Featured Article

A Phase II Trial of Gefitinib (Iressa, ZD1839) in Stage IV and Recurrent Renal Cell Carcinoma

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ABSTRACT

Purpose: **The epidermal growth factor receptor (EGFR) is overexpressed in 75 to 90% of renal cell carcinomas and may play a role in tumor initiation and progression. Gefitinib (Iressa, ZD1839) is a potent, selective EGFR-tyrosine kinase inhibitor. This trial was undertaken to assess the efficacy and toxicity of gefitinib in advanced renal cell carcinoma.**

Experimental Design: **Oral gefitinib, 500 mg once daily, was given continuously. A single-dose reduction to 250 mg daily was allowed for toxicity. The primary end point was response rate (defined as complete remission + partial remission + stable disease). Secondary end points were progression-free survival, overall survival, toxicity, and correlation of response with EGFR status.**

Results: **Twenty-one patients were enrolled on this study, and all are evaluable for response and toxicity. Patient characteristics were median age 61 (range, 35–78 years); 17 males, 4 females; median performance status 0 (range 0–2); median number of prior systemic therapies 1 (range, 0–3). The median and mean number of cycles of therapy received was 3 and 4.7 (range, 1–14+). The best response was stable disease in eight patients (38%). Median progression-free survival was 2.7 months. Median overall survival was 8.3 months. The difference in overall survival was significantly different between patients with progressive disease *versus* stable disease (6.1 months *versus* 16+ months; Log-Rank test *P* value < 0.0001). Three patients required a dose reduction, all for grade 3 diarrhea. There was no apparent correlation between EGFR status and stability of disease or progression of disease.**

Conclusions: **Gefitinib is without significant conventional activity in renal cell carcinoma. The relation of "stable disease" to treatment or to disease-related prognostic heterogeneity remains to be defined.**

INTRODUCTION

Of the estimated 35,710 new cases of renal cell carcinoma diagnosed in the United States in 2004, 30% will have unresectable or incurable disease, with an associated 12,480 estimated deaths (1). Immunotherapy with interferon-α or interleukin-2 will achieve an objective response in 15% and stable disease in 20% (2). Complete responses occur infrequently and patients with less than CR usually die in less than one year. Chemotherapy is generally ineffective. Novel approaches in both previously untreated patients as well as patients failing standard immunotherapy are needed.

Gefitinib (Iressa, ZD1839) is an orally active, selective epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor (3). The hypothesis underlying this trial was that gefitinib would delay progression and induce tumor regression in patients with renal cell carcinoma because of selective inhibition of EGFR-TK activity. *EGFR* gene is constitutively expressed in the normal kidney. Amplification of the *EGFR* gene has been demonstrated in 5 to 25% of renal cell carcinomas (4, 5). Overexpression of the *EGFR* gene as measured by increased *EGFR* mRNA compared with corresponding normal kidney tissue occurs in 60 to 80% of renal cell carcinomas (4, 6, 7). Overexpression of the EGF receptor is thought to take part in tumor initiation and progression in renal cell carcinoma (8–10). Several investigators have reported no correlation between the level of *EGFR* mRNA and tumor grade or stage in renal cell carcinoma, raising the possibility that EGFR overexpression is an independent prognostic factor in renal cell carcinoma (4, 7). EGFR expression measured by immunohistochemistry with a monoclonal antibody directed against EGFR has also been found in 75 to 90% of renal cell carcinoma tumors (5, 11, 12). EGFR content expressed as total binding sites for EGF has been associated with higher-grade tumors and worse prognosis (12, 13). Co-overexpression of both EGFR and p185erbB2 is significantly associated with metastatic disease (14). Anti-EGFR antibodies have been shown to inhibit growth of EGFR-overexpressing tumor cells (15). Mab C225, an anti-EGFR humanized chimeric monoclonal antibody, can delay tumor growth in ACHN human renal cancer cell tumor xenografts (16). Activation of EGFR-TK causes downstream cellular substrates to become phosphorylated on tyrosine, and these are implicated in cancer cell proliferation and survival (17, 18). Inhibition of human renal cell carcinoma by *O*-phospho-L-tyrosine (P-Tyr) has been associated with suppression of EGF-mediated EGFR tyrosine phosphorylation (19).

