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Randomized Phase II Study of Multiple Dose Levels of CCI-779, a Novel Mammalian Target of Rapamycin Kinase Inhibitor, in Patients With Advanced Refractory Renal Cell Carcinoma

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ABSTRACT

Purpose
To evaluate the efficacy, safety, and pharmacokinetics of multiple doses of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma (RCC).

Patients and Methods
Patients (n = 111) were randomly assigned to receive 25, 75, or 250 mg CCI-779 weekly as a 30-minute intravenous infusion. Patients were evaluated for tumor response, time to tumor progression, survival, and adverse events. Blood samples were collected to determine CCI-779 pharmacokinetics.

Results
CCI-779 produced an objective response rate of 7% (one complete response and seven partial responses) and minor responses in 26% of these advanced RCC patients. Median time to tumor progression was 5.8 months and median survival was 15.0 months. The most frequently occurring CCI-779–related adverse events of all grades were maculopapular rash (76%), mucositis (70%), asthenia (50%), and nausea (43%). The most frequently occurring grade 3 or 4 adverse events were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%). Neither toxicity nor efficacy was significantly influenced by CCI-779 dose level. Patients were retrospectively classified into good-, intermediate-, or poor-risk groups on the basis of criteria used by Motzer et al for a first-line metastatic RCC population treated with interferon alfa. Within each risk group, the median survivals of patients at each dose level were similar.

Conclusion
In patients with advanced RCC, CCI-779 showed antitumor activity and encouraging survival and was generally well tolerated over the three dose levels tested.

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 3% of all adult malignancies [1] and 2% of all cancer-related deaths [2]. Systemic chemotherapy produces few and only transient tumor responses in patients with metastatic RCC [3]. High-dose interleukin-2 (IL-2) produces tumor responses in 15% to 20% of patients, with nearly half of all responses persisting for greater than 5 years. In phase II trials that led to the approval of high-dose IL-2 in the United States, the median survival was 16.3 months [4]. Unfortunately, this therapy is associated with severe toxicity [5], necessitating inpatient administration and limiting its use to highly selected patients treated at a few established treatment centers. Interferon alfa (IFN-α) has produced modest survival benefits in some phase III trials; however, few patients achieve durable benefit [5-17]. Low-dose IL-2 regimens, even when combined with IFN-α, have been generally less active than high-dose IL-2 therapy [18]. There are no established therapies for pa-

tients who experience relapse after, or are refractory to, IL-2 and/or IFN-α therapy, and such patients generally have a poor prognosis.

CCI-779 is a novel mammalian target of rapamycin (mTOR) kinase inhibitor. It was shown to bind with high affinity to the immunophilin FKBP [19], and this complex inhibits mTOR kinase activity as evidenced by inhibition of phosphorylation of the eukaryotic translation initiation factor 4E binding protein-1 and the 40S ribosomal protein p70 S6 kinase, the primary downstream effectors of mTOR [20-22]. These CCI-779–induced changes in proteins downstream of mTOR lead to G_1 phase cell cycle arrest [23].

The upstream activator of mTOR is the serine-threonine kinase, Akt. Akt activity, in turn, is regulated by PI3-kinase and the *PTEN* tumor suppressor gene [24]. In *PTEN* heterozygous mice with uterine and adrenal medullary tumors, treatment with CCI-779 produces significant reductions in tumor size [25], which suggest that CCI-779 may be useful in the treatment of human tumors that contain mutations in *PTEN*.

Although mutations in *PTEN* have not been detected in RCC, *PTEN* gene expression is often downmodulated [26,27]. In addition, the mTOR pathway appears to be involved in the development of a hereditary form of RCC seen in patients with tuberous sclerosis. mTOR-mediated downstream signaling appears to be inhibited by a complex composed of tuberin and hamartin, the products of tuberous sclerosis complex (*TSC*)*-2* and *TSC-1* genes, respectively [28]. In states of nutrient sufficiency, Akt phosphorylates tuberin, inactivating the tuberin-hamartin suppressor complex and enabling cell growth and proliferation to proceed [29,30]. Mutations in *TSC-1* or *TSC-2* release mTOR inhibition under all conditions. These mutations have been found in tuberous sclerosis, indicating that failure to inhibit mTOR-mediated downstream signaling is likely to be a critical component of the pathway leading to RCC development in patients with this disease.

