Phase 2 Study of ABT-510 in Patients with Previously Untreated Advanced Renal Cell Carcinoma

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Abstract

Purpose: Angiogenesis is a characteristic of renal cell carcinoma. ABT-510 is an angiogenesis inhibitor that mimics the antiangiogenic properties of thrombospondin-1. This study was designed to assess the safety and efficacy of ABT-510 in patients with advanced renal cell carcinoma.

Experimental Design: Patients with previously untreated metastatic or unresectable renal cell carcinoma were randomized to treatment with one of two doses of ABT-510, self-administered s.c. twice daily in 28-day treatment periods without intervening rest periods. End points were progression-free survival (PFS), objective response rate, overall survival, and toxicity.

Results: The objective response rate was 4% in the 10 mg twice daily group, and there were two unconfirmed PRs in the 100 mg twice daily group. Respective median PFS was 4.2 and 3.3 months, with a 6-month PFS of 39% and 32%. Median overall survival was 27.8 months (10 mg twice daily) and 26.1 months (100 mg twice daily). The most frequent adverse events were injection site reactions (84%), fatigue (50%), headache (20%), and nausea (19%). The incidence of treatment-related, grade 3/4 adverse events was low and included three bleeding episodes (gastrointestinal hemorrhage, intracranial hemorrhage, and hemoptysis) and one thrombotic event (deep vein thrombosis). No deaths were attributed to ABT-510.

Conclusions: There was little evidence of clinical activity for ABT-510, and further evaluation as a single agent for treating advanced renal cell carcinoma is not warranted. The evidence of a favorable safety profile may justify further evaluation in combination therapy.

An estimated 51,190 new cases of renal cell carcinoma will be diagnosed, and an estimated 12,890 deaths will occur in the United States in 2007 (1). Surgery is the only known effective therapy for localized renal cell carcinoma. Systemic therapy of locally advanced or metastatic renal cell carcinoma is hampered by its resistance to virtually all forms of chemotherapy and hormonal therapy. Until recently, immunotherapy with IFN-α and/or interleukin-2 has been the primary therapy for metastatic renal cell carcinoma (2). However, neither agent provides substantial clinical benefit in the majority of patients. The number of durable responses is limited, and the use of these agents is complicated by significant safety and tolerability issues (3). Studies with the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab and the multitargeted kinase inhibitors sunitinib and sorafenib, which target the VEGF family of receptors, as well as other receptor tyrosine kinase inhibitors, have shown significant clinical activity (4–11). The recent Food and Drug Administration approvals of sorafenib and sunitinib, agents known to work in part by inhibiting angiogenesis, offer new approaches to the treatment of advanced renal cell carcinoma.

The microenvironment of renal cell carcinoma is highly angiogenic, driven in large part by frequent loss of the *von Hippel Lindau* tumor-suppressor gene in the most common histologic subtype of renal cell cancer. This leads to overexpression of the α subunit of the hypoxia-inducible factors and drives the overexpression of VEGF and other proangiogenic growth factors by tumor cells. This characteristic of renal cell carcinoma makes it an excellent target for antiangiogenic agents that inhibit VEGF and other signaling pathways.

Thrombospondin-1 is a large, multifunctional protein that is activated by the tumor-suppressor gene *p53* with resultant antiangiogenic activity (12, 13). It inhibits the activity of multiple proangiogenic factors, including VEGF, basic fibroblast growth factor, and interleukin-8 (14). ABT-510 is a nonapeptide analogue of an antiangiogenic sequence from thrombospondin-1, and a single D-amino-acid substitution confers 1,000-fold greater anti angiogenic activity. ABT-510 competes with thrombospondin-1 for binding to endothelial cells, induces Fas ligand expression in endothelial cells, and inhibits VEGF- and basic fibroblast growth factor–stimulated migration of human microvascular endothelial cells.