In vitro studies have demonstrated that gefitinib inhibits autophosphorylation of tumor cell lines and cell growth inhibition in a variety of tumor cell lines, and growth delay and tumor

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regression have been seen in a wide range of established tumor xenograft models (20–22). In human renal cell carcinoma tumor xenografts, gefitinib has been shown to both directly inhibit cell proliferation and also to inhibit tumor angiogenesis (22). Not all tumors known to express high EGFR are growth inhibited, and it is not clear what level of EGFR expression is required for response to gefitinib in these tumor xenografts.

Clinical activity of gefitinib has been demonstrated in two phase 2 trials in non–small-cell lung cancer (NSCLC). Partial responses of 12 and 18% and disease control rates of 42 and 54% were achieved in the IDEAL 2 and IDEAL 1 trials, respectively leading to US Food and Drug Administration approval of this drug for chemotherapy-failed NSCLC (23) Owing to the potential involvement of the EGFR in renal cell carcinoma pathogenesis and progression, we wished to assess the response of patients with advanced renal cell carcinoma to gefitinib. In addition, we sought to correlate the clinical course of patients with evidence of EGFR expression in their tumor cells.

MATERIALS AND METHODS

Eligibility. All of the patients who were enrolled onto this study had histologically confirmed, bidimensionally measurable, metastatic renal cell carcinoma that had clearly progressed before enrollment on this trial. Other entry criteria included age >18 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and adequate organ function defined as leukocytes >3,000/μL, absolute neutrophil count >1,500/μL, platelets >100,000/μL, total bilirubin within normal institutional limits, aspartate aminotransferase/alanine aminotransferase ≤2.5 × the institutional upper limit of normal and creatinine <1.5 × the institutional upper limit of normal. Two prior immunotherapy (interferon-α or interleuken-2) regimens, one prior chemotherapy regimen, and prior radiation therapy were allowed, but these therapies had to be completed >4 weeks before entry in this protocol. Patients with no prior therapy for metastatic disease were also eligible. Patients with active brain metastases; a history of allergic reactions attributed to compounds of chemical or biological composition similar to gefitinib; uncontrolled intercurrent illness including, but not limited to, ongoing or active infection; symptomatic congestive heart failure; unstable angina pectoris, cardiac arrhythmia, psychiatric illness, or social situations that would limit compliance with study requirements; and pregnant women were excluded from this clinical trial. Patients with HIV disease who met all other patient selection criteria were not excluded. Patients with ocular inflammation or infection needed to be fully treated before entry into the trial. Malignant tissue available to assess EGFR expression was required. This could be performed on paraffin-embedded tissue. Although recruitment efforts were aimed at patients agreeable to undergoing pretreatment and one-month-posttreatment biopsies, consent to these biopsies was not required for enrollment on this study. No patient agreed to the biopsy, although all patients were presented with the desirability of obtaining a biopsy. The protocol was approved by the Institutional Review Boards at both the University of Maryland Medical System (UMMS) and the Baltimore Veterans Affairs (VA) Medical Center. Voluntary written informed consent was obtained from every patient.

Treatment Plan. Baseline laboratory evaluations were conducted within 1 week prior to the administration of the study agent. Radiographic studies were completed within 4 weeks of therapy initiation. All of the patients underwent a baseline ophthalmologic assessment, which included visual acuity and slit lamp examination. All of the patients were assessed for signs and symptoms of ocular disease at regular clinic visits, and abnormalities required an ophthalmologic assessment.

Treatment was administered on an outpatient basis. The gefitinib dose for this trial was 500 mg per day (total dose). Study drug was dispensed to patients on Day 1 and every 28 days thereafter until the patient developed progressive disease, experienced unacceptable toxicity, or withdrew from the study. Patients were instructed to take two 250 mg tablets daily in the morning, at approximately the same time each day. If the patient inadvertently did not take the morning dose or had emesis within 30 minutes of taking gefitinib tablets, they were instructed to take the dose anytime up to 10 pm the same day. The daily schedule was resumed the next day with the patient taking the scheduled dose in the morning. Compliance was documented with patient-maintained daily diaries and pill counts of residual drug at the time of the clinic visit every 4 weeks.

