Published in final edited form as:

Cancer. 2012 April 1; 118(7): 1868–1876. doi:10.1002/cncr.26429.

Phase I trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma

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Abstract

Background—Simultaneous inhibition of the vascular epithelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathway may improve treatment response in advanced renal cell carcinoma (RCC). Everolimus, an oral mTOR inhibitor, and sunitinib, an oral tyrosine kinase inhibitor (TKI) targeting VEGF are standard agents in the management of metastatic RCC.

Methods—Sequential cohorts of 3 to 6 patients with advanced RCC received dose escalated combinations of sunitinib (37.5 or 50 mg daily, 4 weeks on / 2 weeks off) with everolimus (2.5–5 mg daily or 20–30 mg weekly). Dose-limiting toxicities (DLTs) were assessed in the first 6-week cycle to determine MTD. Pharmacokinetic profiles were obtained.

Results—20 patients (13 clear cell and 7 non-clear cell RCC) were enrolled in 5 cohorts. Daily everolimus was not tolerated when combined with sunitinib; the first 2 patients on the 2nd cohort suffered DLTs. With weekly everolimus, the MTD was 30 mg everolimus on days 7, 14, 21, and 28, plus 37.5 mg sunitinib on days 1–28 of a 42-day cycle; however, chronic treatment was associated with grade 3 and 4 toxicities. A schedule of 20 mg everolimus weekly/37.5 mg sunitinib was tolerated as chronic therapy. Five patients (25%) had confirmed partial responses, 3 had non-clear cell RCC. No unexpected accumulation of everolimus, sunitinib, or N-desethyl sunitinib was observed.

Conclusions—The combination everolimus and sunitinib is associated with significant acute and chronic toxicities and is only tolerated at attenuated doses. Responses were observed in non-clear cell and clear cell RCC.

Keywords

renal cell carcinoma; everolimus; sunitinib; targeted therapy; combination drug therapy

INTRODUCTION

Increased understanding of the molecular pathophysiology of renal cell carcinoma (RCC) has led to development and approval of several targeted agents, including 3 multitarget TKI

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Financial disclosures: Robert J. Motzer – research funding from Pfizer and Novartis. Ana M. Molina – research funding from Novartis. Darren R. Feldman – research funding from Pfizer; consulting with Pfizer. Dion R. Brocks – consulting with Novartis. Patricia M. Fischer – consulting with Novartis.

(sorafenib, sunitinib, and pazopanib), an anti-VEGF monoclonal antibody (bevacizumab, given in combination with interferon), and two mTOR inhibitors (temsirolimus and everolimus), each shown to be superior to either immunotherapy or placebo in randomized phase III trials.^{1–6} Targeted agents have been combined in an attempt to improve efficacy and overcome drug resistance.^{7, 8} For this, it is essential to understand the precise interplay between VEGF, the hypoxia-inducible factor 1 alpha (HIF-1 α), and the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway. Through its downstream effectors, mTOR raises levels of VEGF and HIF-1 α .⁹ HIF-1 α induces a further increase in VEGF, which in turn activates the PI3K/Akt/mTOR axis.¹⁰ As suggested by preclinical models,^{11, 12} inhibiting steps in this autocrine loop (mTOR–HIF–VEGF–mTOR) could prove superior to single sequential agents.¹³ We hypothesized that synchronous blockade of VEGF and mTOR with sunitinib and everolimus might enhance antitumor activity, especially since patients resistant to sunitinib benefit from everolimus,¹ which argues against significant cross-resistance. This study evaluated the safety and identified the MTD of sunitinib administered with everolimus.