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In phase 1 studies, ABT-510 was evaluated as a single agent (89 cancer patients) or in combination with either 5-fluorouracil/leucovorin or gemcitabine/cisplatin (25 cancer patients; refs. 15–17). ABT-510 showed a favorable safety profile and linear and time-independent pharmacokinetics with biologically relevant plasma concentrations (>100 ng/mL lasting at least 3 h/d). The most common treatment-related toxicities (reported for ≥10% of patients receiving single-agent ABT-510) were injection site reaction, injection site inflammation, ecchymosis, headache, nausea, and asthenia. Although a maximum tolerated dose was not defined, 260 mg was defined as the maximum clinically practical dose. Efficacy data for 89 patients who received single-agent ABT-510 in these phase 1 studies show that after 8, 16, 24, and 32 weeks of treatment, 43 (48%), 21 (24%), 9 (10%), and 7 patients (8%) had stable disease (SD). Three patients experienced SD for >1 year. In addition, a partial response (PR) in a patient with soft tissue sarcoma was observed. Six of 13 patients (46%) with refractory renal cell carcinoma were progression-free for 16 or more weeks on study.

Given the need for additional therapeutic approaches to advanced renal cell carcinoma, the angiogenic characteristics of the tumor, and the preliminary safety and efficacy findings for ABT-510, we conducted this phase 2 study to further evaluate single-agent ABT-510 as a treatment option for patients with previously untreated, advanced renal cell carcinoma.

Patients and Methods

Eligibility criteria. Enrollment was limited to patients with locally recurrent or metastatic, histologically documented, renal cell carcinoma with measurable disease who had not received prior therapy other than primary tumor excision. Patients were at least 18 years of age; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; were able to self-administer s.c. injections or had a caregiver to assume this responsibility; and had adequate bone marrow, renal, and hepatic function defined as leukocytes ≥3,000/μL, platelets ≥100,000/μL, hemoglobin ≥9 g/dL, serum creatinine ≤2.0 mg/dL, aspartate aminotransferase/alanine aminotransferase ≤1.5 times the institutional upper limit of normal, lactate dehydrogenase ≤1.5 times the institutional upper limit of normal, bilirubin ≤1.5 mg/dL, corrected calculated calcium ≤10 mg/dL, and albumin ≥3.0 g/dL. In the presence of liver metastases, adequate hepatic function was defined as aspartate aminotransferase/alanine aminotransferase ≤5.0 times the institutional upper limit of normal. Patients could not be pregnant or lactating, nor could they have clinically significant cancer-related bleeding events, other clinically significant signs of bleeding, or require therapeutic anticoagulation therapy other than low-dose anticoagulation for catheter prophylaxis. The protocol was approved by the institutional review boards/independent ethics committees of all participating study centers. Voluntary written informed consent was obtained from all patients before performing any study-specific procedures or modifying medications to comply with the protocol.

Treatment plan. Treatment was administered on an outpatient basis. Patients were randomized in a 1:1 ratio to twice daily treatment with either 10 or 100 mg ABT-510 without interruption. The 10 mg twice daily dose was selected because it achieves the minimum time over a plasma concentration of 100 ng/mL (3 h), which was defined as the minimal effective exposure in preclinical studies (18), whereas the 100 mg twice daily dose is the highest practical clinical dose that can be administered by two injections daily. Dose modifications were not permitted. An interruption in ABT-510 administration of ≤14 days was required for a grade 3/4 toxicity attributable to ABT-510. The toxicity had to return to the baseline pretreatment value or to ≤grade 2 before resuming treatment with ABT-510 at the assigned dose. Patients who required a single interruption in excess of 14 days or more than one interruption were discontinued from the study.

Baseline evaluations, consisting of a medical and detailed oncology history; physical examination, including measurement of weight and vital signs; ECOG performance status; 12-lead electrocardiogram; chest X-ray (if a chest computed tomography scan was not done); and laboratory tests (chemistry, hematology, clotting factors, and urinalysis) were conducted within 14 days before day 1. Safety assessments were conducted at all study visits, which were scheduled at baseline; at weeks 2, 4, 6, and 8; and at the beginning of every subsequent treatment period. After 6 months of therapy, safety evaluations were done at least every 6 weeks. Tumor assessments, based on imaging (i.e., computed tomography scans, magnetic resonance imaging scans, and chest X-rays) and clinical measurements of superficial lesions, were conducted within 28 days before the initial dose of ABT-510 and subsequently after every 8 weeks or at least every 12 weeks after completion of treatment period 6.