Concomitant use of medications known to affect the conductive system such as β-blockers, calcium channel blockers, digoxin, and other antiarrhythmics were allowed under investigator supervision. Concomitant use of medication with known ocular toxicity or known to inhibit cytochrome P450 3A4 such as chloroquine, hydroxychloroquine, amiodarone, tamoxifen, chlorpromazine, ketoconazole, itraconazole, troleandomycin, erythromycin (and other macrolides), diltiazem, and verapamil were avoided. Patients requiring these medications were informed of the possible increased risk of side effects. Oral retinoids were not allowed because of theoretical concerns about negatively affecting gefitinib action. Use of oral steroids for the treatment of skin toxicities was discouraged. Treatment with immunotherapy, chemotherapy, other investigational drugs, or radiation was not permitted. Any indication for radiotherapy after protocol treatment was begun constituted disease progression.

Dose Modification Criteria. Only one dose reduction of 50% was allowed, decreasing from 500 mg per day to 250 mg per day, according to criteria described below. Adverse events were assessed with the descriptions and grading scales found in the revised National Cancer Institute Common Toxicity Criteria (CTC)

Dermatologic Toxicity. Grade 2 skin rash did not require automatic discontinuation of treatment because this toxicity often improved despite continued treatment with gefitinib. For grade 2 skin rash that was unacceptable to the patient for symptomatic reasons, gefitinib could be temporarily held until resolution and subsequently restarted at the same dose. If symptomatic grade 2 skin rash recurred after reinstituting treatment at the 500 mg daily dose and required temporary discontinuation, treatment was held until resolution to grade 1 or less and was reinstituted at 250 mg daily. For grade 3 and 4 skin toxicity, gefitinib was held until resolution to grade 1 or less and then could be resumed at the same dose or reduced at the investiga-

tor's discretion. Patients with unresolving toxicity after 2 weeks were taken off study. Once a dose had been reduced for a patient, it could not be subsequently increased. A second dose reduction was not allowed.

Gastrointestinal Toxicity. Nausea and/or vomiting associated with gefitinib were controlled with adequate antiemetics before administration. The dose of gefitinib was repeated if emesis occurred within 30 minutes of taking the tablet. In the event of CTC grade 1–2 diarrhea, no specific supportive care was usually needed or indicated. For CTC grade 3 diarrhea, gefitinib was discontinued up to a maximum of 14 days until resolution or until diarrhea decreased in severity to CTC grade 1. Dose was reinstituted at 250 mg daily if diarrhea was felt to be clearly drug related. Treatment approaches to gefitinib-related diarrhea include both standard doses of loperamide administered as a 4-mg dose followed by 2-mg doses every 4 h, and a higher dose schedule of 2-mg every 2 hours. If, despite the dose reduction, CTC grade 3 diarrhea recurred, gefitinib was discontinued, and the patient withdrawn from the trial. For CTC grade 4 diarrhea, gefitinib was discontinued, and the patient was withdrawn from the trial.

Hepatic Toxicity. The day-1 bilirubin value of each 28-day cycle was used to determine the dose of gefitinib. If the serum bilirubin was $>1.5 \times$ normal value, the gefitinib was discontinued for a maximum of 14 days until resolution or decrease in severity to CTC grade 1. Gefitinib could be restarted with a dose reduction to 250 mg daily if the investigator thought that the hepatic toxicity was clearly drug related. If, despite the dose reduction, CTC grade-2 bilirubin recurred, gefitinib was permanently discontinued.

Ocular Toxicity. Patients experiencing subjective symptoms of visual disturbance, eye pain, eye itchiness, or redness had treatment with the trial drug temporarily interrupted until the patient could be evaluated by an ophthalmologist. For grade 2 toxicity that was medically concerning, treatment was held until resolution and was reinstituted at 250 mg daily. For grade 3 and 4 toxicity, treatment was discontinued until resolution to grade 1 or less and then reinstituted at a dose of 250 mg daily.

Response Criteria. Response and progression were evaluated in this study with the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (24). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. All of the patients enrolled had measurable lesions defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques [positron emission tomography, computed tomography (CT), magnetic resonance imaging, X-ray] or as >10 mm with spiral CT scan.

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions and recorded and measured at baseline. A sum of the longest diameter for all target lesions was calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter was used as reference by which the objective tumor response was characterized. Tumor lesions situated in a previously irradiated area were not considered measurable.

