of vascular endothelial growth factor and platelet-derived growth factor.¹¹ These growth factors promote tumor angiogenesis, which likely contributes to the hypervascularity of RCC.¹¹ Thus, inhibition of vascular endothelial growth factor and platelet-derived growth factor signaling pathways may, in part, reverse the physiologic consequences of losing von Hippel-Lindau protein function and inhibit tumor progression.¹¹

Sunitinib malate (Pfizer Inc, La Jolla, Calif) is a novel, oral, multitargeted tyrosine kinase inhibitor that specifically inhibits vascular endothelial growth factor receptor (types 1-3) and platelet-derived growth factor receptor (α and β), as well as other tyrosine protein kinases.¹²⁻¹⁵ An evaluation of sunitinib in metastatic RCC was of priority based on this profile of tyrosine kinase inhibition (FIGURE 1), and was further supported by responses in RCC patients observed in a phase 1 trial.¹⁶

In an initial phase 2 study of sunitinib in cytokine-refractory metastatic RCC patients, an objective response rate of 40% was observed in 63 patients (95% confidence interval [CI], 28%-53%), which is unprecedented in this patient population.¹⁷ The multicenter phase 2 trial described in this article was conducted to confirm the antitumor efficacy of single-agent sunitinib in patients with metastatic clear-cell RCC whose disease was refractory to 1 prior cytokine therapy. An analysis of response and progression-free survival for combined data from the initial trial and this phase 2 study is also reported.

METHODS

Patients

Between February and November 2004, 106 patients were enrolled in the study at 11 centers (listed at the end of this article; range of accrual 2-18 patients/cen-

Table 1. Historical Experience With Systemic Therapy for Metastatic Renal Cell Carcinoma

	No. of Patients	No. of Studies	Objective Response Rate, %	Reference
Chemotherapy	1347	51	5	Motzer and Russo, ³ 2000
Interferon- α	1042	29	12	Wirth, ⁴ 1993
IL-2 high-dose, bolus	537	10	19	Law et al, ⁵ 1995
IL-2 other, inpatient	650	22	15	
IL-2 low-dose, outpatient	104	6	20	
Interferon- α plus IL-2	607	23	19	Vogelzang et al, ⁶ 1993

Abbreviation: IL, interleukin.

ter) in the United States. Eligibility criteria included provision of written informed consent; participant age of 18 years or older; prior nephrectomy; histological confirmation of clear-cell RCC with metastases; measurable disease; failure of 1 cytokine therapy (IL-2, interferon- α , or combination) due to disease progression (radiographic confirmation); Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate organ function (based on tests of hematologic, hepatic, renal, and cardiac function). Eligibility required prior cytokine therapy to be discontinued for at least 4 weeks before study entry. Patients were excluded if they had brain metastases or significant cardiac events within the 12 months prior to study drug administration.

Study Design and Treatment

Study was approved by the institutional review board at the participating centers and was performed under the Declaration of Helsinki and Good Clinical Practice Guidelines.

The multicenter study followed an open-label, single-arm design. The primary objective was to determine the antitumor efficacy (response rate) of single-agent sunitinib in patients with metastatic RCC refractory to 1 prior cytokine therapy (interferon- α , IL-2, or the combination). Secondary objectives included evaluations of duration of response, progression-free survival, overall survival, and safety.

Patients received sunitinib at a starting dose of 50 mg per day in repeated 6-week cycles for 4 consecutive weeks followed by 2 weeks off treatment. Sunitinib was self-administered orally once daily without regard to meals. Dose re-

duction for toxicity was allowed (to 37.5 mg/d then 25 mg/d) depending on the type and severity of toxicity encountered. Sunitinib treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Evaluation