PATIENTS AND METHODS

Eligible patients had progressive metastatic RCC of any histological subtype, and could have received 3 prior regimens for metastatic RCC, with the exception of sunitinib or an mTOR inhibitor. All were required to have ECOG performance status 0–1 as well as adequate organ function defined by the following criteria: serum AST and ALT $\leq 2.5 \times$ upper limit of normal (ULN) or $< 5 \times$ ULN in the presence of liver metastases, serum bilirubin ≤ 1.5 mg/dL, leukocyte count ≥ 3000 cells/ μ L, absolute neutrophil count ≥ 1500 / μ L, platelets $\geq 100,000$ / μ L, hemoglobin ≥ 9.0 g/dL, prothrombin time ≤ 1.5 ULN, serum calcium ≥ 12.0 mg/dL, and serum creatinine $\leq 2.0 \times$ ULN. Patients were excluded for any of the following: poorly controlled blood pressure ($>150/100$ mmHg); cardiac dysrhythmias or QTc prolongation (>450 msec for males and >470 msec for females); severe vascular disease in the past year, including cardiovascular, cerebrovascular, or peripheral vascular disease; uncontrolled brain metastases; chronic systemic steroids or other immunosuppressive agent; history of bleeding diathesis, coagulopathy, or therapy with full-dose warfarin; surgery; radiation therapy; systemic therapy; or grade 3 hemorrhage within 4 weeks. Prior gastrointestinal perforation, intraabdominal abscess within 6 months, or impairment of gastrointestinal function that could limit drug absorption were also reasons for exclusion from enrollment. Informed consent was obtained from all patients in this trial.

Study Design

This was a single-center, open-label, phase I study with a standard 3+3 dose escalation design. Cohorts of 3 to 6 patients were enrolled sequentially to receive concurrent sunitinib and everolimus at escalating doses (Table 1). Everolimus was administered on a continuous schedule either daily or weekly in combination with sunitinib given daily using a standard 4 weeks on 2 weeks off (4/2) schedule to establish the MTD (i.e., highest dose level at which zero or 1 of 6 patients experienced a DLT). The starting dose of everolimus (2.5 mg daily) was chosen as the lowest daily dose expected to provide adequate inhibition of mTOR.^{14, 15} The starting dose of sunitinib was 37.5 mg daily (4/2), 75% of the MTD as a single agent. Following determination of the MTD, additional patients were enrolled to obtain further information about safety and efficacy. Therapy was planned for 1 year, but patients could continue treatment until disease progression or intolerability.

Treatment Plan

Treatment consisted of 42-day cycles. Per original protocol, patients were to receive everolimus at increasing daily doses (2.5 or 5 mg) along with escalating daily doses of

sunitinib (37.5 or 50 mg daily on a standard 4/2 schedule). Because of poor tolerability at the lowest daily dosing cohorts (1 & 2), study protocol was amended; in subsequent cohorts, everolimus was escalated on a weekly dosing schedule (20 or 30 mg once weekly) with concurrent daily sunitinib (4/2 schedule).

Adverse events were evaluated by NCI CTCAE v3.0 on days 0, 14, and 28 of cycles 1 and 2, and days 0 and 28 of subsequent cycles. Escalation to a new dose cohort was based on safety evaluation of the previous cohort after 1 cycle of treatment. Hematologic DLTs included grade 4 neutropenia lasting >7 days, any episode of febrile neutropenia, and grade 3 thrombocytopenia lasting >7 days or complicated by bleeding. Nonhematologic DLTs included any grade 3 or 4 toxicity lasting >7 days, with the exception of skin or hair discoloration, alopecia, and hyperamylasemia or hyperlipasemia without clinical or other evidence of pancreatitis. In addition, persistent grade 3 or 4 nausea, vomiting, or diarrhea despite maximal medical care, clinical evidence of congestive heart failure, grade 4 hypertension or grade 3 hypertension not controlled by medication were considered DLTs. Also included were grade 4 proteinuria, episodes of gastrointestinal perforation, grade 4 hemorrhage, wound dehiscence requiring intervention, and any grade thromboembolic event.

Patients who experienced grade 3 and 4 adverse events received dose adjustments to 1 or both drugs, as per protocol. Dose reductions to sunitinib were made in 12.5 mg decrements. Everolimus was reduced in 2.5 mg decrements for daily dosing; patients receiving everolimus weekly decelerated to the next lower level. Toxicities warranting dose reductions of sunitinib <25 mg/day or everolimus <2.5 mg every other day (daily dosing) or 15 mg/week (weekly dosing) were cause to be withdrawn from study. Patients were followed for adverse events for 30 days after the last dose of everolimus and sunitinib.

Antitumor Assessment

Treatment response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 at day 28 of the first 4 cycles and on even cycles thereafter, earlier when PD was suspected. Imaging was repeated to confirm partial (PR) or complete response (CR) at least 4 weeks after initial documentation of response and at the end of treatment. Progression-free survival (PFS) was measured from the first dose of study drug until documented disease progression or death, whichever occurred first. Patients who did not meet these endpoints were censored at their last tumor assessment. Those removed from the study because of toxicity were censored at study termination.