Complete response was defined as disappearance of all target lesions. Partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Progressive disease was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions. Stable disease was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

For a status of partial response or complete response to be assigned, changes in tumor measurements were confirmed by repeat assessments performed 4 weeks after the criteria for response were first met. In the case of stable disease, follow-up measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

The duration of overall response was measured from the time that measurement criteria are met for complete response or partial response (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started. Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-free survival was determined for each patient from the initiation of therapy until the patient reaches objective disease progression. Death constituted a progression event in those patients who die before disease progression. Patients without documented objective progression at the time of final analysis were censored at the date of their last objective tumor assessment. An expert, independent of the study, verified the response for all subjects based on key radiologic images.

Immunohistochemical Analysis for Epidermal Growth Factor Receptor. Immunohistochemical analysis for EGFR was undertaken in formalin-fixed paraffin-embedded specimens, with the Zymed (San Francisco, California) anti-EGFR antibody. The criteria used for grading for EGFR was (*a*) negative; no staining; (*b*) weakly positive (1+): focal areas positive in tumor cells displaying slight staining at targeted antigenic site; (*c*) moderately positive (2+): staining in some areas of tumor cells with less intense staining than 3+; (*d*) strongly positive (3+): staining intense over targeted antigenic site area with a majority of cells (>50%) stained.

Statistical Methods. The primary end point of this trial was response rate, defined as complete remission + partial remission + stable disease rate. The secondary end points were progression-free survival, overall survival (OS), and correlation between response and tumor EGFR expression. Patient characteristics, toxicity, response rates, and survival were determined for all of the treated patients. All responses were assessed by an independent radiology review on key images. Overall survival time was calculated from the date of treatment to the date of death or last follow-up. Progression-free survival was measured from the start of treatment to the date when the patient reached objective disease progression. Death was regarded as a progressive event in those patients who died before disease progression was determined. Patients who withdrew from the study were

censored for both overall survival and progression-free survival at the time of last assessment. Actuarial estimates of overall survival and progression-free survival were calculated according to the Kaplan–Meier method (25) and was compared by using the Log-Rank test. All of the statistical analyses were performed with SAS 8.02 software package (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics. Between February 2001 and March 2002, 21 patients with metastatic renal cell carcinoma were enrolled in this study. Patient characteristics are displayed in Table 1. The median number of different metastatic sites was two (range, one to five sites). Seven patients had received prior radiation; five received one course, one received two courses, and one received five prior courses. Two patients had prior central nervous system metastasis and had undergone successful gamma knife radioablation for a single brain metastasis. Five patients had radiation to symptomatic bone metastases. One patient had brachytherapy for a soft tissue mass, and a second patient had radiofrequency ablation of a large paraspinal mass. Six patients had prior surgery for metastatic disease. Two had resections of pulmonary nodules, two had partial resections and orthopedic stabilization of bone metastases involving the femur, one patient underwent adrenalectomy, and one patient had a resection of a soft tissue mass in his arm. Eight patients had received no prior systemic therapy, seven patients had received one prior systemic therapy regimen, four had received two prior systemic therapy regimens, and two had received three prior systemic therapy regimens. These therapies were variably given in combination or as single agent, both of which were designated a treatment regimen.

Table 1 Demographics

No. registered/evaluable	21/21
Age, median/mean (range)	61/59 (35–78)
Gender	
Male	17
Female	4
ECOG performance status	
0	12
1	8
2	1
No. of metastatic sites	
Median	2
1	4
2	8
3	5
4	3
5	1
Tumor sites	
Lung	17
Lymph nodes	12
Bone	9
Liver	4
Soft tissue	3
Renal fossa	3
Adrenal gland	2
Primary tumor	1
Prior nephrectomy	20
Prior therapy for metastatic disease	
Immunotherapy (interferon α or interleukin 2)	12
Thalidomide	6
Chemotherapy	3
Vaccine	1
Radiotherapy	7
Surgery	6
No. adverse prognostic factors	
0 (good)	10
1–2 (intermediate)	11
≥3 (poor)	0

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

The pathologic subtype was pure clear-cell carcinoma in 11 patients, clear- cell plus granular cell carcinoma in three patients, clear cell with focal sarcomatoid features in two patients, clear-cell plus granular cell plus spindle cell sarcomatoid carcinoma in one patient, granular cell carcinoma in two patients, and papillary carcinoma with sarcomatoid features in one patient. One patient's pathology subtype could not be determined because the biopsy source was bone.