In addition, the genetics and pathophysiology of RCC suggest that the inhibition of mTOR might produce other salutary effects. Sporadic RCC is associated with the loss of function of the von Hippel Lindau (*VHL*) tumor suppressor gene by mutation, deletion, or hypermethylation. As a component of an E3 ubiquitin ligase, the VHL protein normally targets the oxygen-sensitive transcription factors hypoxia-inducible factor 1-alpha (HIF-1α) and HIF-2α for destruction by the proteasome [31]. Loss of VHL function prevents the degradation of these factors, leading to their accumulation and increased expression of HIF-regulated proteins such as vascular-endothelial growth factor (VEGF), PDGF, TGFβ, and other angiogenic and growth stimulatory molecules [32]. mTOR activation increases *HIF-1*α gene expression at both the levels of mRNA translation and protein stabilization [33]. Thus, inhibition of mTOR by CCI-779 could also prevent the enhanced angiogenesis associated with sporadic RCC and loss of VHL function [34].

In a phase I study in patients with advanced solid tumors, CCI-779 was administered at doses ranging from 7.5 to 220 mg/m^2 as a weekly 30-minute infusion [35]. CCI-779 was well tolerated over a wide range of doses, with the most frequently occurring drug-related adverse events being skin toxicity and mucositis. One patient with advanced RCC who received 15 mg/m^2 CCI-779 and one patient with metastatic breast cancer who received 220 mg/m^2 had partial tumor responses. Pharmacokinetic evaluations indicated that sirolimus was a major metabolite of CCI-779 and exposure to both CCI-779 and sirolimus increased less than proportionally with increasing dose. Analysis of the exposure obtained with dosages based on body-surface area indicated that dose normalization did not improve variability in patients over that seen with flat doses. Therefore, to further characterize the relationships between dose and both efficacy and toxicity, patients with advanced RCC in our study were randomly assigned to receive treatment with flat doses of either 25, 75, or 250 mg CCI-779.

PATIENTS AND METHODS

Patients

Patients with advanced refractory RCC were randomly assigned to receive one of three dose levels of CCI-779 between April and October 2000. Eligible patients had histologically confirmed advanced RCC and either had received previous therapy for advanced disease or were not considered appropriate candidates for first-line IL-2–based therapy.

Patients were required to have bidimensionally measurable disease (both diameters of the tumor $\geq$ 1 cm) and to have documented disease progression. They had to be at least 18 years of age; have adequate hematologic, renal, and hepatic function (absolute neutrophil count [ANC] $\geq$ 1,500/μL, platelet count $\geq$ 100,000/μL, hemoglobin $\geq$ 8.5 g/dL, serum creatinine $\leq$ 1.5 $\times$ the upper limit of normal or calculated creatinine clearance $\geq$ 60 mL/min, bilirubin levels $\leq$ 1.5 $\times$ upper limit of normal, AST levels $\leq$ 3 $\times$ upper limit of normal or $<$ 5 $\times$upper limit of normal in patients with liver metastases); and have serum cholesterol $\leq$ 350 mg/dL and serum triglycerides $\leq$ 300 mg/dL. Patients also had to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and a life expectancy of at least 12 weeks.

Patients were excluded if they had a history of CNS metastases or were receiving hepatic enzyme-inducing anticonvulsants; surgery or local radiotherapy within 3 weeks or chemotherapy, biologic therapy, or investigational drug use within 4 weeks of treatment start; prior malignancy, other than basal cell or squamous cell carcinoma of the skin, within 3 years or a history of systemic treatment for prior malignancy; active infection; known HIV infection; use of immunosuppressive agents including systemic corticosteroids; significant cardiovascular disease including unstable angina or myocardial infarction within 6 months of treatment start or a history of life-threatening arrhythmia; or hypersensitivity to macrolide antibiotics. Women who were pregnant, nursing, or of childbearing potential and not using an effective contraceptive method also were excluded.

The study was conducted according to the Declaration of Helsinki and its amendments. The study protocol was approved by

institutional review boards of the participating institutions, and all patients gave written informed consent.

