



Published in final edited form as:

*Clin Genitourin Cancer*. 2008 March ; 6(1): 21–24.

## A University of Chicago Consortium Phase II Trial of SB-715992 in Advanced Renal Cell Cancer

Richard T. Lee<sup>1</sup>, Kathleen E. Beekman<sup>2</sup>, Maha Hussain<sup>2</sup>, Nancy B. Davis<sup>3</sup>, Joseph I. Clark<sup>4</sup>, Sachdev P. Thomas<sup>5</sup>, Katherine F. Nichols<sup>1</sup>, and Walter M. Stadler<sup>1</sup>

<sup>1</sup>Department of Medicine, Section of Hematology/Oncology, The University of Chicago, IL

<sup>2</sup>University of Michigan, Ann Arbor

<sup>3</sup>Medical College of Wisconsin, Milwaukee

<sup>4</sup>Loyola University Medical Center, Maywood, IL

<sup>5</sup>Oncology-Hematology Associates of Central Illinois, Peoria

### Abstract

**Background**—Advanced renal cell cancer (RCC) continues to have a poor overall prognosis despite new FDA-approved therapies. Although taxane-based therapies are generally ineffective in RCC, research into the role of the von Hippel-Lindau protein has shown an association with microtubule dynamics. Mitotic kinesins are a class of molecular motors that also interact with microtubules and are required for proper mitotic function. SB-715992 is a new agent that inhibits the function of a mitotic kinesin known as kinesin spindle protein and leads to cell death.

**Patients and Methods**—Twenty previously treated advanced RCC patients were enrolled in this phase II trial of SB-715992, with response rate as a primary endpoint.

**Results**—No patients responded with complete or partial remission. Six patients had stable disease, and one patient continues on therapy after 12 cycles. Common toxicities included anemia (80%), elevated creatinine (70%), lymphopenia (45%), fatigue (50%), hyperglycemia (50%), and dyspnea (45%). Reported grade 3/4 toxicities included dyspnea, fatigue, neutropenia with skin infection, dizziness, hyperuricemia, and hypertension.

**Conclusion**—This dose and schedule of SB-715992 does not appear to have a significant cytotoxic effect for patients with previously treated advanced RCC.

### Keywords

Kinesin spindle inhibitor; Multidrug resistance-associated protein 2; von Hippel-Lindau protein

### Introduction

The American Cancer Society anticipates over 51,000 new cases of renal cell carcinoma (RCC) will be diagnosed in the United States in 2007, and almost 13,000 patients will die of this disease.<sup>1</sup> Incidence and mortality have steadily increased over time.<sup>2</sup> An estimated 20% of patients will have locally advanced disease at diagnosis, and up to 40% of patients treated by nephrectomy for localized disease will relapse.<sup>3</sup> Another 25% will have metastatic disease at diagnosis. The prognosis for recurrent or metastatic disease is poor, with a 5-year survival rate

of < 10%, but individual patient outcome is highly variable, with median survival of 20 months in good-prognosis, 10 months in intermediate-prognosis, and 4 months in poor-prognosis patients.<sup>4</sup> In addition, there is increasing recognition that RCC is composed of multiple histologic subtypes with distinct pathologic and biologic characteristics, of which clear cell is the most common. Although high-dose interleukin-2 offers long-term survival to a small percentage of patients with clear cell RCC, the majority of patients are not candidates for this relatively toxic approach.<sup>5</sup> More recently, antiangiogenic therapies have been shown to significantly increase progression-free survival in patients with good- and intermediate-prognosis clear-cell disease.<sup>6-9</sup> The mammalian target of rapamycin inhibitor temsirolimus has also been shown to improve survival of patients with poor-prognosis RCC.<sup>10</sup> These therapies, however, are not curative. Thus, alternative treatments are still needed.