Treatment Cycle Administered. A total of 99 cycles of treatment had been administered during this trial at the time of analysis. The median duration of therapy received was three months, and the mean duration was 4.7 months (range, 1–14+). Four patients received only one cycle of therapy because of rapidly progressive disease at the planned 1-month tumor assessment. Dose modification for toxicity was necessary in three patients, in each case, because of grade 3 diarrhea.

Toxicity Data Complete toxicity data are provided in Table 2. Nearly all patients experienced skin toxicities. In all patients, skin toxicity was grade 1 or 2 and dramatically improved with topical clindamycin antibiotic solution. Moisturizing creams ameliorated dry or itchy skin. In two patients with stable disease, spontaneous improvement in skin lesions at 7 and 11 months, respectively, heralded documented progression of disease.

Diarrhea was the second most common toxicity occurring in 81% of patients. Three patients had grade 3 diarrhea, which decreased to grade 1 or less with dose reduction. Diarrhea could be adequately managed in most patients with loperamide and by avoidance of foods associated with exacerbation of diarrhea. One patient did develop dehydration and secondary reversible renal insufficiency that required hospitalization. The drug was held and then dose reduced without additional problems. This was a late event occurring in cycle 10 for this patient.

Three patients developed grade 2 hematuria. All three patients had undergone nephrectomy for their primary malignancy. Hematuria resolved with intravenous hydration in one patient, with bladder irrigation in a second patient, and with temporary cessation of warfarin in the third patient. A fourth patient with massive lung metastases developed temporary hematemesis secondary to gastritis and an esophageal tear that resolved spontaneously.

There were no deaths associated with treatment. No patients were removed from the study for toxicity. Only one patient had grade 4 toxicity consisting of dyspnea requiring hospitalization and supplemental oxygen. At the time, this adverse event was thought to be disease related because of known bulky pulmonary metastases and progressive bilateral pulmonary effusions. Drug was stopped because of progressive disease. Recent reports have described the uncommon occurrence

Table 2 Toxicity

Adverse events	National Cancer Institute CTC grade					
	1	2	3	4	Total	%
Skin toxicities	6	13			19	90
Diarrhea	11	3	3		17	81
Fatigue	7	5	1		13	62
Bleeding	5	3	2		10	48
Pain	2	6	1		9	43
Nausea	7	1			8	38
Neurology	4	4			8	38
Brain metastases					8	38
Eyes	5	2	1		8	38
Edema	4	1	1		6	29
Cough	5	1			6	29
Shortness of breath		3	1	1	5	24
Constipation	4				4	19
Anorexia	3	1			4	19
Alopecia	1	2			3	14
Reflux	1	2			3	14
Vomiting	2	1			3	14
Infection	1	2			3	14
Hyperbilirubinemia	2				2	10
Dysgeusia	2				2	10
Headache	1		1		2	10
Leg cramps		2			2	10
Depression	1				1	5
Insomnia	1				1	5
Anemia			1		1	5
AST elevation		1			1	5
ALT elevation			1		1	5
Hypoglycemia	1				1	5
Swollen tongue	1				1	5
Urinary incontinence	1				1	5
Dehydration			1		1	5

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

of interstitial lung disease in patients receiving gefitinib. In retrospect, this may have been a contributing factor, but there was no suggestion of this toxicity.

Response and Survival Data. All 21 patients enrolled on this study were evaluable for response and survival. One patient withdrew from the study and was censored for both overall survival and progression-free survival at the time of last assessment. There were no complete or partial responses. Eight patients achieved stable disease as their best response. One of these patients had a good minor response with a 27% tumor reduction (30% reduction is required for partial response). Thirteen patients had no response, with progression of disease at first assessment. In four patients, disease progression was rapid, requiring cessation of therapy after $\leq$1 month.

Five (62.5%) of 8 patients with stable disease were categorized as low risk compared with 5 (38%) of 13 patients with progressive disease based on the established criteria of Motzer *et al.* (26) No patient on this trial was categorized as high risk.