Concomitant treatments. While enrolled in the study, patients could not receive cytotoxic chemotherapy, immunotherapy, radiotherapy, or investigational therapy. Local radiation involving a small radiation field done for supportive reasons was permitted, but not within 28 days from the first day of ABT-510 administration. Best supportive care (e.g., antiemetics, antibiotics, transfusions, nutritional support, pain control, hematopoietic growth factors, etc.) was administered as appropriate.

Toxicities. Toxicities were graded at each study visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Toxicities not captured by the National Cancer Institute Common Terminology Criteria for Adverse Events were categorized as grade 1 (mild), grade 2 (moderate), grade 3/4 (severe, incapacitating, or life-threatening), or grade 5 (death) by the investigator. Toxicity information was collected from the time of ABT-510 initial administration until 30 days after discontinuation of ABT-510.

Although formal interim analyses and data monitoring were not done, ad hoc safety and efficacy interim analyses were done throughout the duration of the study.

Response criteria. Tumor assessments for response and disease progression were determined by individual investigators using the Response Evaluation Criteria in Solid Tumors (19). A complete response (CR) or PR was to be confirmed by repeat assessments done at least 4 weeks after the criteria for response were initially met. Similarly, SD was to be confirmed at least once after study entry at a minimum interval of 6 weeks.

Because ABT-510 is an inhibitor of angiogenesis, it was possible that an extended time interval between the initiation of therapy and the maximal inhibition of angiogenesis and antitumor effect would exist. For this reason, patients could remain on study beyond the period at which response criteria for progressive disease (PD) were met. If the investigator and the patient agreed that the patient was benefiting from administration of ABT-510 and no other active therapeutic options were available, the patient could continue to receive ABT-510 until the sum of the longest diameter of target lesions increased in size by 50% from baseline. This modification did not affect the definition of PD; it involved only the criteria for discontinuation from the study.

Statistical methods. Data were summarized using SAS, version 8.2, software package (SAS Institute, Inc.). Statistical significance was determined by a two-sided P value of ≤0.05. Baseline patient characteristics and efficacy analyses were done for all randomized patients, whereas safety analyses were done for all treated patients. Because all randomized patients received treatment, the efficacy and safety populations were identical. The primary efficacy end point, progression-free survival (PFS), was defined for each patient as the number of days from the day of randomization to the day the patient experienced an event of PD or to the date of death if PD was not reached. All events of PD were included, regardless of whether the patient was taking ABT-510 at the time of the event or had previously

discontinued ABT-510. Events of death were included only if the death occurred within 30 days of the last available evaluation. Data for patients without documented PD or death were censored at the date of the last available evaluation.

Secondary efficacy end points included the objective response rate (ORR) and overall survival. The ORR was defined as the proportion of patients with a confirmed CR or PR based on Response Evaluation Criteria in Solid Tumors. Survival time was calculated from the date of randomization to the date of death or in the absence of death, to the date of the last study visit, the last contact date, or the date the patient was last known to be alive, whichever was last. All events of death were included. The best percentage change from baseline in tumor size was calculated for each patient with both baseline and subsequent tumor measurements from the sum of the longest diameters of target lesions at each assessment, and was displayed in a histogram. To facilitate comparisons across studies, PFS and overall survival results were converted from units of days to units of months by defining 28 days as equal to 1 month.

The distributions of PFS were estimated using Kaplan-Meier methodology (20) and compared using the log-rank test. In addition, this methodology was used to compute 90% confidence intervals for the 4- and 6-month PFS rates. The ORRs for both groups were compared using Fisher's exact test. Survival distributions were estimated using Kaplan-Meier methodology and compared using the log-rank test. Toxicities were summarized using the Medical Dictionary for Regulatory Activities, version 9.0, adverse event coding dictionary. Clinical laboratory toxicities were summarized using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

The Memorial Sloan-Kettering Cancer Center (MSKCC) risk categories were applied to the database with a minor modification, using an ECOG performance status >1 as a risk factor in place of the Karnofsky performance status criterion (21).