Treatment

Patients were randomly assigned to receive 25, 75, or 250 mg CCI-779 as a weekly 30-minute intravenous infusion. Treatment continued until evidence of disease progression or unacceptable toxicity. During the course of this study, pretreatment with diphenhydramine 25 to 50 mg was given approximately 30 minutes before the start of each CCI-779 infusion to try to prevent acute hypersensitivity reactions. If a patient developed a hypersensitivity reaction despite this pretreatment, a histamine H_2-receptor antagonist could also be administered.

The National Cancer Institute Common Toxicity Criteria, version 2.0, was used to grade toxicity. CCI-779 dose modifications were made as follows. A decrease in ANC to between 750 and 1,000/μL or platelet count to between 50,000 and 80,000/μL, or grade 3 nonhematologic adverse event (AE) resulted in a 25% dose reduction. A decrease in ANC to less than 750/μL or platelet count less than 50,000/μL, or grade 4 nonhematologic AE resulted in a 50% dose reduction. Patients were allowed two dose reductions. If continued toxicity required withholding treatment for more than 2 consecutive weeks, the patient was removed from additional treatment.

Evaluation of Patients

Patients underwent clinical evaluation at baseline and at 4-week intervals during the course of therapy. Tumor size assessments were made at 8-week intervals. Response was defined using standard bidimensional measurements in accordance with WHO guidelines for complete response (CR), partial response (PR), and stable disease (SD). In addition, minor response (MR) was defined as a $\geq$ 25% decrease but less than 50% decrease in the sum of the products of the two greatest perpendicular diameters of all measurable lesions. Two observations not less than 4 weeks apart were required to confirm CR or PR; confirmation of MR was not required. Progressive disease was defined as the appearance of new lesions or an increase $\geq$ 25% (over the minimum measurement) in the sum of the products.

Statistical Considerations

The primary efficacy end point of this study was objective tumor response rate (the percentage of patients with CR or PR). In addition, the percentage of patients with CR, PR, or MR, or SD $\geq$ 24 weeks was determined. The primary efficacy analysis was based on the intent-to-treat population (n = 111). The number of patients chosen for the study was based on mainly clinical considerations. Assuming a 15% dropout rate, approximately 105 eligible patients were to be randomly assigned to have at least 30 assessable patients per treatment arm. If the true objective tumor response rate was 25%, the probabilities that the 95% CIs would not include the spontaneous remission rates of 0.8% [36] to 7% [37] were 0.998 and 0.80, respectively. These probabilities were reduced to 0.95 and 0.29, respectively, if the true response rate was 15%.

All patients were considered assessable for tumor response if they completed the 8-week tumor assessment. Patients who died or experienced disease progression before the first 8-week tumor evaluation were considered assessable but nonresponders. Patients were assessable for safety if they received at least one dose of CCI-779.

Time to tumor progression (TTP) was measured as the interval from the date of first CCI-779 dose until the first date of documented PD. Survival was measured from the date of first CCI-779 dose until the date of death or the last date that a censored patient was known to be alive. Results for survival and time to tumor progression were analyzed according to Kaplan-Meier estimates and compared using the log-rank test. Incidences of AEs among dose groups were compared using the Fisher's exact test. The data cutoff date for reporting tumor response, TTP, and AEs was August 12, 2002. The data cutoff date for reporting survival was June 9, 2003.

Pharmacokinetic Assessment

CCI-779 and sirolimus, a major metabolite, were measured in whole blood samples of patients. Blood samples were drawn for full pharmacokinetic profiling from a subset of patients at 0 (predose), 0.5 (end of infusion), 1, 2, 6, 24, 72, 96, and 168 hours during weeks 1 and 4 of treatment. Concentrations of CCI-779 and sirolimus were measured using a modification of a validated high-performance liquid chromatography–mass spectrometry–mass spectrometry procedure (Taylor Technology Inc, Princeton, NJ) [38].