Overall, the median progression-free survival was 2.7 months and the median overall survival was 8.3 months (Figs. 1 and 2). Of interest, there was a marked difference between patients achieving stable disease and those who did not. The median progression-free survival was 8.5 months [95% confidence interval (95% CI), 4.5–11 months] for patients with stable disease compared with 2.2 months (95% CI, 1.3–2.7 months) for patients with progression of disease (Log-Rank test P value $<$ 0.0001; Fig. 3). The overall median survival was only 6.1 months for patients with progression of disease. The median overall survival had not been reached at 16+ months for patients with stable disease (Fig. 4). The difference in survival between these two groups was significant (Log-Rank test P value $<$ 0.0001). At the time of analysis, all 13 patients with progression of disease as best response had died, compared with 2 of 8 patients with stable disease. Although patients presented for this trial with recent evidence of disease progression, their prior rate of progression could not be determined because they came to a referral center having had a very heterogeneous prior follow-up and treatment. Hence it is uncertain whether "stable disease" can be attributed to the effect of the drug.

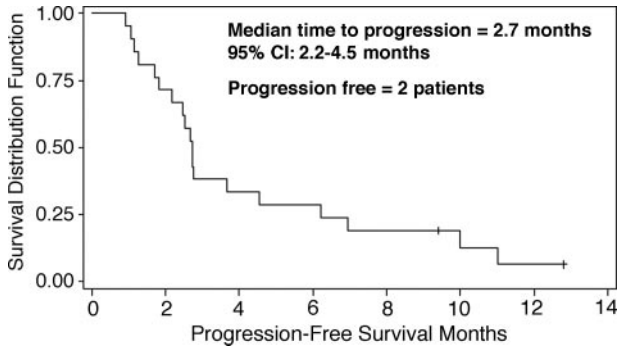

Fig. 1 Progression-free survival.

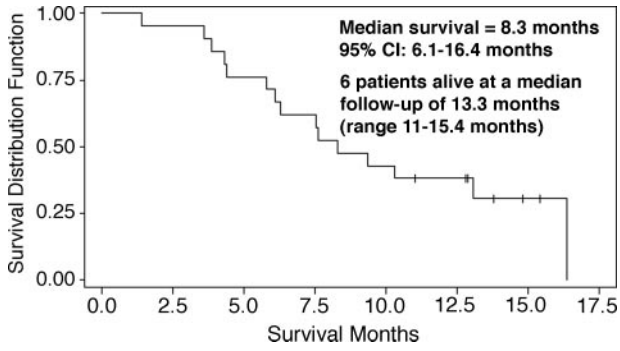

Fig. 2 Overall survival.

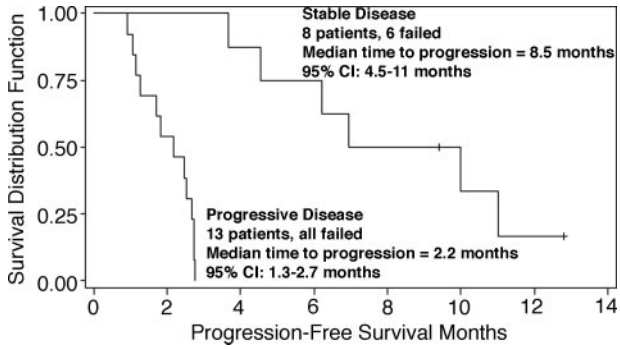

Fig. 3 Progression-free survival; stable *versus* progressive disease.

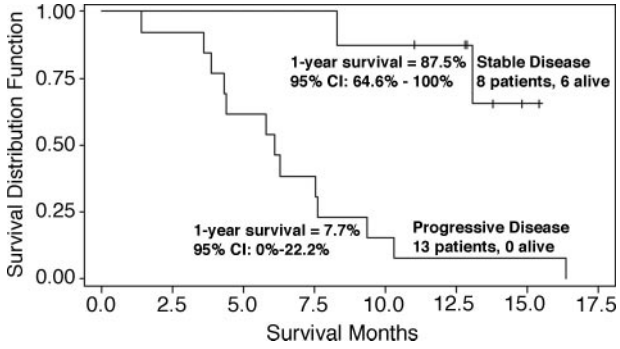

Fig. 4 Overall survival; stable *versus* progressive disease.