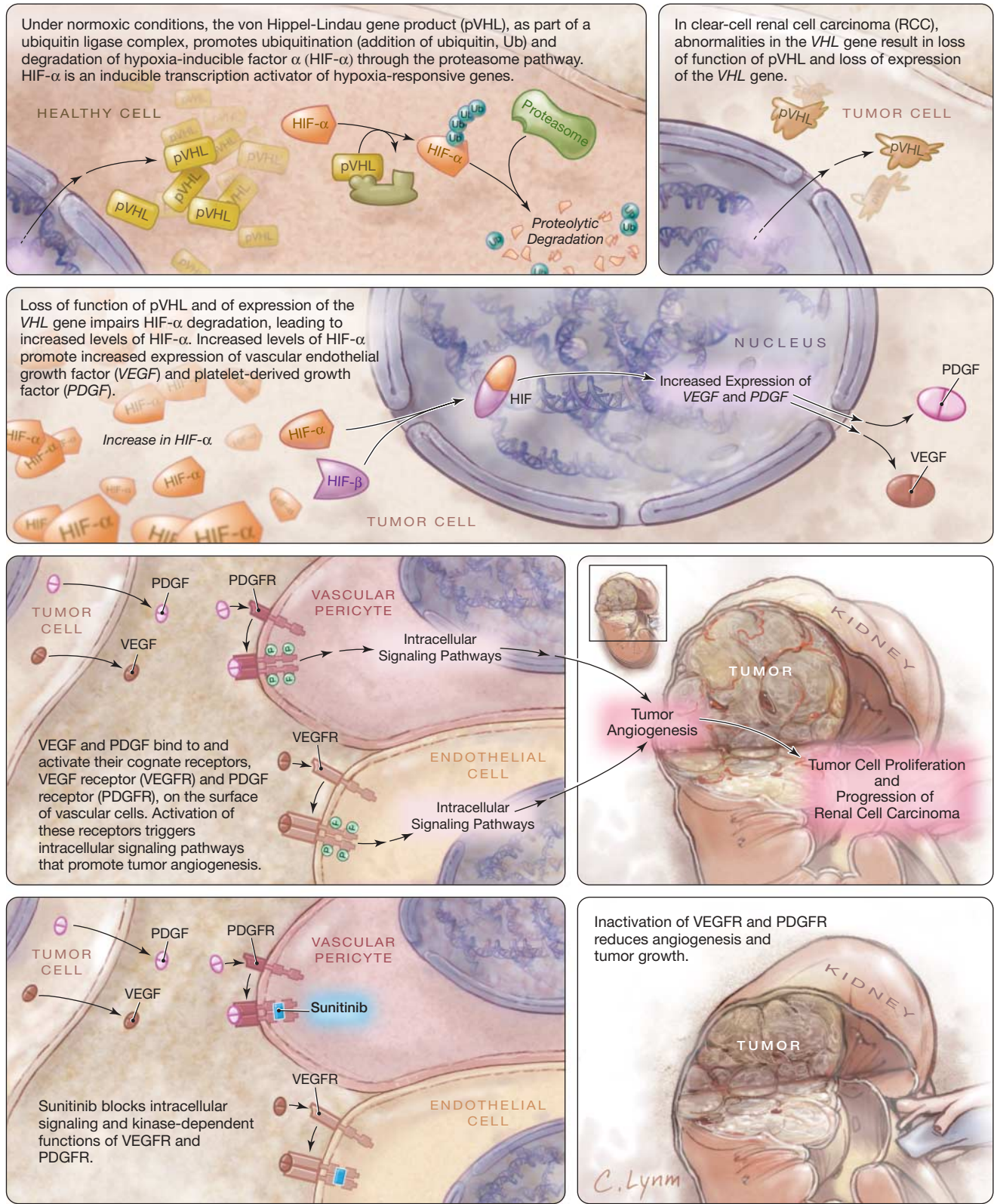
Baseline evaluations included medical history and physical examination; tumor assessments (tumor imaging with computed tomography [CT] or magnetic resonance imaging [MRI] scans of the chest, abdomen, and pelvis; CT/MRI brain scan; and bone scan); assessment of ECOG performance status; laboratory measurements (hematology, clinical chemistry, coagulation, urinalysis, and pregnancy test); 12-lead electrocardiogram; and assessment of left ventricular ejection fraction by multigated acquisition scan. Multigated acquisition scans were obtained to assess heart function since decline in heart function had been raised as a possible adverse effect of sunitinib in preclinical studies and a phase 1 trial.¹⁴

Assessment of Efficacy and Safety

The primary study end point was overall objective response rate, defined as the proportion of patients with confirmed complete or partial responses. Clinical response (complete response, partial response, stable disease, and progressive disease) was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST)¹⁸ using CT/MRI scans and bone scans (if bone metastases were present at baseline) after each cycle for the first 4 cycles and every other cycle thereafter until the end of treatment.

The responses were assessed by treating physicians (investigator

Figure 1. Role of VHL Protein in Clear-Cell RCC and Site of Activity of Sunitinib



assessment) and also by a third-party core imaging laboratory where the scan images of all patients were read by 2 radiologists for each time point (independent third-party assessment).