Targeting the mitotic spindle is one such approach. Recent evidence has demonstrated that the von Hippel-Lindau protein (pVHL), which is mutated or methylated in the majority of clear-cell RCC, is associated with microtubule function.<sup>11,12</sup> The taxanes are classic spindle targeting agents that bind to microtubules and modify microtubule polymer dynamics. These agents are also known to be ineffective in the treatment of RCC. The mechanism of resistance to taxanes in RCC has not yet been fully elucidated. However, it might be related to alterations in the expression of tubulin isotypes or enhanced expression of the multidrug resistance-related transporter efflux pumps such as P-glycoprotein and multidrug resistance associated protein 2.<sup>13,14</sup> The epothilone ixabepilone, which also binds to microtubules, has shown some promising activity in RCC.<sup>15,16</sup> Another mitotic spindle protein is the mitotic kinesin spindle protein (KSP). This protein plays an exclusive and essential role in assembly and function of the mitotic spindle. Kinesin spindle protein expression is higher in many cancer tissues compared with adjacent normal tissue and thus represents a novel target for cancer treatment. Additional data suggests that KSP inhibitors might be effective in taxane-resistant cells.<sup>17,18</sup>

SB-715992 is a polycyclic, nitrogen-containing heterocyclic inhibitor of KSP, and it is the first of its class to enter clinical trials. This agent blocks assembly of the functional mitotic spindle, thereby causing cell-cycle arrest in mitosis and subsequent cell death. Preclinical models have shown a broad spectrum of activity against cancer, including models that are refractory to cytotoxic chemotherapy. Several phase I studies of SB-715992 have already been conducted, and the dose-limiting toxicity of both the weekly (7 mg/m<sup>2</sup>) and every-21-day regimens (18 mg/m<sup>2</sup>) is neutropenia.<sup>19-21</sup> Other toxicities include constipation, fatigue, and transaminitis. Given the association of pVHL with microtubule function and the overall safety profile to date, including the absence of neuropathy, further study of this agent for RCC is warranted.

## Patients and Methods

### Patient Eligibility Criteria

Patients aged < 18 years age were eligible if they met the following conditions: Eastern Cooperative Oncology Group performance status  $\leq 2$ , histologically or cytologically confirmed metastatic RCC or unresectable primary tumor, a minimum of 1 but no more than 2 prior therapies in the 8 months prior to enrollment, < 28 days since prior treatment, absolute granulocyte count  $\geq 1500$  cells/mm<sup>3</sup>, hemoglobin  $\geq 9$  mg/dL, platelet count  $\geq 100,000$  cells/mm<sup>3</sup>, total bilirubin < 2 mg/dL, aspartate aminotransferase and alanine aminotransferase  $\leq 2.5 \times$  institutional upper limit of normal, serum creatinine  $\leq 2.0$  or calculated creatinine clearance  $\geq 40$  mL/min, and corrected QT interval of < 0.47 seconds. Patients were excluded for any of the following reasons: if they had received prior tubule, DNA, or mitosis targeting agents for the treatment of RCC; if they were pregnant or nursing women; if they were HIV positive; or if they had a history of brain metastases. Because SB-715992 is an in vitro inhibitor of CYP3A4, medications or substances that are known significant inhibitors or inducers of CYP3A4 were prohibited within 14 days (< 6 months for amiodarone) prior to the administration of the first

dose of SB-715992. All patients were required to provide written informed consent according to federal, state, and institutional guidelines.

### Treatment Plan

SB-715992 was administered at 7 mg/m<sup>2</sup> intravenously on days 1, 8, and 15, every 28 days. Patients who experienced any response or stable disease continued protocol treatment until progression, unacceptable toxicity, intercurrent illness, or delay of treatment for < 3 weeks for any reason. For grade 4 neutropenia or thrombocytopenia lasting < 4 days, grade 3/4 neutropenia associated with fever, nonhematologic toxicity of grade ≤ 3, or grade 2 neurotoxicity, dose reductions were made by 1-mg/m<sup>2</sup> increments up to a minimum dose of 5 mg/m<sup>2</sup>. Grade 3 or greater neurotoxicity resulted in the removal of the patient from protocol treatment.