The null hypothesis was that the true PFS rate at 6 months was ≤20%; the alternative hypothesis was that it was ≥40%. With a sample size of 50 patients per group, the approximate power of this procedure was 90% at a significance level of 0.05 using Kaplan-Meier methodology.

Results

Patient disposition and characteristics. Between June 2003 and July 2004, 103 patients with previously untreated, advanced renal cell carcinoma were enrolled in this study at 13 centers in the United States and one center in Europe. Five of the U.S. sites enrolled eight or more subjects (range, 8-23; mean, 13). Fifty-one patients were randomized to the 10 mg twice daily group and 52 patients were randomized to the 100 mg twice daily group. Disease progression was the primary reason for discontinuing ABT-510; overall, 82% of patients discontinued for this reason (39 patients in the 10 mg twice daily group and 45 patients in the 100 mg twice daily group). ABT-510 was discontinued for one patient in the 10 mg twice daily group due

Table 1. Patient characteristics

Characteristic	Twice daily dose		Total (*N* = 103)
	10 mg (*n* = 51)	100 mg (*n* = 52)	
Age, y			
<55	11 (22)	18 (35)	29 (28)
55-64	20 (39)	21 (40)	41 (40)
65-74	12 (24)	10 (19)	22 (21)
75-84	8 (16)	3 (6)	11 (11)
Median/mean/range	62/61.3/20-80	58/58.0/37-78	59/59.6/20-80
Sex			
Male	31 (61)	36 (69)	67 (65)
Female	20 (39)	16 (31)	36 (35)
ECOG performance status			
0	37 (73)	35 (67)	72 (70)
1	13 (25)	16 (31)	29 (28)
2	0 (0)	1 (2)	1 (1)
Unknown	1 (2)	0 (0)	1 (1)
Histology			
Clear cell	37 (73)	41 (79)	78 (76)
Nonclear cell	14 (28)	11 (21)	25 (24)
Sites of metastasis			
Lung	36 (71)	30 (58)	66 (64)
Liver	12 (24)	14 (27)	26 (25)
Bone	5 (10)	4 (8)	9 (9)
No. metastatic sites			
1	25 (49)	23 (44)	48 (47)
2	15 (29)	15 (29)	30 (29)
3 or more	11 (22)	14 (27)	25 (24)
Modified MSKCC risk category*†			
Favorable‡	16 (31)	18 (35)	34 (33)
Intermediate/poor§	34 (67)	34 (65)	68 (66)

*Modified MSKCC risk category criteria were as follows: ECOG score >1, hemoglobin <lower limit of normal, lactate dehydrogenase >1.5 times the upper limit of normal, calcium >10/dL, and <1 y time interval between initial diagnosis and start of study drug. Value in table expressed as *n* (%).

†*N* = 102 because complete baseline-modified MSKCC risk category criteria were not available for one patient.

‡Patients with no risk factors per modified MSKCC risk category criteria.

§Patients with at least one risk factor per modified MSKCC risk category criteria.

Table 2. Summary of efficacy

Variable	Twice daily dose		Total (N = 103)
	10 mg (n = 51)	100 mg (n = 52)	
Best response (RECIST criteria)			
CR	2 (4)	0 (0)	2 (2)
PR	0 (0)	2 (4)*	2 (2)
SD	28 (55)	24 (46)	52 (50)
PD	18 (35)	24 (46)	42 (41)
Incomplete data	3 (6)	2 (4)	5 (5)
ORR% (90% CI)	3.92 (0.70-11.83)	0.0	1.94 (0.35-5.99)
PFS			
Median PFS, mo	4.2	3.3	NA
Observed 4-mo PFS% (90% CI)	54 (42-66)	41 (30-53)	48 (39-56)
Observed 6-mo PFS% (90% CI)	39 (27-51)	32 (21-43)	35 (27-43)
Overall survival			
Median survival, mo	27.8	26.1	26.1