According to RECIST, the longest dimension of each tumor deposit is measured (ie, a unidimensional measurement), and the sum of these measurements is used to evaluate response assessment. At baseline, tumor lesions were categorized by size as measurable or nonmeasurable. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total were identified as target lesions and recorded and measured at baseline, and other nonmeasurable lesions were recorded as nontarget lesions. The sum of the longest diameter for all target lesions was calculated and reported as the baseline sum. A partial response represented at least a 30% decrease in the sum of the longest diameter of target lesions, using the baseline sum as the reference and stable nontarget lesions. Progressive disease represented at least a 20% increase in the sum of the longest diameter of target lesions (taking as a reference the smallest sum of the longest dimensions recorded since the treatment started), progression of nontarget lesions, or the appearance of 1 or more new lesions. Stable disease represented neither a decrease for a partial response nor an increase for progressive disease. Complete response represented the disappearance of all lesions. To be assigned a partial or complete response, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies performed 4 weeks or longer after the criteria were first met.¹⁸

Secondary efficacy end points were duration of response, progression-free survival, and overall survival. Duration of response is defined as the time from first documentation of objective response to progressive disease or death due to any cause during the on-study period, with patients being censored on the last day of the on-study period if no progression or death has occurred. The on-study period is defined as the time of first study dose until the last on-treatment tu-

mor assessment or 28 days after last study drug, whichever is greater. Progression-free survival is defined as the time from the start of treatment to progressive disease or death due to any cause during the on-study period (whichever comes first), with censored observations handled as described previously. Overall survival is the time from start of treatment to death due to any cause, or to last follow-up for patients who did not die.

Other assessments conducted throughout the study included: adverse events (severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE, Version 3.0]); ECOG performance status; and hematology and clinical chemistry profiles. All blood samples were sent to a central laboratory for analysis. Cardiac function was assessed by electrocardiogram on day 28 of cycle 1 and as clinically indicated, and by multigated acquisition scan on day 28 of every even cycle until the end of treatment. According to the CTCAE, adverse events are assessed by severity and denoted as grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening; and grade 5, death.

Statistical Evaluation

Assuming a historical objective response rate (the primary end point in this trial) of less than 5%, a sample size of 100 patients would provide 90% power for testing that the objective response rate for sunitinib was 15% or more (overall 2-sided significance level of .05, exact binomial test). If 11 or more responses were observed, then the lower bound of the 95% CI would exclude 5%. Median survival CIs are based on the sign test.¹⁹ The number of patients who achieved an objective response was summarized along with the corresponding exact 2-sided 95% CI. Time-to-event variables were estimated using the Kaplan-Meier method.²⁰

An analysis of response and progression-free survival according to investigator assessment for combined data from the initial trial and this phase 2 study is also reported, since investigator assessment was exclusively used in the first trial. The eligibility and treat-

Table 2. Patient Baseline Characteristics

Characteristics	No. (%)
Total intent-to-treat population	106 (100)
Sex	
Men	67 (63)
Women	39 (37)
Age, median (range), y	56 (32-79)
ECOG performance status	
0	58 (55)
1	48 (45)
Prior systemic treatment	
Interferon-alfa	47 (44)
IL-2	50 (47)
Interferon-alfa plus IL-2	9 (9)
Prior radiation therapy	20 (19)
Main sites of metastatic disease	
Lung	86 (81)
Liver	29 (27)
Bone	27 (26)
Lymph nodes	62 (59)
No. of disease sites	
1	13 (12)
2	38 (36)
≥3	55 (52)
No. of MSKCC risk factors for second-line therapy*	
0	61 (58)
≥1	45 (42)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IL, interleukin; MSKCC, Memorial Sloan-Kettering Cancer Center.