### Patient Evaluation

Patients were required to have a clinical visit and laboratory tests done within 7 days of registration. In addition, all baseline radiographic studies were completed within 4 weeks of registration. Disease status was assessed according to RECIST criteria every 8 weeks.<sup>22</sup>

### Statistical Analysis

The primary objective of this phase II trial was to evaluate the objective response rate to SB-715992 in patients with metastatic RCC. An optimal 2-stage accrual design was implemented with a null hypothesis that SB-715992 would have a ≤ 10% true response rate.<sup>23</sup> The alternative hypothesis would be a true response of ≥ 30%, and α and β errors of 0.05 and 0.10, respectively, was adopted. Initially, 18 patients were to be accrued, with expansion to a total of 35 if > 2 patients responded. Further evaluation of this agent would then be recommended if ≥ 7 of the 35 eligible patients demonstrated a response. Secondary analysis included evaluation of toxicity, including overall and type of toxicity.

### Results

A total of 20 patients were enrolled in this multiinstitutional study between December 2005 and January 2007. The median age was 62 years, with a male predominance (16 of 20). Patients had a median of 2 previous therapies (range, 1-3), and most patients fell into an intermediate risk category (15 of 20).<sup>24</sup> Cancer histology was predominantly clear cell, except for 3 patients: 2 papillary and 1 mixed or unclassified pathology. Characteristics of the enrolled patients are shown in Table 1.

### Efficacy

Only 19 of the 20 patients enrolled were evaluated for disease response because 1 patient withdrew after 9 days of treatment because of enrollment into hospice. This patient had no significant toxicities reported. A total of 51 complete cycles of treatment were given during this study with a median of 2 cycles per patient. No patients experienced a complete or partial response. Six patients demonstrated stable disease after 8 weeks of therapy, 1 of whom withdrew before completing cycle 2 after deciding to pursue other treatment options. Therefore, only 5 patients continued on therapy for > 2 cycles, and 1 of them had progressive disease after another 2 cycles. Another 3 patients progressed after 6 cycles, leaving 1 patient with clear-cell histology, who continues to receive treatment after 12 cycles with stable disease.

### Safety

The major side effects were hematologic, with anemia (80%), lymphopenia (45%), leukopenia (25%), and neutropenia (10%) being the most common. There was only 1 grade 3 neutropenic

event, which was associated with a grade 3 skin infection. At baseline, anemia was present in 11 of the 16 patients, and 4 of these patients progressed to grade 2 anemia. Fatigue was reported in half the patients. Two cases of grade 3 fatigue reported also had grade 2 fatigue upon initial evaluation, and only 1 was recorded as possibly related to treatment. Although not described in earlier studies, elevated serum creatinine (70%), dyspnea (45%), and elevated glucose (50%) were commonly observed. The serum creatinine became newly elevated in 8 of the 14 subjects, and 2 of these were reported as possibly related to SB-715992. None of the reported cases of grade 3 dyspnea were attributed to therapy. Of note, the 1 patient with grade 3/4 hyperuricemia was recorded as having grade 1 hyperuricemia at baseline, and this toxicity was believed to be unrelated to treatment. Neither the grade 3 hypertension nor dizziness were reported to be therapy related. One patient received a dose modification (receiving 2 of 3 doses) during the first cycle because of clinical deterioration, which included grade 3 dyspnea and grade 2 anorexia and fatigue. Toxicities are summarized in Table 2.

## Discussion

Kinesin spindle protein inhibitors are novel agents and have shown promise in preclinical trials. SB-715992 is the first member of this class to be used in clinical trials. As a single agent in the treatment of advanced RCC, at the dose and schedule utilized in this trial, little clinical benefit was observed. A few patients demonstrated stable disease after 2 cycles of treatment, and 1 of these patients continued to receive treatment for approximately 12 months. Nevertheless, considering the heterogeneous disease progression seen in RCC and the fact that the vast majority of patients went off study after only 2 cycles, our study suggests that SB-715992 does not significantly alter the natural history of this disease.

SB-715992 was well tolerated therapy with few serious toxicities. As in previous phase I clinical trials, prolonged neutropenia was a major toxicity, and this trial led to a serious skin infection in 1 patient. Other hematologic toxicities included anemia, lymphopenia, and leukopenia, and these side effects are consistent with other phase II trials involving breast, ovarian, and lung cancer.<sup>25</sup> Previous studies have also reported frequent fatigue, diarrhea, and nausea. In our study, fatigue was frequently reported, but the majority of cases were not attributed to therapy. In addition, elevated serum creatinine, dyspnea, and elevated serum glucose were commonly observed in patients, but the majority of cases were also considered unrelated to treatment.