NOTE: There were no statistically significant differences in ORR (P = 0.243, Fisher's exact test), PFS (P = 0.803, log-rank test), or overall survival (P = 0.588, log-rank test) between groups. Values in table expressed as n (%).
Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; 90% CI, 90% confidence interval; NA, not available.
*The two partial responses were not confirmed by a second tumor assessment within 60 days of the initial observation of the response. For this reason, they were not included in the calculation of the ORR.

to a treatment-related adverse event of intracranial bleeding (grade 4) and for three patients in the 100 mg twice daily group due to treatment-related adverse events of gastrointestinal bleeding (grade 3), hemoptysis (grade 3), and neck pain in conjunction with headache (both grade 2). Other reasons for discontinuing ABT-510 occurred at similar frequencies in both groups and included adverse events considered by the investigator to be not related or probably not related to treatment (10%), withdrawal of consent (2%), and other reasons (11%).

Patient characteristics are summarized in Table 1. The distribution of ECOG performance scores was similar between groups, with 70% of patients having a score of 0 at baseline. The predominant histology in both groups was clear cell renal cell carcinoma. Overall, 92% had a prior nephrectomy. Metastases were limited to a single site in 47% of patients, and the lungs were the most common metastatic site. Thirty-three percent of patients had favorable risk characteristics and 60% had intermediate risk characteristics as defined by modified MSKCC criteria.

Exposure to ABT-510. The median duration of exposure to ABT-510 was longer in the 10 mg twice daily group (112 days, range 14-727 days) than in the 100 mg twice daily group (91 days, range 22-473 days). Four patients in each group self-administered ABT-510 for >1 year. Approximately 20% of patients (11 of 51 in the 10 mg twice daily group and 10 of 52 in the 100 mg twice daily group) received <8 weeks of treatment. Disease progression was the most common reason for discontinuation among these 21 patients, with 9 of 11 in the 10 mg twice daily group and 8 of 10 in the 100 mg twice daily group discontinuing for this reason.

Efficacy. Efficacy end points are summarized in Table 2. There were no significant differences between treatment groups in PFS (P = 0.803), ORR (P = 0.243), or overall survival (P = 0.588). Median PFS was 4.2 months for the 10 mg twice daily group and 3.3 months for the 100 mg twice daily group (Fig. 1). Based on Kaplan-Meier estimates, the 6-month PFS rates were 39% (10 mg twice daily), 32% (100 mg twice daily), and 35% (combined treatment groups). Median PFS for combined treatment group patients meeting modified MSKCC criteria for favorable risk (N = 34) was 4.0 months, whereas for those in the intermediate/poor risk category (N = 68), the median PFS was 2.2 months (P = 0.194).

The ORR (confirmed CR + PR) for the 10 mg twice daily group was 4%, based on two confirmed CRs observed in one patient with clear cell renal cell carcinoma and one patient with chromophobe renal cell carcinoma. Two PRs were observed in the 100 mg twice daily group but were unconfirmed. The longest duration of SD was noted for a patient in the 10 mg twice daily group, who had SD at all tumor assessments, including the last assessment on day 690.

Figure 2 displays the best percentage change from baseline in tumor size. Decreases from baseline in tumor size corresponding to best percentage changes of -2% to -100% were observed for 18 of 98 patients with a minimum of a baseline and one follow-up tumor assessment. The five remaining patients discontinued ABT-510 before the first disease assessment was done.

Median overall survival was 27.8 months for the 10 mg twice daily group and 26.1 months for the 100 mg twice daily group (P = 0.588; Fig. 3). For patients in both treatment groups in the favorable risk category (n = 34), median overall survival was not reached at the time of analysis, whereas for patients in the intermediate/poor risk category (n = 68), median overall survival was 20.1 months (P = 0.091).