*Risk factors associated with shorter survival in second-line therapy were low serum hemoglobin, elevated serum corrected calcium, and poor performance status.⁷

ment plan for this trial was nearly identical to that of the current study and has been previously described.¹⁷ This prior study differed in eligibility from the current trial in that prior nephrectomy was not required and any RCC histology was allowed, but nearly 90% of patients enrolled had clear-cell RCC.¹⁷

In order to examine the potential influence of selected baseline patient characteristics on response and progression-free survival, data from this trial were combined with the data from the initial phase 2 study mentioned previously. The pretreatment clinical features of responders vs nonresponders were compared using the 2-tailed Fisher exact test. The relationship between progression-free survival and each of the selected baseline patient characteristics was then analyzed using the log-rank test. A significance level of 10% was used as the criterion for the inclusion of a variable in a multivariate Cox proportional hazards model. A backward elimination method, with a .05 significance level for removing explanatory variables, was then applied to identify the final set of relevant factors. Interactions and further

model assessments were not performed because the focus of this analysis was to get a better sense of whether similar risk factors were found in this patient population as in previous analyses. Statistical analyses were performed using SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

All 106 patients (100%) received at least 1 dose of sunitinib (TABLE 2). The median age was 56 years. The lungs were the most prevalent site of metastases and 55 (52%) patients had 3 or more disease sites. One patient enrolled with a diagnosis of clear-cell RCC was withdrawn from the study because a repeat biopsy after treatment was initiated resulted in a diagnosis of cancer different than clear-cell RCC. This patient is included in the safety analysis but excluded from efficacy analyses.

Efficacy

Objective Response Rate. Of the 105 evaluable patients, the independent third-party core imaging laboratory assessment of response resulted in 36 patients with partial response (TABLE 3) (34%; 95% CI, 25%-44%), and an additional 30 patients (29%) with stable disease for 3 or more months.

According to the investigator assessment, 45 (43%) patients achieved a partial response and 1 (1%) patient achieved a complete response resulting in an overall response rate of 44% (95% CI, 34%-53%). An additional 23 patients (22%) had stable disease for 3 or more months (Table 3).

Tumor images from a patient included in this study are shown as an example of a partial response according to RECIST criteria (FIGURE 2), defined as a 30% or greater decrease in summed unidimensional measurements of all target tumor lesions on CT scan imaging

obtained during therapy compared with baseline. The longest diameter of a right adrenal mass measured 3 cm at baseline. A CT scan obtained 2.5 months after the baseline assessment showed the right adrenal mass as measuring 1.8 cm in longest diameter. The sum of all target lesions represented at least a 30% decrease in the sum of the longest diameter of the target lesions. A follow-up scan 1 year after baseline demonstrated durability with the sum of all target lesions maintaining at least a 30% decrease from baseline.

Duration of Response. At the time of data analysis, only 10 patients of the 36 responders identified by independent third-party review of response had progressed or died; therefore, median duration of response has not been reached. Of the 46 patients who experienced objective responses (complete or partial) identified by the investigators, 12 patients subsequently developed disease progression and 34 responders remain progression-free, including one patient with a complete response for over 10 months. The median duration of response for the 46 patients was 10 months (95% CI, 8 months–not calculable).

Progression-Free and Overall Survival. Fifty-six of the 105 patients (53%) had developed disease progression or died on study. The median progression-free survival based on independent third-party assessment of response was 8.3

Table 3. Best Response to Sunitinib Treatment

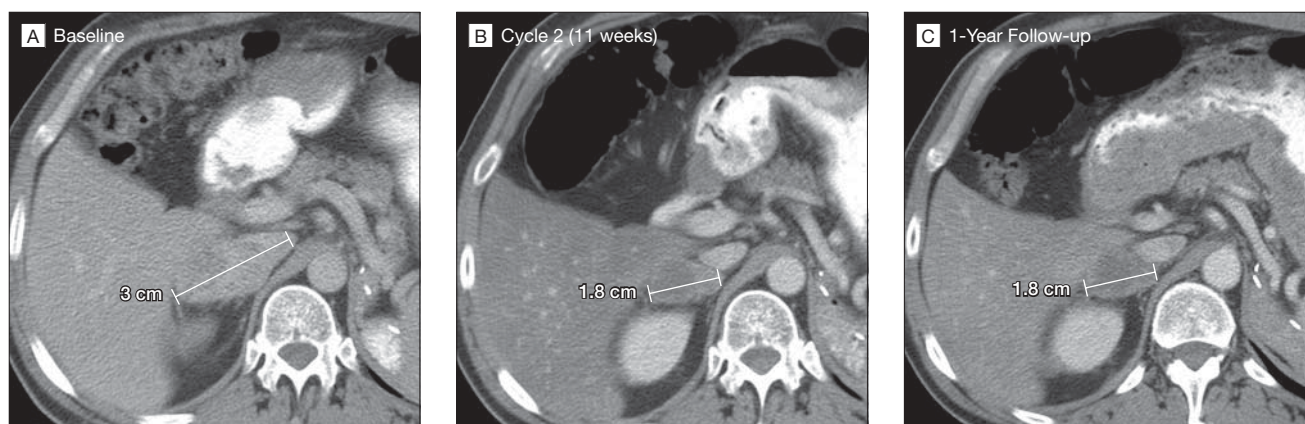
Response	Patients Assessed, No. (%) [*]	
	Independent Third Party [†]	Investigator [‡]
Complete response	0	1 (1)
Partial response	36 (34)	45 (43)
Stable disease for ≥ 3 mo	30 (29)	23 (22)
Progressive disease, stable disease for <3 mo, or not evaluable	39 (37)	36 (34)