## Conclusion

In summary, this phase II trial of SB-715992 did not find a significant cytotoxic effect in patients with advanced RCC. Without new information regarding the pharmacology of SB-715992, further study in patients with clear-cell RCC is not recommended.

## Acknowledgments

The authors would also like to thank Dr. Edem Agamah, Dr. Stuart J. Wong, nurses, clinical staff, and patients for their help in this clinical trial. Supported by NO1CMS57018-16

## References

1. Detailed Guide: Kidney Cancer. What are the key statistics for kidney cancer (renal cell carcinoma)? [9/1/07]. Available at: [http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_4\\_1X\\_What\\_are\\_the\\_key\\_statistics\\_for\\_kidney\\_cancer\\_22.asp?nav=cri](http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_kidney_cancer_22.asp?nav=cri)
2. Chow WH, Devesa SS, Warren JL, et al. Rising incidence of renal cell cancer in the United States. *JAMA* 1999;281:1628–31. [PubMed: 10235157]

3. Stephenson AJ, Chetner MP, Rourke K, et al. Guidelines for the surveillance of localized renal cell carcinoma based on the patterns of relapse after nephrectomy. *J Urol* 2004;172:58–62. [PubMed: 15201737]
4. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;17:2530–40. [PubMed: 10561319]
5. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol* 2003;21:3127–32. [PubMed: 12915604]
6. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–34. [PubMed: 17215530]
7. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427–34. [PubMed: 12890841]
8. Yang JC. Bevacizumab for patients with metastatic renal cancer: an update. *Clin Cancer Res* 2004;10:6367S–70S. [PubMed: 15448032]
9. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–24. [PubMed: 17215529]
10. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271–81. [PubMed: 17538086]
11. Hergovich A, Lisztwan J, Barry R, et al. Regulation of microtubule stability by the von Hippel-Lindau tumour suppressor protein pVHL. *Nat Cell Biol* 2003;5:64–70. [PubMed: 12510195]
12. Lolkema MP, Mehra N, Jorna AS, et al. The von Hippel-Lindau tumor suppressor protein influences microtubule dynamics at the cell periphery. *Exp Cell Res* 2004;301:139–46. [PubMed: 15530850]
13. Ferguson RE, Jackson SM, Stanley AJ, et al. Intrinsic chemotherapy resistance to the tubulin-binding antimetabolic agents in renal cell carcinoma. *Int J Cancer* 2005;115:155–63. [PubMed: 15645438]
14. Ferguson RE, Taylor C, Stanley A, et al. Resistance to the tubulin-binding agents in renal cell carcinoma: no mutations in the class I beta-tubulin gene but changes in tubulin isotype protein expression. *Clin Cancer Res* 2005;11:3439–45. [PubMed: 15867246]
15. Zhuang SH, Menefee M, Kotz H, et al. A phase II clinical trial of BMS-247550 (ixabepilone), a microtubule-stabilizing agent in renal cell cancer. *Proc Am Soc Clin Oncol* 2004;22:393. Abstract 4550
16. Goodin S, Kane MP, Rubin EH. Epothilones: mechanism of action and biologic activity. *J Clin Oncol* 2004;22:2015–25. [PubMed: 15143095]
17. Iliopoulos O, Levy AP, Jiang C, et al. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. *Proc Natl Acad Sci U S A* 1996;93:10595–9. [PubMed: 8855223]
18. Tao W, South VJ, Zhang Y, et al. Induction of apoptosis by an inhibitor of the mitotic kinesin KSP requires both activation of the spindle assembly checkpoint and mitotic slippage. *Cancer Cell* 2005;8:49–59. [PubMed: 16023598]
19. Burris HA, Lorusso P, Jones S, et al. Phase I trial of novel kinesin spindle protein (KSP) inhibitor SB-715992 IV days 1, 8, 15 q 28 days. *Proc Am Soc Clin Oncol* 2004;22:128. Abstract 2004
20. Chu Q, Holen KD, Rowinsky EK, et al. A phase I study to determine the safety and pharmacokinetics of IV administered SB-715992, a novel kinesin spindle protein (KSP) inhibitor, in patients (pts) with solid tumors. *Proc Am Soc Clin Oncol* 2003;22:131. Abstract 525
21. Chu QS, Holen KD, Rowinsky EK, et al. Phase I trial of novel kinesin spindle protein (KSP) inhibitor SB-715992 IV Q 21 days. *Proc Am Soc Clin Oncol* 2004;22:146. Abstract 2078
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16. [PubMed: 10655437]
23. Simon R. Designs for efficient clinical trials. *Oncology (Williston Park)* 1989;3:43–9. [PubMed: 2701811]discussion 51-3
24. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;22:454–63. [PubMed: 14752067]
25. Cytokinetics: SB-715992 Investigator's Brochure. Version 2.0. 2007.