Toxicity data. Adverse events with an overall incidence of at least 10% (all grades) included injection site events (e.g., bruising, irritation, pain, pruritis, and reaction; 84%), fatigue (50%), headache (20%), and nausea (19%). The incidence of these adverse events was similar for both groups. The overall incidence of grade 3/4 adverse events was 29% in the 10 mg twice daily group and 21% in the 100 mg twice daily group with 12% and 8%, respectively, judged possibly or probably treatment-related by the investigators (Table 3). Serious adverse events were reported for 18% of patients (10 patients in the 10 mg twice daily group and 9 patients in the 100 mg twice daily group). In most cases, serious adverse

events were judged not related to study drug. Four treatment-related, grade 3/4 adverse events met serious adverse event criteria. These were intracranial hemorrhage (10 mg twice daily) and gastrointestinal hemorrhage, hemoptysis, and deep vein thrombosis (100 mg twice daily). Study drug was discontinued for the events involving bleeding and was interrupted for the thrombotic event. One additional treatment-related serious adverse event, grade 2 dehydration, was reported for a patient in the 10 mg twice daily group. Deaths for 22 patients in each group have been reported, and none was treatment related. The most frequent cause of death, which was described as PD or renal cell carcinoma, was recorded for 16 of 22 patients in each treatment group. In addition, PD or renal cell carcinoma was recorded as a contributory cause of death for three patients in the 100 mg twice daily group where the primary cause of death was pulmonary edema, respiratory arrest, or hepatic failure. Although no patients died while receiving study drug, six patients died within 30 days after the last dose of study drug. Four of these six deaths were due to renal cell carcinoma (one 10 mg twice daily and three 100 mg twice daily), one to pulmonary edema secondary to heart failure (10 mg twice daily), and one to hepatic failure and disease progression (100 mg twice daily).

The incidence of grade 3 hematologic toxicities was low, and there were no grade 4 hematologic toxicities. Decreases from baseline in hemoglobin, platelet count, and neutrophil count corresponding to grade 3 toxicities were observed for one patient each in the 10 mg twice daily group. In the 100 mg twice daily group, two patients experienced decreases from baseline in hemoglobin, whereas one patient each experienced decreases from baseline in neutrophil count and lymphocyte count that met grade 3 criteria. Hyperglycemia was the most common grade 3 chemistry abnormality; it was observed in one patient in the 10 mg twice daily group and three patients in the 100 mg twice daily group. Other grade 3 abnormalities (elevated [calcium, potassium, bilirubin, and transaminases] or decreased [sodium, phosphate, and albumin]) were rare, reported for one patient each, and equally distributed between groups. A single grade 4 aspartate aminotransferase result was reported for the patient that died due to hepatic failure.

Discussion

Chemotherapy with cytotoxic agents and hormonal therapies is generally ineffective in renal cell carcinoma. Until recently, the approach to treatment of patients with advanced renal cell carcinoma has been limited to administration of immunotherapeutic agents such as the IFNs and the interleukins. Clinical benefit has been modest, whereas toxicities have been considerable. Newer approaches focus on antiangiogenic agents, and thus take into consideration the molecular events that lead to the disease pathophysiology of renal cell carcinoma. The recent approvals of sorafenib and sunitinib have improved the treatment options for patients with advanced renal cell carcinoma.

At the time this study began, immunotherapy with IFN-α and interleukin-2 was the standard of care for patients with advanced renal cell carcinoma. The MSKCC prognostic model, based on administration of IFN-α, provided respective 4- and 6-month PFS rate estimates of 55% and 42% as benchmarks for comparison with new investigational therapies, including angiogenesis inhibitors (21). Because preclinical and clinical data for some of the angiogenesis inhibitors suggest that robust tumor responses may not be observed or necessary for appropriate evaluation of such agents, PFS is a more appropriate efficacy end point. The 6-month PFS rate observed for ABT-510 in this study was 35% when treatment group data were pooled. Whereas this rate estimate was sufficient to reject the null hypothesis (i.e., that the true rate estimate at 6 months was ≤20%), progress in the treatment of advanced renal cell