^{*}N = 105 (1 patient enrolled with a diagnosis of clear-cell renal cell carcinoma was withdrawn after a repeat biopsy showed a diagnosis of a different type of cancer).

[†]Assessed by independent third-party core imaging laboratory.

[‡]Assessed by treating physician.

Figure 2. Example of Partial Response According to RECIST Guidelines in a Patient Treated With Sunitinib



Abbreviation: RECIST indicates Response Evaluation Criteria in Solid Tumors.

months (95% CI, 7.8-14.5 months) (FIGURE 3). The median progression-free survival based on investigator assessment was 8.1 months (95% CI, 5.5-10.4 months).

Seventy-four of the evaluable patients were still alive at the time of data analysis. The median overall survival has not been reached and the 6-month survival is 79% (95% CI, 70%-86%).

Safety Results. The median number of completed 6-week treatment cycles was 5 (range, 0-11 cycles), equivalent to 7 months. Diarrhea and fatigue were the most commonly reported treatment-related adverse events (TABLE 4). Diarrhea was managed by oral hydration and oral antidiarrheal agents (eg, loperamide hydrochloride) as needed. Other adverse events included stomatitis, hand-foot syndrome (characterized by painful lesions on the palms and soles), and hypertension (Table 4). Selected laboratory abnormalities are also listed in Table 4. Neutropenia was reported, but there were no reports of associated fever or sepsis. Elevated serum concentrations of lipase were not associated with clinical signs or symptoms of pancreatitis.

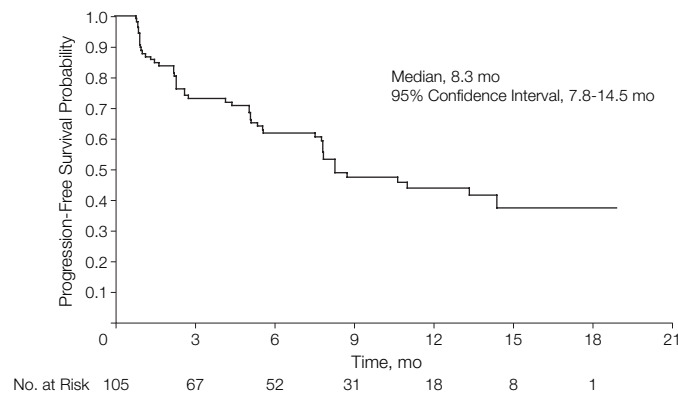
Eight patients (4.7%) experienced a decline in left ventricular ejection fraction as assessed by multigated acquisition scans obtained at regular intervals during therapy. Of these, 5 patients had a decrease from baseline of 20% or more and to less than the lower limit of normal, but there were no reports of clinical signs and symptoms suggesting congestive heart failure.

Of the 31 patients who died, 10 died within 28 days of their last dose of study medication, and 1 of these on-study deaths (myocardial infarction) was considered as possibly related to treatment with sunitinib. This patient had clear-cell RCC metastatic to the mediastinum and lung with symptoms of episodic dyspnea. Following 28 days of sunitinib therapy, the patient presented with symptoms and medical imaging studies consistent with acute cholecystitis. The patient experienced severe dyspnea, was diagnosed with an acute myocardial infarction, and died shortly thereafter.

Pooled Analysis of 2 Studies in RCC. The demographics and efficacy data were combined from this study and the initial phase 2 trial¹⁷ (TABLE 5). A pooled analysis of prognostic features for response and progression-free survival based on investigator assessment

was performed on the total evaluable patient population of 168. Overall, 71 patients (42%) were responders; 40 (24%) had stable disease of 3 or more months' duration; and 57 (34%) had stable disease less than 3 months, progressive disease, or were not evalu-

Figure 3. Progression-Free Survival by Independent Third-Party Core Imaging Laboratory Assessment (N = 105)



One patient enrolled with a diagnosis of clear-cell renal cell carcinoma was withdrawn after a repeat biopsy showed a diagnosis of a different type of cancer.