Pharmacokinetics

Blood levels of everolimus, sunitinib, and its active metabolite N-desethyl sunitinib were evaluated at hours 0, 1, 2, 5, and 24 on days 14, 28, and 42 of cycles 1 and 2 in patients receiving daily sunitinib with weekly everolimus (i.e., cohort 3–5).

Pharmacokinetic methods

Everolimus concentrations were determined by use of a liquid chromatography/mass spectroscopy assay.¹⁶ Sunitinib and N-desethyl sunitinib were extracted from 0.100 mL of human plasma by a liquid-liquid extraction procedure. The extracts were analyzed using liquid chromatography/tandem mass spectrometry by an outside contractor (Anapharm, Québec, Canada). The measured plasma or blood concentration versus time data were subjected to noncompartmental analysis to determine pharmacokinetic data. All data were assumed to represent steady-state values. The time to (t_{max}) and value of the maximum blood or plasma concentration (C_{max_{ss}}) were determined by visual inspection of the concentration vs time data for each analyte of interest. The terminal phase rate constant (λ_z)

was obtained by applying linear regression to the natural-log (ln) transformed concentration vs time data in the terminal phase based on the concentrations measured from 0 to 24 h post-dose. The terminal phase half-life ($t_{1/2}$) was determined by the quotient of $0.693/\lambda_z$.

For both everolimus and sunitinib, the area under the concentration (AUC) from time of dosing to the time of the last measured concentration at 24 h was determined using the linear trapezoidal rule. For sunitinib, this also represented the steady-state AUC over the dosing interval ($AUC_{0-\tau}$), due to once-daily administration. For weekly everolimus, $AUC_{0-\tau}$ was determined by 1 of 2 methods. 1) For patients with a pre-dose (hour 0) everolimus concentration above the lower limit of quantitation, the 0 h sample was used as the 168 h postdose sample for the prior dose, permitting calculation of the steady-state AUC over the dosing interval ($AUC_{0-\tau}$). 2) For patients with 0 h everolimus concentrations below the lower limit of quantification, the AUC from time of dosing to infinity ($AUC_{0-\infty}$) was determined instead. It was approximated as the sum of the AUC_{0-24} and the quotient of the 24 h concentration divided by λ_z .

Statistics

The primary study objectives were to evaluate safety and tolerability and to identify MTD for the combination of everolimus and sunitinib. Toxicities were described by frequency and grade with the maximum grade over all cycles used as the summary measure per patient. The anticipated rates of DLTs were estimated between 10%–50%. Based on binomial distribution properties, the probability of dose escalation was estimated at 0.91, 0.71, 0.49, 0.31, and 0.17 if the true rates of DLTs were 10%, 20%, 30%, 40%, and 50%.

Secondary endpoints included objective response rate (ORR), PFS, and pharmacokinetic properties of both drugs. PFS was estimated with 95% confidence intervals using Kaplan-Meier methods.¹⁷ Graphical methods analyzed plasma and blood concentrations of study drugs and their metabolites.

RESULTS

Patient Characteristics

Twenty patients were enrolled at Memorial Sloan-Kettering Cancer Center (MSKCC) between October 2006 and December 2008 (Table 2). Most patients (85%) had undergone prior nephrectomy; none had received prior systemic therapy. Thirteen patients (65%) had tumors of conventional clear cell type, and 7 patients (35%) had non-clear cell histology. Nineteen patients (95%) were classified as good or intermediate risk based on MSKCC Criteria.¹⁸

Treatment and Adverse Events

A total of 87 treatment cycles were administered to 20 patients (median 2 completed cycles per patient). Four of 5 patients with DLT were removed from study prior to the end of cycle 1 and were not evaluable for response.

Patients were enrolled in 1 of 5 cohorts with defined dosing levels (Table 1). All 3 patients in cohort 1 tolerated the first cycle of therapy, but patient #3 was removed for toxicity before the end of cycle 2. Two patients were enrolled in cohort 2. Both had DLT (grade 3 thrombocytopenia and mucositis; grade 3 vomiting, respectively), precluding additional enrollment to this cohort. One of the 2 discontinued study treatment; the other continued after a dose reduction and received therapy for 53 weeks, at which time both drugs were discontinued because of worsening diarrhea.