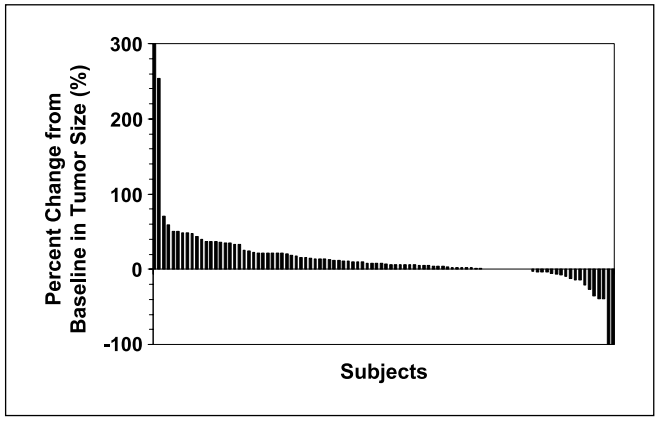

Fig. 2. Best percentage change from baseline in tumor size after administration of ABT-510.

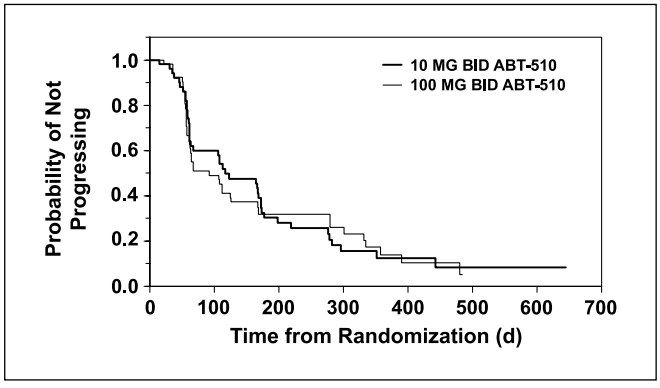

Fig. 1. Kaplan-Meier plot of PFS after administration of ABT-510.

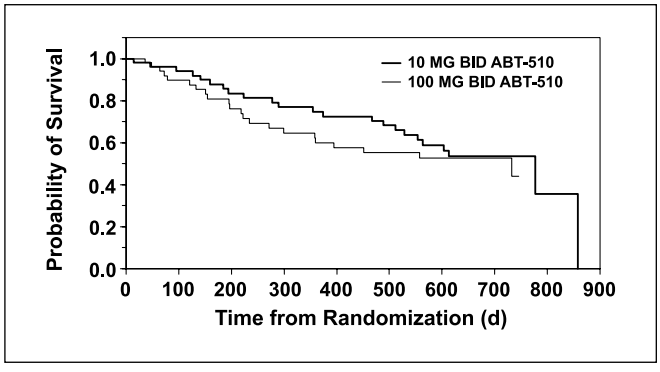

Fig. 3. Kaplan-Meier plot of overall survival after administration of ABT-510.

Table 3. Treatment-related, grade 3/4 adverse events

Event category and adverse event*	10 mg twice daily (*n* = 51)	100 mg twice daily (*n* = 52)	Total (*n* = 103)
Any adverse event	6 (12)	4 (8)	10 (10)
General			
Anemia	1 (2)	0 (0)	1 (1)
Injection site urticaria	0 (0)	1 (2)	1 (1)
Neutrophil count decreased	1 (2)	0 (0)	1 (1)
Anorexia	2 (4)	0 (0)	2 (2)
Decreased appetite	1 (2)	0 (0)	1 (1)
Bleeding			
Gastrointestinal hemorrhage †	0 (0)	1 (2)	1 (1)
Intracranial hemorrhage †	1 (2)	0 (0)	1 (1)
Hemoptysis †	0 (0)	1 (2)	1 (1)
Thrombosis			
Deep vein thrombosis †	0 (0)	1 (2)	1 (1)

NOTE: Adverse events are possibly or probably related to study drug based on investigator's assessment of causality. Values in table expressed as *n* (%).
*Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 9.0.
† Serious adverse event.

carcinoma since the inception of the study reduces the importance and relevance of this finding. The recently approved agents sunitinib and sorafenib have replaced IFN-α as the standard of care for this patient population, and as such are the relevant therapies with which new investigational therapies should be compared.