Data were analyzed using both compartmental (for CCI-779) and noncompartmental (for sirolimus) analysis techniques [39]. Compartmental model fitting for CCI-779 was performed using a two-compartment model with zero-order infusion and solved using the ADAPTII software package, Release 4 (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA). This approach was chosen to permit an evaluation of population pharmacokinetics with data from all patients (to be reported in a separate publication). Noncompartmental analysis for sirolimus was performed using the SAS version 8.1 (SAS Institute, Cary, NC) application on the Unix operating system. The following pharmacokinetic parameters were determined: C_{max}, the peak observed concentration; t_{max}, the time to C_{max}; $t_{1/2}$, terminal half-life; AUC, area under the concentration-versus-time curve; CL, total body clearance; Vd_{ss}, steady-state volume of distribution; AUC_{ratio}, the uncorrected ratio of sirolimus to CCI-779 AUCs; and AUC_{sum}, the algebraic sum of CCI-779 and sirolimus AUCs.

RESULTS

Patient Characteristics

A total of 111 patients were enrolled onto this trial, with 36, 38, and 37 patients randomly assigned to receive 25, 75, and 250 mg CCI-779, respectively. Demographic characteristics are listed in Table 1. The median age of the total patient population was 57 years and was similar for the individual dose groups. Fewer patients in the 250-mg dose group had an ECOG PS of 1 than did patients in the 25-mg and 75-mg dose groups. Patients had extensive disease and were heavily pretreated: 83% of patients had two or more sites of metastases, with lung as the most common site, and 51% had received two or more prior immunotherapy or chemotherapy regimens.

Summary of CCI-779 Treatment

Treatment information is listed in Table 2. The total population received a median of 19 doses of CCI-779 and was on study for a median of 5.6 months. The median number of doses of CCI-779 and the median months of

Table 1. Patient Characteristics

Characteristic	CCI-779 Dose Level							
	Total (n = 111)		25 mg (n = 36)		75 mg (n = 38)		250 mg (n = 37)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	57		55		58		57	
Minimum	17		40		17		40	
Maximum	81		79		78		81	
Sex								
Male	77	69	24	67	32	84	21	57
Female	34	31	12	33	6	16	16	43
ECOG PS								
0	39	35	12	33	9	24	18	49
1	72	65	24	67	29	76	19	51
No. of sites of metastases*								
1	19	17	8	22	4	11	7	19
2	38	35	7	19	16	43	15	42
≥ 3	52	48	21	58	17	46	14	39
Site of metastases†								
Lung	83	75	29	81	29	76	25	68
Lymph node	37	33	9	25	17	45	11	30
Bone	26	23	13	36	10	26	3	8
Liver	22	20	9	25	5	13	8	22
Prior therapy								
Immunotherapy or chemotherapy	101	91	32	89	36	95	33	89
Interleukins	94	85	30	83	34	90	30	81
Interferon	50	45	18	50	16	42	16	43
Nephrectomy	89	80	27	75	31	82	31	84
Radiotherapy	39	35	14	39	12	32	13	35
No. of prior immunotherapy or chemotherapy regimens								
0	10	9	4	11	2	5	4	11
1	44	40	17	47	15	40	12	32
2	26	23	6	17	10	26	10	27
≥ 3	31	28	9	25	11	29	11	30

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*Two patients, one in the 75-mg and one in the 250-mg group, did not have these data reported.
†With or without other sites.

therapy decreased as the dose level increased. These differences can be attributed, at least in part, to more frequent dose withholding because of toxicity in patients receiving the higher dose levels. The median amount of CCI-779 received per week and cumulatively was 22 and 456 mg for the 25-mg dose group, 54 and 977 mg for the 75-mg dose group, and 171 and 3,412 mg for the 250-mg dose group, respectively.

Efficacy

One patient with diffuse lung metastases at the 250-mg dose level had a CR. This patient remains disease free well into his third year and continues with CCI-779 treatment. Two, three, and two patients in the 25-, 75-, and 250-mg dose groups, respectively, had PRs (Table 3). Thus, the objective response rate (CR + PR) was 7% for the total population (95% CI, 3.2 to 13.7). An additional 29 patients (26%) had MRs. For the total patient population, 51% had CR, PR, or MR, or SD ≥ 24 weeks.

Median TTP was 5.8 months for the total patient population and 6.3, 6.7, and 5.2 months for patients in the 25-, 75-, and 250-mg dose groups, respectively (Fig 1). Median survival was 15.0 months for the total patient population, and 13.8, 11.0, and 17.5 months for patients in the 25-, 75-, and 250-mg dose groups (Fig 2). The probability of survival at 2 years was 29% for the total patient population and 24%, 26%, and 36% for patients in the 25-, 75-, and 250-mg dose groups, respectively.