Table 4. Most Commonly Reported Treatment-Related Adverse Events and Selected Laboratory Abnormalities by Grade*

Adverse Event	Patients (N = 106)			Total‡
	Grade 2	Grade 3	Grade 4†	
Treatment-related adverse events, No. (%)				
Fatigue	18 (17)	12 (11)	0	30 (28)
Diarrhea	18 (17)	3 (3)	0	21 (20)
Dyspepsia	16 (15)	1 (1)	0	17 (16)
Hypertension	11 (10)	6 (6)	0	17 (16)
Hand-foot syndrome	9 (8)	7 (7)	0	16 (15)
Nausea	14 (13)	0	0	14 (13)
Stomatitis	9 (8)	5 (5)	0	14 (13)
Anorexia	12 (11)	1 (1)	0	13 (12)
Mucosal inflammation	12 (11)	1 (1)	0	13 (12)
Vomiting	11 (10)	0	0	11 (10)
Dysgeusia	10 (9)	0	0	10 (9)
Extremity pain	6 (6)	1 (1)	0	7 (7)
Rash	3 (3)	0	0	3 (3)
Laboratory abnormalities, No. (%)				
Neutropenia§	28 (26)	15 (14)	2 (2)	45 (42)
Lipase increased	12 (11)	15 (14)	3 (3)	30 (28)
Anemia	21 (20)	4 (4)	2 (2)	27 (26)
Thrombocytopenia¶	16 (15)	6 (6)	0	22 (21)

*Occurring in at least 20% of patients.

†All severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0); see "Assessment of Efficacy and Safety" section for descriptions of adverse event grades.

‡Patients with grade 2-4 adverse events.

§Neutropenia graded by lowest neutrophil count measured during treatment as follows: grade 2, <1500-1000/mm³; grade 3, <1000-500/mm³; and grade 4, <500/mm³.

||Anemia graded by lowest hemoglobin measured during treatment as follows: grade 2, <10-8 g/dL; grade 3, <8.0-6.5 g/dL; and grade 4, <6.5 g/dL.

¶Thrombocytopenia graded by lowest platelet count measured during treatment as follows: grade 2, <75 000-50 000/mm³; and grade 3, <50 000-25 000/mm³.

able. The median progression-free survival for all 168 patients was 8.2 months (95% CI, 7.8-10.4) (FIGURE 4). The median progression-free survival in patients who achieved a complete or partial response was 14.8 months (95% CI, 10.9-24.2). The median progression-free survival for patients with best response of stable disease of 3 or more months was 7.9 months (95% CI, 5.5-8.2).

The pretreatment clinical features of responders were compared with those of nonresponders (patients with disease stabilization as best response or pro-

gression). There was a higher proportion of patients among responders with a normal serum hemoglobin vs a baseline value below the lower limit of normal compared with nonresponders (78% vs 43%; $P < .001$, 2-tailed Fisher exact test). Also, a higher proportion of patients had an ECOG performance status of 0 vs 1 among responders compared with nonresponders (66% vs 45%; $P = .008$, Fisher exact test). Anemia and poor performance status were previously reported to be associated with a shorter survival with second-line treatment of metastatic RCC.⁷

A univariate analysis was performed to examine the relationship between pretreatment clinical features and progression-free survival (TABLE 6). A longer progression-free survival was observed in patients with favorable ECOG performance status, normal serum hemoglobin, as well as several other selected clinical features. In the multivariate analysis, a low hemoglobin was found to be the independent predictor of a shorter progression-free survival (hazard ratio 0.37; 95% CI, 0.25-0.56; $P < .001$). Further model development and assessment of features predictive of survival will be done when additional follow-up for these patients is collected.