Because of toxicity in cohort 2, the dosing schedule was altered, and subsequent cohorts received everolimus on an escalated weekly schedule concurrent with daily sunitinib. With weekly everolimus, none of the initial 3 patients in cohorts 3 or 4 had DLT. Two patients in cohort 5 (everolimus 30 mg weekly, sunitinib 50 mg daily) experienced DLT (grade 3 mucositis and grade 3 thrombocytopenia with bleeding, respectively). Therefore, 3 additional patients were treated on the previous dose level (cohort 4: everolimus 30 mg weekly, sunitinib 37.5 mg daily). DLT were observed in 1 of these additional 3 patients, and consisted of grade 3 mucositis and febrile neutropenia. Overall, 1 of 6 patients in cohort 4 experienced DLT; this dosing level was determined as the MTD.

Frequent adverse events were observed beyond cycle 1 in cohort 4. One patient developed endocarditis during cycle 4, required valve replacement and suffered a cerebral vascular accident. A second experienced a gastrointestinal bleed secondary to a gastric ulcer during cycle 3 and was taken off study. The third patient had progressive disease at the end of cycle 1 and was removed from study. A fourth patient had severe mucositis and neutropenic fever during cycle 1. The fifth patient completed 6 full cycles on study despite multiple toxicities including grade 2 weight loss and diarrhea during cycle 2, and 1 episode of grade 3 diarrhea during cycle 6. His dose was reduced to the next lower level (everolimus 20 mg weekly, sunitinib 37.5 mg daily) and continued treatment until disease progression during cycle 16. A sixth patient was taken off treatment during cycle 2 after a grade 4 embolic event (pulmonary embolism). Thus, only 1/6 Cohort 4 patients tolerated therapy beyond cycle 4.

Given the frequency of adverse events with chronic therapy at the MTD, 3 additional patients were enrolled on the next lower dosing level (cohort 3, everolimus 20 mg weekly, sunitinib 37.5 mg daily). This was done to confirm the highest dose level that allowed administration of multiple cycles. None of the 6 patients enrolled in cohort 3 were removed from study for toxicity, neither were 2 additional patients (1 each from cohorts 4 and 5) reduced to the cohort 3 dose level.

Treatment-emergent adverse events appear in Table 3. Pulmonary embolism was the only grade 4 adverse event. There were no treatment-associated deaths. Table 4 shows the most frequent hematologic toxicities.

Response and Survival

Four of 20 patients (20%) were removed for DLT prior to the end of cycle 1 and were not evaluable for response (Table 5). Five out of 16 evaluable patients (31%) achieved confirmed PR (including 2 patients with clear cell histology, 2 patients with chromophobe histology, and 1 patient with papillary RCC). Ten out of 16 evaluable patients (62.5%) had stable disease (including 8 clear cell RCC patients and 2 unclassified histology patients). 1 patient (6%) had PD as best response (papillary histology). PRs occurred with both daily and weekly everolimus.

Seven patients were removed from study for PD, 8 for DLT or other toxicity. Five patients completed planned treatment (therapy for 1 year). One of the 5 was enrolled in cohort 2, but received most therapy on the lowest dosing level after a reduction during cycle 1. He was taken off therapy for grade 3 colitis after 53 weeks of therapy. The 4 remaining patients who completed the study were treated on cohort 3 dosing level; 2 had undergone dose reductions from higher cohorts (Table 1). Eventually, 2/5 patients had PD (after 58 and 95 weeks, respectively); 2 developed toxicity requiring discontinuation (1 with recurrent grade 3 diarrhea at week 53; 1 with recurrent grade 2 ear infections at week 75); after 17 cycles, the fifth patient was taken off treatment for surveillance. He eventually progressed and is receiving treatment with single agent sorafenib.

There were 8 deaths unrelated to treatment among the 20 treated patients, 6 of 8 had been removed for PD and 2 for excessive toxicity. With a median follow-up for survivors of 12 weeks (patients discontinued because of toxicity were censored at the time of removal), the median PFS was 35 weeks (95% CI, 16 weeks - not reached).