Safety

Of the 111 patients enrolled in this study, 110 received CCI-779 and were evaluated for safety. The most common CCI-779–related AEs of all grades were maculopapular rash (76%), mucositis (70%), asthenia (50%), and nausea (43%) (Table 4). Grade 3 or 4 CCI-779–related AEs that occurred with an overall frequency ≥ 5% included hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%) (Table 5). There were no statisti-

Table 2. Treatment of RCC Patients With CCI-779

Treatment Parameter	CCI-779 Dose Level			
	Total (n = 110)	25 mg (n = 36)	75 mg (n = 38)	250 mg (n = 36)
No. of doses administered				
Median	19	23	18	15
Minimum	1	1	2	2
Maximum	87	87	74	72
Median months from first dose to study conclusion*	5.6	6.6	5.8	4.1
95% CI	4.1 to 6.9	3.7 to 9.0	3.7 to 7.6	3.5 to 6.7
% patients with ≥ 1 dose reduction	54	36	66	58
Amount of CCI-779 received per week, mg				
Median	54	22	54	171
Minimum	3	3	13	59
Maximum	250	26	75	250
Amount of CCI-779 received, mg				
Total	1,005	456	977	3,412
Minimum	25	25	150	500
Maximum	10,909	1,644	4,050	10,909

Abbreviation: RCC, renal cell carcinoma.
*Kaplan-Meier estimates.

cally significant differences in the percentages of patients in the different dose groups who had either grade 1 to 4 or grade 3 to 4 CCI-779–related AEs.

Six patients were reported to have had possible nonspecific pneumonitis, including five at the 75-mg dose level and one at the 25-mg dose level. Of these, two were withdrawn from additional treatment and four were re-treated, with two patients experiencing recurrent pneumonitis.

Reasons for dose reductions included thrombocytopenia (20% of all patients), mucositis (16%), hypertriglyceridemia (5%), and neutropenia (1%). Twenty-one patients (five, seven, and nine in the 25-, 75-, and 250-mg dose groups, respectively) discontinued treatment because of CCI-779–related AEs. Maculopapular rash (five patients) was the most frequent reason for treatment discontinuation. No patients died from CCI-779–related AEs.

Pharmacokinetics

The pharmacokinetic parameters of CCI-779 and sirolimus, a major metabolite of CCI-779, in whole blood are reported for 16 patients after their initial dose of CCI-779. Mean values for each dose group are reported (Table 6).

For CCI-779, C_{max} and AUC values increased in a less-than-proportional manner with increasing dose. High-

Table 3. Tumor Response Rates of RCC Patients Treated With CCI-779

Response	CCI-779 Dose Level							
	Total (n = 111)		25 mg (n = 36)		75 mg (n = 38)		250 mg (n = 37)	
	No.	%	No.	%	No.	%	No.	%
CR	1	0.9	0	0	0	0	1	2.7*
PR	7	6.3	2	5.6	3	7.9	2	5.4
CR/PR	8	7.2	2	5.6	3	7.9	3	8.1
95% CI	3.2 to 13.7		0.7 to 18.7		1.7 to 21.4		1.7 to 21.9	
MR†	29	26.1	5	13.9	13	34.2	11	29.7
SD ≥ 8 weeks, < 24 weeks	23	20.7	8	22.2	6	15.8	9	24.3
SD ≥ 24 weeks	19	17.1	12	33.3	5	13.2	2	5.4
CR/PR/MR/SD ≥ 24 weeks	56	50.5	19	52.8	21	55.3	16	43.2
95% CI	40.8 to 60.1		35.5 to 69.6		38.3 to 71.4		27.1 to 60.5	
PD	22	19.8	6	16.7	9	23.7	7	18.9
Unknown	10	9.0	3	8.3	2	5.3	5	13.5

Abbreviations: RCC, renal cell carcinoma; CR, complete response; PR, partial response; MR, minor response; SD, stable disease, PD, progressive disease.
*Confirmation was after the date of data cutoff.
†No confirmation was required for MR. Unconfirmed PR was considered MR.

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