Central Nervous System Progression. Eight (38%) of the 21 patients developed either new or recurrent brain metastases during their disease course. For the two patients with known prior brain metastases, this occurred subsequent to their declared disease progression on gefitinib. In one patient, the development of brain metastases was the site of disease progression. In one patient, symptomatic brain metastases occurred simultaneously with disease progression elsewhere. In six patients, brain metastases were documented after clear progression at other metastatic disease sites at 1, 2, 5, 6, 7, and 16 weeks after ending the study drug because of progressive disease.

Epidermal Growth Factor Receptor Analysis. EGFR analysis and corresponding best response are shown in Table 3. In 19 of the 20 patients with adequate tissue for EGFR analysis, the tumor specimens stained positive for EGFR. One patient's submitted tissue was inadequate for staining. There was no correlation between the intensity of EGFR staining (0 or 1 *versus* 2 or 3) and having stable *versus* progressive disease ($P = 0.6$, Fisher's Exact test).

DISCUSSION

Epidermal growth factor receptor as a target for cancer therapy was first proposed 2 decades ago (27–29). It is a logical target based on its pivotal role in signaling pathways, mediating tumor cell proliferation and maturation, angiogenesis, invasion/metastasis, and inhibition of apoptosis (17, 30, 31). Gefitinib, an ATP-competitive tyrosine kinase inhibitor has now been extensively tested in phase I to III trials and has received US Food and Drug Administration approval in 2003 as monotherapy for advanced non–small-cell lung cancer after failure of both platinum-based and docetaxel chemotherapy (20, 32–35). EGFR is overexpressed in renal cell carcinoma, and this has been associated with both higher-grade malignancy and worse prognosis supporting the assessment of an EGFR antagonist in kidney cancer.

Although EFGR inhibitors may cause tumor regression, their more predominant actions may be cytostatic. Hence, in designing this trial, we included the "softer" clinical end points of time-to-disease progression and stabilization of disease to capture the potential clinical benefit in the absence of classic tumor responses. If these end points are clinically meaningful, they should translate into improvement in survival.

No patients in this trial achieved a partial or complete response, with only one patient demonstrating a minor response with 27% tumor shrinkage. However, eight patients (38%) had durable stable disease. All of the patients experienced recent progression of disease at the time of trial entry. The overall survival was significantly longer, >16 months for patients with stable disease, compared with 6.1 months for patients with progression. This may reflect a beneficial effect of gefitinib on disease course or, alternatively, may be attributed to better pretreatment prognostic features for the patients with prolonged stable disease.

Investigators at Memorial Sloan Kettering have developed a model predictive for survival based on multivariate analysis of 670 patients with advanced renal cell carcinoma (26). They identified five pretreatment features associated with shorter survival; these included a low Karnofsky performance (<80%), high serum lactate dehydrogenase (>1.5 times the upper limit of normal), low hemoglobin (less than the lower limit of normal), high serum calcium (>10 mg/dL), and absence of prior nephrectomy. Patients who had no risk factor had a median survival time of 20 months. With one or two risk factors, median survival time decreased to 10 months; and for three or more risk factors, median survival was only 4 months. Using the Motzer criteria (26), we categorized the majority of patients (62.5%) with stable disease as low-risk, compared with only 38% of patients with progressive disease.

Multiple metastatic organ sites have also been associated with poorer survival (36). The median number of metastatic sites was two in both groups. However, the range was one to three for patients with stable disease compared with one to six for patients with progressive disease. In the latter group, 5 of the 13 patients had four or more sites of metastatic disease.

Retrospective analysis of risk factors does suggest that patients on this trial with stable disease had certain features of an overall better prognostic group. The impact of prognostic factors on survival cannot be mitigated. The fact that patients with progressive disease had poorer than predicted survival of only 6.1 months based on the Motzer risk classification could be indicative of a poorer outcome with the experimental therapy or could reflect the limitations of this model.