Pharmacokinetics

Serial serum everolimus, sunitinib, and N-desethyl sunitinib levels were collected on 13 of 15 patients receiving everolimus on a weekly schedule. For comparison, everolimus levels were normalized to 20 mg/week, sunitinib levels and N-desethyl sunitinib levels to 37.5 mg/day. For all 3 analytes, findings did not vary significantly at different time points throughout cycles 1 and 2 (Fig1). For everolimus, mean values at each time point for C_{max} (range 91.3±41 to 131±51 ng/ml), t_{1/2} (range 16.2±5.6 to 21.5±10.1 hrs), and AUC₀₋₂₄ (range 723±256 to 897±297 ng·h/mL) were similar across days 14, 28, and 42 of cycles 1 and 2. Similarly, for sunitinib and its active metabolite N-desethyl sunitinib, mean C_{max} (sunitinib, 46.1±15.0 to 61.7±16.5 ng/mL; metabolite 20.6±9.7 to 23.6±9.3 ng/mL), AUC (sunitinib, 1022±357 to 1360±375 ng·h/ml; metabolite, 454±206 to 523±225 ng·h/ml), and C_{min} (sunitinib, 39.5±16.1 to 53.4±14.0 ng/ml; metabolite, 18.6±9.2 to 21.0±9.1 ng/ml) were similar across days 14 and 28 of cycles 1 and 2. No unexpected accumulation of everolimus, sunitinib, or N-desethyl sunitinib was observed.

Discussion

In this phase I trial, sunitinib and everolimus were combined in a treatment-naïve population with advanced RCC. The combination was poorly tolerated at standard doses, and the everolimus schedule was changed from daily to weekly administration. DLTs included thrombocytopenia with bleeding, febrile neutropenia, mucositis, and vomiting. The MTD for the combination was determined to be everolimus 30 mg weekly, sunitinib 37.5 mg daily. However, most patients did not tolerate this schedule with subsequent cycles, and the highest dosing level for chronic treatment was everolimus 20 mg weekly/sunitinib 37.5 mg daily. One recent pharmacodynamic study suggests that our derived weekly dose of everolimus has suboptimal activity¹⁹. Therapy in higher dosing cohorts was associated with grade 3/4 toxicities.

The increased toxicity when combining both drugs at low doses does not appear related to pharmacokinetic interactions. There was no evidence of unexpected accumulation of everolimus, sunitinib, or its primary active metabolite through cycles 1 and 2 (Fig.1). Everolimus pharmacokinetics was similar to previous reports for the single agent,¹⁴ arguing against alterations in everolimus pharmacokinetics because of sunitinib. On a dose-normalized basis, assuming an intermittent schedule of 37.5 mg daily, we observed somewhat higher mean C_{min} levels for drug and metabolite than has been reported.²⁰ The C_{min} and AUC_{0-τ} seem closer to previous reports for 50 mg daily on a standard intermittent schedule.^{21, 22} Comparisons with previous trials, however, are influenced by small patient numbers and significant interpatient variation for sunitinib pharmacokinetic parameters.^{23, 24}

A secondary study objective was to assess antitumor activity with the combination of sunitinib and everolimus. Only 2 out of 10 evaluable patients with clear cell RCC achieved a PR, and only 1 remained on therapy for >1 year. In contrast, 3 of 6 patients with non-clear cell RCC attained a PR (chromophobe, n=2; papillary, n=1), all 3 of whom achieved disease control for >1 year. Note, previous studies of sunitinib in advanced non-clear cell RCC have been disappointing. Our group recently reported a phase II trial of single-agent sunitinib in 23 patients with advanced non-clear cell RCC, showing no responses with a median PFS of 5.5 months.²⁵ Similarly disappointing results have been reported by other investigators.^{26, 27} Our findings suggest that antitumor activity might be due to everolimus, which has not been

studied in non-clear cell RCC. Data for temsirolimus, a different mTOR inhibitor, suggest benefit to this drug class in non-clear cell histology.²⁸

Combined targeted agents in RCC have been under investigation by several groups, and toxicity has been a common theme. Several trials have evaluated the safety of combining an mTOR inhibitor with a VEGF TKI. A phase I study of sunitinib plus temsirolimus was terminated early because of DLT at the starting dose of temsirolimus 15 mg weekly and sunitinib 25 mg daily.²⁹ Adverse events included hemorrhage, thrombocytopenia, gastrointestinal toxicity, and severe infection. Because of efficacy concerns at lower dosing levels, the study was terminated. Similarly, the combination of sorafenib with temsirolimus was associated with adverse effects at full doses, particularly mucocutaneous toxicity.³⁰ Sorafenib with everolimus was better tolerated in a previously reported dose-finding study,³¹ but everolimus was reduced because of DLTs in 2 out of 4 patients treated at the dose of 5 mg daily. Of 10 patients treated in the trial, 3 had a PR, 2 had SD, 5 showed evidence of progression. For clear cell RCC, combinations of TKIs and mTOR inhibitors appear to be feasible only at attenuated doses, which result in diminishing efficacy and added toxicity.