Table 5. Characteristics and Treatment Outcome for Patients Included in the Pooled Analysis

Characteristics	Patients		
	Trial 1 (N = 63)	Trial 2 (N = 105)*	Pooled Analysis (N = 168)
Sex, No. (%)			
Men	43 (68)	66 (63)	109 (65)
Women	20 (32)	39 (37)	59 (35)
Age, median, y	60	56	57
ECOG performance status, No. (%)			
0	34 (54)	57 (54)	91 (54)
1	29 (46)	48 (46)	77 (46)
Renal cell carcinoma histology, No. (%)			
Clear cell	55 (87)	105 (100)	160 (95)
Other	8 (13)	0 (0)	8 (5)
Prior nephrectomy	58 (92)	105 (100)	163 (97)
Prior systemic treatment, No. (%)†			
Interferon-alfa	35 (56)	47 (45)	82 (49)
Interleukin-2	19 (30)	49 (47)	68 (40)
Interferon-alfa plus interleukin-2	9 (14)	9 (9)	18 (11)
Prior radiation therapy	25 (40)	20 (19)	45 (27)
Main sites of metastatic disease, No. (%)			
Lung	51 (81)	86 (82)	137 (82)
Liver	10 (16)	28 (27)	38 (23)
Bone	32 (51)	27 (26)	59 (35)
No. of disease sites, No. (%)			
1	8 (13)	13 (12)	21 (13)
2	16 (25)	38 (36)	54 (32)
≥3	39 (62)	54 (51)	93 (55)
MSKCC risk factors for second-line therapy, No. (%)‡			
0	34 (54)	61 (58)	95 (57)
≥1	29 (46)	44 (42)	73 (43)
Best response, No. (%)			
Complete response	0 (0)	1 (1)	1 (<1)
Partial response	25 (40)	45 (43)	70 (42)
Stable disease ≥3 mo	17 (27)	23 (22)	40 (24)
Progressive disease, stable disease <3 mo, or not evaluable	21 (33)	36 (34)	57 (34)
Median progression-free survival, mo	8.7	8.1	8.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center.
 *One patient enrolled with a diagnosis of clear-cell renal cell carcinoma was withdrawn after a repeat biopsy showed a diagnosis of a different type of cancer.
 †May have included additional agents other than cytokines.
 ‡Motzer et al 2004.⁷

COMMENT

Metastatic RCC is one of the most challenging malignancies to treat, showing nearly universal resistance to all cytotoxic chemotherapeutic agents and limited sensitivity to radiation therapy. Cytokine therapy with interferon-alfa or IL-2 produces response in approximately 15% of patients, and a multitude of new agents previously studied as second-line therapy after cytokines failed to show any evidence of clinical benefit.

Clear-cell RCC was selected as a tumor type for initial clinical study with sunitinib, based on the inhibitory properties against vascular endothelial growth factor receptor and platelet-derived growth factor receptor. The high expression of proangiogenic growth factors to these receptors is a consequence of genetic abnormalities that characterize clear-cell RCC, and are believed to contribute to RCC tumor growth and angiogenesis. The initial phase 2 trial of sunitinib conducted in 63 patients showed a 40% response rate, a median time to tumor progression of 8.7 months, and good tolerability.¹⁷

The results of this trial confirm that sunitinib given once daily according to a 4 weeks on/2 weeks off schedule has substantial antitumor effects against metastatic clear-cell RCC. Of the 105 evaluable patients, 36 patients achieved partial response (34%; 95% CI, 25%-44%), and a median progression-free

survival of 8.3 months as evaluated by the independent third-party core imaging laboratory (resulting in a value considerably longer than expected in this clinical setting).

The sunitinib adverse event profile was acceptable as an orally administered outpatient therapy. Diarrhea and fatigue were the most commonly reported treatment-related adverse events, followed by gastrointestinal complaints. Other commonly reported treatment-related adverse events were stomatitis, hand-foot syndrome, and hypertension. In most instances, symptoms improved with dose modification; however, in 12 patients (11%), sunitinib was discontinued due to adverse events. In some instances, the adverse events and laboratory abnormalities were consistent with conditions associated with advanced metastatic RCC.

The 2 trials had similar eligibility and treatment plans and assessed antitumor activity in patients as second-line therapy following progression to standard cytokine treatment. When the data were combined, the response rate according to investigator assessment was 42% in 168 evaluable patients, and an additional 24% had stable disease of 3 or more months' duration. The objective responses observed in these 2 trials were partial responses with the exception of 1 patient who experienced a complete response. The median progression-free survival observed for all 168 assessable patients was 8.2 months.