Treatment with ABT-510 resulted in a median PFS of 4.2 months (10 mg twice daily) and 3.3 months (100 mg twice daily) for patients with previously untreated renal cell carcinoma. Median PFS observed in two phase 2 trials of sunitinib in previously treated patients and a phase 3 trial in previously untreated patients were 8.2 and 11 months, respectively (6, 7, 11). For sorafenib, median PFS was 6 months as reported in a phase 2 study in previously untreated renal cell carcinoma patients and 5.5 months in a phase 3 study in renal cell carcinoma patients who had relapsed after one prior systemic treatment (8, 10). Median overall survival for patients treated with ABT-510 was 27.8 months (10 mg twice daily) and 26.1 months (100 mg twice daily). In studies of sunitinib, median overall survival had not yet been reached at the time of analysis (6, 7), whereas in a phase 3 study of sorafenib, median overall survival was 19.3 months (10). Because ABT-510 is a cytostatic agent, the low ORR of 4% (10 mg twice daily) was not surprising. However, this ORR is similar to that seen in patients with clear cell renal carcinoma with spontaneous remissions. In this study, one of the two patients that achieved CRs had clear cell histology, whereas the other patient had chromophobe renal cell carcinoma. Treatment with ABT-510 resulted in a best response of SD for 50% of patients, and the probability of not experiencing disease progression for 4 months was 54% (10 mg twice daily) and 41% (100 mg twice daily). Twenty-one percent of patients receiving ABT-510 had a complete or PR or SD for at least 6 months. The reported incidence of SD for ≥3 months for sunitinib ranged from 27% to 29%; however, sunitinib had an ORR ranging from 31% to 40% (6, 7). Other agents under development for treatment of renal cell carcinoma include bevacizumab and temsirolimus. As a single agent, bevacizumab treatment resulted in a 10% ORR (4). When bevacizumab was administered in combination with erlotinib in a relatively small nonrandomized study, a 25% ORR and median PFS of 11 months were observed (5). A 7% ORR, 17% incidence of SD for ≥6 months, and median overall survival of 15 months were reported for single-agent temsirolimus in a phase 2 study (22). Results from a phase 3 study in poor risk patients with advanced renal cell carcinoma included a median PFS of 3.8 months and median survival of 10.9 months when temsirolimus was administered as a single agent (23).

The ABT-510 safety profile seen in this study was similar to that observed in phase 1 trials and a phase 2 trial in patients with advanced soft tissue sarcoma (24). The most common treatment-related adverse events in this study were events involving the injection site, fatigue, headache, and nausea. The incidence of grade 3/4 treatment-related adverse events was low. There were three grade 3/4 bleeding events and one thrombotic event. Grade 3/4 hematologic and blood chemistry toxicities were infrequent occurrences. The safety profile is consistent with the mode of administration and mechanism of action of ABT-510, making it predictable and manageable. The ABT-510 safety profile is more benign than safety profiles reported for sunitinib and sorafenib, which included a higher incidence of grade 3/4 hematologic and nonhematologic toxicities. This is also the case for bevacizumab and temsirolimus, with respective safety profiles that included grade 3 hypertension and bleeding events (bevacizumab) and grade 3/4 hypophosphatemia, hyperglycemia, and hypertriglyceridemia (temsirolimus).

Although the toxicity profile of ABT-510 might be slightly better than the recently approved agents sunitinib and sorafenib, in the context of clinical activity observed with those agents, the current observations with ABT-510 do not warrant further investigation of ABT-510 as a single agent in renal cell carcinoma. A biomarker identifying patients who would most likely respond to treatment could improve the potential utility of single-agent ABT-510 and baseline

concentration of circulating endothelial cells may be predictive of favorable outcome (25). The novel mechanism of action combined with a favorable safety profile justifies further evaluation in combination therapy to target separate pathways critical to tumor growth.

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