Promising results of a phase I/II trial of temsirolimus and bevacizumab³² led to an ongoing randomized phase II trial comparing this combination to sunitinib or bevacizumab with interferon- α in the first-line setting. Recent interim findings from the randomized phase II trial³³ include more toxicity, higher drop-out rates and no improvement in clinical efficacy in the temsirolimus/bevacizumab arm. Everolimus and bevacizumab were tolerated in combination at full doses in a phase I trial,³⁴ and a subsequent phase II study was recently reported.³⁵ In 50 untreated patients, ORR was 30%, with a median PFS of 9.1 months. Several ongoing phase II and III trials are investigating the combination of mTOR inhibition and bevacizumab.

In conclusion, in this phase I trial of metastatic RCC, the combination of everolimus and sunitinib produced a high degree of toxicity requiring dose attenuation of both drugs. Efficacy was observed, but was infrequent in clear cell histology and less than expected with single-agent sunitinib at full doses. Responses observed in papillary and chromophobe histology subtypes are intriguing, but require a dedicated phase II trial for better characterization.

Acknowledgments

Sponsor: Novartis International AG

The authors thank Carol Pearce (MSKCC Department of Medicine writer/editor) for her review of the manuscript.

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Figure 1.

Mean steady-state blood concentration vs time curves of everolimus (A), sunitinib (B) and N-desethyl sunitinib (C) measured across various study days in cycles 1 and 2. All concentrations are normalized to the most common dose level used in this study (everolimus 20 mg once weekly, sunitinib 37.5 mg once daily).

Table 1**Dosing Cohorts with Duration of Treatment and Long-term Tolerability**

Patient number	Number of weeks Treated	Dose Reduction	Reason for Removal from Study
<i>Cohort 1: Everolimus 2.5 mg daily, Sunitinib 37.5 mg daily^a</i>			
1	27	No	PD
2	22	No	PD
3	10	No	Toxicity (G3 herpes stomatitis, G3 leukopenia, G2 fever)
<i>Cohort 2: Everolimus 5 mg daily, Sunitinib 37.5 mg daily^a</i>			
4	53	Yes	Completed 1 year study requirement ^b
5	2	No	Toxicity (G3 vomiting=DLT)
<i>Cohort 3: Everolimus 20 mg weekly, Sunitinib 37.5 mg daily^a</i>			
6	19	No	PD
7	16	No	PD
8	102	No	Completed 1 year study requirement
18	58	No	Completed 1 year study requirement
19	35	No	PD
20	16	No	PD
<i>Cohort 4: Everolimus 30 mg weekly, Sunitinib 37.5 mg daily^a</i>			
9	22	No	Toxicity (G3 Strep-viridans endocarditis)
10	15	No	Toxicity (G3 gastrointestinal hemorrhage; G4 anemia)
11	5	No	PD
15	2	No	Toxicity (G3 mucositis & G3 febrile neutropenia = DLT)
16	95	Yes	Completed 1 year study requirement
17	7	No	Toxicity (G4 pulmonary embolism)
<i>Cohort 5: Everolimus 30 mg weekly, Sunitinib 50 mg daily^a</i>			
12	75	Yes	Completed 1 year study requirement
13	2	No	Toxicity (G3 mucositis = DLT)
14	5	No	Toxicity (G3 thrombocytopenia with bleeding = DLT)

Abbreviations: PD, progression of disease; G3, grade 3; G2, grade 2; G4, grade 4; DLT, dose- limiting toxicity

^aEverolimus administered continuously, Sunitinib administered 4 weeks on/2 weeks off

^bPatient dose reduced after DLT (G3 thrombocytopenia & G3 mucositis)

Table 2

Patient Characteristics (N=20)

Characteristic	Number	Percentage
Median age (range)	61.5 (23–69)	
Gender (M:F)	16:4	
Histology		
Clear Cell	13	65
Papillary	3	15
Chromophobe	2	10
Unclassified	2	10
Select sites of metastases		
Lung	11	55
Lymph Nodes	10	50
Bone	7	35
Liver	5	25
Adrenal	4	20
Kidney	2	10
Renal Bed	2	10
Number of metastatic sites		
1	5	25
2	7	35
3	4	20
4	4	20
Prior therapy		
Nephrectomy	17	85
Chemotherapy	0	0
Radiation therapy	3	15
MSKCC risk group		
Good	11	55
Intermediate	8	40
Poor	1	5