Investigators at the University of Chicago analyzed survival in 153 patients treated with gemcitabine/5-fluorouracil-based regimens, and confirmed the predictive value of the Motzer model (37). However, they found the independent risk factors for poor survival to be poor performance status, absent prior nephrectomy, three or more metastatic sites, decreased albumin, and elevated alkaline phosphatase. Additionally, sarcomatoid features and elevated calcium had borderline significance. In a separate retrospective review of 2,385 patients

Table 3 Response and EGFR staining

	EGFR Staining			
	None	1+	2+	3+
Clinical best response				
Minor response ($n = 1$)	0	1	0	0
Stable disease ($n = 6$)	0	1	3	2
Progressive disease ($n = 13$)	1	5	3	4

undergoing nephrectomy for renal cell carcinoma, the presence of a sarcomatoid component was associated with poorer prognosis (38). In our trial, one patient with stable disease had granular cell carcinoma, the remainder of the patients with stable disease had clear-cell or predominantly clear-cell carcinoma. Inclusion in this trial of patients with non–clear-cell carcinoma may have potentially influenced the results of this trial because the role of EGFR in tumor initiation and progression may be limited to the clear-cell type of renal cancer. Furthermore, inclusion of patients with sarcomatoid histology may have contributed to the shorter survival rate in the patients with progressive disease.

EGFR expression was demonstrated in all but one tumor specimen. There was no correlation between the degree of overexpression and having stable *versus* progressive disease. The recent documentation of EGF receptor mutations in patients with lung cancer who responded to gefitinib (39) calls for more detailed analysis of renal cell carcinoma patients with respect to this variable. Because the sample size of this trial was small, patients with such a mutation may not have been included, or, alternatively, mutations may be of low prevalence in this patient population.

The toxicity profile of gefitinib is well established based on phase I and II trials (20, 32–35). The most common toxicities occurring in the majority of patients include nonbloody, nonmucoid diarrhea and skin reactions, primarily a pustular rash on an erythematous base, sometimes with pruritis and dry skin. Uncommon side effects include international normalized ratio elevation or bleeding in patients on warfarin; corneal erosion, sometimes in association with aberrant eyelash growth; and interstitial lung disease. Toxicity is usually reversible and may be managed with brief discontinuation of the drug followed by reinstitution at a lower dose with better tolerance.

The toxicity in this trial were similar to that previously reported. There was no correlation between the development of skin toxicity and prolonged stable disease, because these reactions were nearly universal. However, of note, two patients with prolonged stable disease, had unexpected improvement in their skin coincident with disease progression, which raises the question of adaptation of the molecular target. Alternatively, this could be secondary to a drop in blood levels due to increased metabolism of gefitinib.

The development of brain metastases occurred at the time of progression or, subsequently, in 38% of the patients. In a reported series of 109 patients with metastatic renal cell carcinoma, the incidence of brain metastases was 17% (40), which corresponds to a 95% CI of 10.8–25.9%. For this smaller series of 21 patients, the incidence of brain metastases was 38% (95% CI, 18.1–61.6%); because the two sets of CIs are overlapped, our results are consistent with the previously reported data. Reviews of available data from completed clinical trials with gefitinib show no increased incidence of central nervous system metastases (personal communication, Judy Ochs, Astra Zeneca).[1] In fact, the drug is thought to probably cross the blood–brain barrier (21), and anticancer activity has been documented in patients with brain metastases treated with gefitinib monotherapy (41–43).

Although there were no partial or complete responses in this trial, one patient did have a 27% reduction in tumor volume, and 38% of previously progressing patients had stable disease with an associated prolonged survival. Hence it seems premature to abandon EGFR antagonists in the treatment of renal cell carcinoma. Alternate EGFR antagonists with monoclonal antibodies directed against the ligand-binding extracellular domain of the EGFR and *EGFR* antisense gene therapy are in clinical trials (44, 45). ABX-EGF, a human IgG2 monoclonal antibody, has demonstrated activity in both *in vitro* and *in vivo* models of renal cell carcinoma (46). In a dose-escalating open-label phase II clinical trial of ABX-EGF (Abgenix, Fremont, California) in renal cell carcinoma, 6% partial or minor responses and 50% stable disease were reported in 88 patients (43). Future clinical development of EGFR inhibitors alone or in combination with other signal-transduction-targeted agents should be considered. However, if such studies are to occur, they must be designed with the conscientious effort to determine the rate of prior progression of disease if the value of "stable disease" is to be adequately assessed.

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