These assessments of antitumor activity compare favorably with the response rate observed for conventional therapies (Table 1).⁴⁻⁶ Patients with metastatic RCC who progress to cytokine therapy are generally managed by supportive care (including radiation therapy) or treatment in clinical trials of experimental agents. The median time to progression for patients treated in clinical trials with other experimental agents as second-line therapy or receiving supportive care is estimated to be between 2 and 4 months.^{7,21,22}

Sunitinib is one of several agents (including sorafenib and bevacizumab) that target the inhibition of proangiogenic

growth factor activity and show activity in clinical trials against metastatic clear-cell RCC. The data from these trials^{21,22} confirm that the approach is a valid therapeutic strategy for clear-cell RCC. Moreover, since systemic therapy options for RCC have been limited to cytokines, these therapies represent a new paradigm in the management of this notoriously elusive malignancy.

The conduct of the current study as a single-arm trial was justified based on the high response rate observed in the first trial and the lack of effective therapy previously established in the second-line setting to be used as a comparator arm for a randomized trial. Since the response rate for sunitinib as a second-line therapy is more than double that reported with cytokines in first-line treatment, a com-

Figure 4. Progression-Free Survival by Investigator Assessment (Pooled Population, N=168)

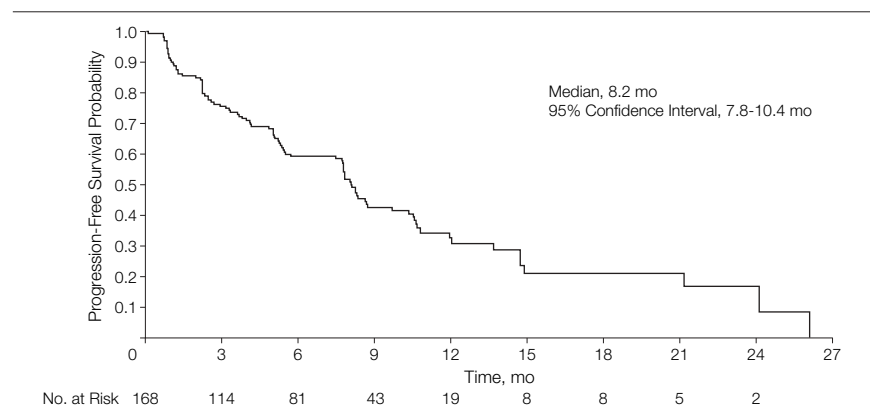


Table 6. Pretreatment Predictors of Progression-Free Survival for Patients Treated With Sunitinib (N = 168)

	No. of Patients (N = 168)*	No. Progression-Free or Alive	Progression-Free Survival, mo		P Value
			Median	95% Confidence Interval	
Hemoglobin					<.001
≥Lower limit of normal	97	52	10.9	8.7-14.8	
<Lower limit of normal	71	18	4.2	2.6-5.5	
Corrected calcium					.23
≤10 mg/dL	162	69	8.2	7.8-10.4	
>10 mg/dL	6	1	3.6	1.5-12.0	
Eastern Cooperative Oncology Group performance status					.002
0	91	42	10.4	8.2-12.1	
1	77	28	5.1	2.8-8.1	
Liver metastases					.03
Yes	38	11	5.5	4.1-8.4	
No	130	59	8.8	7.9-12.0	
Lung metastases					.65
Yes	137	56	7.9	5.8-9.8	
No	31	14	8.8	5.4-13.8	
No. of disease sites					.04
0 or 1	21	12	13.8	7.9-21.2	
2 or ≥3	147	58	7.9	5.5-8.7	
Alkaline phosphatase					.06
≤120 U/L	123	57	8.3	7.9-10.6	
>120 U/L	45	13	5.5	2.3-10.7	

*Pooled analysis population.

parison of sunitinib to standard cytokine therapy was undertaken. A phase 3 randomized trial that recently completed accrual of over 700 patients aims to compare the efficacy of sunitinib vs interferon- α as first-line therapy for metastatic clear-cell RCC. The outcome will define the role of sunitinib in first-line therapy. Response to targeted therapy for other malignancies with agents such as gefitinib and imatinib mesylate have been linked to specific mutations in the tumors.^{23,24} Studies to assess the relationship between response and genetic abnormalities and proangiogenic growth factor pattern in patients with metastatic renal carcinoma are under way.

CONCLUSIONS

The results of this trial demonstrate the efficacy of sunitinib as a single agent in second-line therapy for patients with cytokine-refractory metastatic clear-cell RCC. The initial observation of antitumor activity for sunitinib has been confirmed in a larger trial. Sunitinib as a first-line therapy for metastatic clear-cell RCC is currently being investigated vs interferon α in a randomized phase 3 study.

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Author Contributions: Dr Motzer, as principal investigator of this study, had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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