MSKCC: Memorial Sloan-Kettering Cancer Center

Table 3Treatment-related Adverse Events^a

Clinical Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	All grades	%
Fatigue (asthenia, lethargy, malaise)	13	2			15	75
Mucositis (clinical exam or symptoms)	8	2	3		13	65
Diarrhea	5	1	4		10	50
Hemorrhage	7	2	1		10	50
Rash, other	5	4			9	45
Pain, various sites	4	1	2		7	35
Hypertension	4	2	1		7	35
Rash, hand-foot skin reaction	4	3			7	35
Nausea	6	1			7	35
Constipation	3	2			5	25
Infection	1	1	2		4	20
Fever (in the absence of neutropenia)	3		1		4	20
Vomiting	3		1		4	20
Weight loss	3	1			4	20
Dyspnea	4				4	20
Dry skin	3				3	15
Dysgeusia	3				3	15
Diaphoresis	2				2	10
Pulmonary embolism			1		1	5
Dysphagia			1		1	5
Febrile neutropenia			1		1	5
Neuropathy, sensory			1		1	5
Gastrointestinal, other		1			1	5
Pneumonitis/pulm infiltrates		1			1	5

^aGrade 1 toxicities occurring in <10% of patients are excluded

Table 4Treatment-related Hematologic & Biochemical Abnormalities^a

Abnormalities	Grade 1	Grade 2	Grade 3	Grade 4	All grades	%
<i>Hematologic</i>						
Anemia	9	6	2	1	18	90
Leukopenia	7	7	4		18	90
Thrombocytopenia	11	3	4		18	90
Neutropenia		10	2		12	60
INR, prolonged	7				7	35
Lymphopenia			3	1	4	20
PTT, prolonged	2	1			3	15
<i>Biochemical</i>						
Hyperglycemia	14	4			18	90
Hypercholesterolemia	16	1			17	85
AST, SGOT, elevated	14	1	1		16	80
Hypertiglyceridemia	15	1			16	80
ALT, SGPT, elevated	11	2	2		15	75
Creatinine elevation	14	1			15	75
Hypoalbuminemia	10	4			14	70
Hypophosphatemia		9	4		13	65
Lipase, elevated	5		7		12	60
Alkaline phosphatase, elevated	8		1		9	45
Hyperamylasemia	7	2			9	45
Hypematremia	9				9	45
Hyperkalemia	6	1	1		8	40
Hyponatremia	5		2		7	35
Hypokalemia	4		1		5	25
Hyperbilirubinemia	1	2	1		4	20
Hypothyroidism	2	2			4	20
Hypoglycemia	2				2	10

^aGrade 1 toxicities occurring in <10% of patients are excluded.

Table 5**Dosing Cohorts with Histology and Best Response**

Patient number	Histology	Best Response
<i>Cohort 1: Everolimus 2.5 mg daily, Sunitinib 37.5 mg daily</i>		
1	Clear Cell	SD
2	Clear Cell	SD
3	Clear Cell	SD
<i>Cohort 2: Everolimus 5 mg daily, Sunitinib 37.5 mg daily</i>		
4	Clear Cell	PR
5	Clear Cell	Not evaluable
<i>Cohort 3: Everolimus 20 mg weekly, Sunitinib 37.5 mg daily</i>		
6	Clear Cell	SD
7	Clear Cell	SD
8	Chromophobe	PR
18	Clear Cell	PR
19	Unclassified	SD
20	Unclassified	SD
<i>Cohort 4: Everolimus 30 mg weekly, Sunitinib 37.5 mg daily</i>		
9	Clear Cell	SD
10	Clear Cell	SD
11	Papillary	PD
15	Papillary	Not evaluable
16	Papillary	PR
17	Clear Cell	SD
<i>Cohort 5: Everolimus 30 mg weekly, Sunitinib 50 mg daily</i>		
12	Chromophobe	PR
13	Clear Cell	Not evaluable
14	Clear Cell	Not evaluable

Abbreviations: SD, stable disease; PR, partial response; PD, progression of disease