**Table 1****Baseline Characteristics (N = 20)**

Characteristic	
<b>Median Age, Range</b>	62 (50-83)
<b>Male/Female</b>	16/4
<b>ECOG Performance Status (0/1)</b>	13/7
<b>*MSKCC Prognostic Groups</b>	
Favorable	4
Intermediate	15
Poor	1
<b>Histology</b>	
Clear cell	17
Papillary	2
Mixed or unclassified	1
<b>Prior Nephrectomy</b>	15
<b>Previous Therapy History</b>	
Systemic chemotherapy	5
Immunotherapy	9
Antiangiogenic treatment	12
<b>Median Number (Range) of Previous Therapies</b>	2 (1-3)

\* MSKCC Prognostic Groups for previously treated metastatic RCC: 1 point for each of the following factors: Karnofsky performance status < 80%, corrected calcium < 10 mg/dL, and hemoglobin < 13 g/dL for males and < 11.5 g/dL for females. Risk stratification: good - 0 risk factors; intermediate - 1 risk factor; poor - 2 or 3 risk factors.<sup>24</sup>

Abbreviations: ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan-Kettering Cancer Center

**Table 2**  
**Summary of Toxicities in > 10% of Subjects or Any Grade 3 or 4 Toxicities**

Toxicity	Any Grade n, (%)	Grade 3 or 4 n, (%)	At Baseline n, (%)
<b>Constitutional</b>			
Fatigue	10 (50)	2 (10)	6 (30)
Sweating	4 (20)		3 (15)
Anorexia	4 (20)		2 (10)
Insomnia	4 (20)		1 (5)
<b>Dermatologic</b>			
Skin disorder	5 (25)		2 (10)
Skin infection	1 (5)	1 (5)	
<b>Gastroenterology</b>			
Constipation	6 (30)		2 (10)
Nausea	6 (30)		1 (5)
Diarrhea	4 (20)		1 (5)
Vomiting	3 (15)		1 (5)
<b>Hematologic</b>			
Low hemoglobin	16 (80)		12 (60)
Lymphopenia	9 (45)		3 (15)
Leukopenia	5 (25)		
Low ANC	2 (10)	1 (5)	
<b>Hepatic</b>			
High ALT/AST	6 (30)		4 (20)
High alkaline phosphatase	5 (25)		2 (10)
<b>Metabolic</b>			
High glucose	10 (50)		4 (20)
Low glucose	3 (15)		2 (10)
Low albumin	7 (35)		4
<b>Neurological</b>			
Headache	5 (25)		
Peripheral neuropathy	5 (25)		4 (20)
Dizziness	3 (15)	1 (5)	
<b>Pain</b>			
Extremity/joint pain	7 (35)		1 (5)
Other pain	7 (35)		3 (15)
<b>Pulmonary</b>			
Dyspnea	9 (45)	3 (15)	2 (10)
Cough	7 (35)		
<b>Renal/Electrolytes</b>			
High creatinine	14 (70)		5 (25)
High potassium	5 (25)		4 (20)
High calcium	3 (15)		2 (10)
High uric acid	3 (15)	1 (5)	1 (5)
Low sodium	3 (15)		
Low magnesium	3 (15)		3 (15)

<b>Toxicity</b>	<b>Any Grade n, (%)</b>	<b>Grade 3 or 4 n, (%)</b>	<b>At Baseline n, (%)</b>
Hypertension	3 (15)	1 (5)	2 (10)
<b>Fracture</b>	1 (5)	1 (5)	

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase