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Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

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ABSTRACT

BACKGROUND

Since sunitinib malate has shown activity in two uncontrolled studies in patients with metastatic renal-cell carcinoma, a comparison of the drug with interferon alfa in a phase 3 trial is warranted.

METHODS

We enrolled 750 patients with previously untreated, metastatic renal-cell carcinoma in a multicenter, randomized, phase 3 trial to receive either repeated 6-week cycles of sunitinib (at a dose of 50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment) or interferon alfa (at a dose of 9 MU given subcutaneously three times weekly). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, patient-reported outcomes, and safety.

RESULTS

The median progression-free survival was significantly longer in the sunitinib group (11 months) than in the interferon alfa group (5 months), corresponding to a hazard ratio of 0.42 (95% confidence interval, 0.32 to 0.54; P<0.001). Sunitinib was also associated with a higher objective response rate than was interferon alfa (31% vs. 6%, P<0.001). The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the group treated with interferon alfa, whereas diarrhea was more frequent in the sunitinib group (P<0.05). Patients in the sunitinib group reported a significantly better quality of life than did patients in the interferon alfa group (P<0.001).

CONCLUSIONS

Progression-free survival was longer and response rates were higher in patients with metastatic renal-cell cancer who received sunitinib than in those receiving interferon alfa (ClinicalTrials.gov numbers, NCT00098657 and NCT00083889).

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ENAL-CELL CARCINOMA IS THE MOST common cancer of the kidney.¹ Up to 30% of patients with renal-cell carcinoma present with metastatic disease,²,³ and recurrence develops in approximately 40% of patients treated for a localized tumor.²,⁴ Since renal-cell carcinoma is highly resistant to chemotherapy, interleukin-2 or interferon alfa is widely used as first-line treatment of metastatic disease. Response rates with these cytokines are low (5 to 20%), and median overall survival is approximately 12 months.⁵-9

Alternative treatments have been lacking for renal-cell carcinoma that is resistant to cytokines. In two recent uncontrolled trials, sunitinib malate, an antiangiogenic agent, showed clinical activity in patients who had undergone previous cytokine therapy. 10,11 In a pooled analysis of these phase 2 studies of sunitinib, the objective response rate was 42%. 11 This rate exceeds the rates reported for cytokines as first-line treatment of metastatic disease. 5,7,9

Sunitinib is an orally administered inhibitor of tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR).12-14 These receptor tyrosine kinases play a key role in the pathogenesis of clear-cell carcinoma, the predominant type of renal-cell carcinoma, through involvement of the von Hippel-Lindau (VHL) gene. VHL is inactivated in up to 80% of sporadic cases of clear-cell carcinoma by deletion, mutation, or methylation. This tumor-suppressor gene encodes a protein that is involved in the regulation of the production of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and a number of other hypoxia-inducible proteins. Inactivation of the VHL gene causes overexpression of these agonists of VEGFR and PDGFR, and the resulting persistent stimulation of the receptors may promote tumor angiogenesis, tumor growth, and metastasis.15-18 Yang et al.19 demonstrated that bevacizumab, an anti-VEGF antibody, has efficacy in renal-cell carcinoma. All these considerations make the receptors for VEGF and PDGF rational targets in the treatment of clearcell renal-cell carcinoma.

We report on the results of a randomized, phase 3 trial of sunitinib, as compared with interferon alfa, as first-line treatment of metastatic renal-cell carcinoma. We selected interferon alfa as a comparator because it is widely used as stan-

dard treatment for metastatic renal-cell carcinoma. The response rates, median progression-free survival, and overall survival with first-line interferon alfa treatment have been characterized from the extensive use of this drug as a comparator in previous phase 3 trials.²⁰

METHODS

PATIENTS

The study population consisted of patients who were at least 18 years of age and had metastatic renal-cell carcinoma with a clear-cell histologic component, confirmed by the participating centers. Patients who had not received previous treatment with systemic therapy for renal-cell carcinoma were enrolled in the study. Other key eligibility criteria included the presence of measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate hematologic, coagulation, hepatic, renal, and cardiac function. Patients were ineligible if they had brain metastases, uncontrolled hypertension, or clinically significant cardiovascular events or disease during the preceding 12 months. All patients gave written informed consent.

STUDY DESIGN

The study was an international, multicenter, randomized, phase 3 trial of sunitinib (Sutent [also called SU11248], Pfizer), as compared with interferon alfa. Randomization was stratified according to baseline levels of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), ECOG performance status (0 vs. 1), and previous nephrectomy (yes vs. no). Patients were randomly assigned in a 1:1 ratio to receive either sunitinib or interferon alfa. Random permuted blocks of four were used to attain balance within strata.

Sunitinib was administered orally at a dose of 50 mg once daily, taken without regard to meals, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. Sunitinib was provided by Pfizer, the sponsor of the trial. Commercially available interferon alfa-2a (Roferon-A, Roche) was used in this study and was provided by Pfizer. Interferon alfa was given as a subcutaneous injection three times per week on nonconsecutive days at 3 MU per dose during the first week, 6 MU per dose the second week, and 9 MU per dose thereafter. A reduction in the dose of sunitinib (to 37.5 mg and then to 25 mg

daily) or of interferon alfa (to 6 MU and then to 3 MU three times per week) was allowed for the management of adverse events, depending on the type and severity of adverse events, according to a nomogram specified in the protocol. Treatment in both groups was continued until the occurrence of disease progression, unacceptable adverse events, or withdrawal of consent.

The study was approved by the institutional review board or ethics committee at each participating center and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

EFFICACY, SAFETY, AND QUALITY OF LIFE

The primary end point of the study was progression-free survival, defined as the time from randomization to the first documentation of objective disease progression or to death from any cause, whichever occurred first. Secondary end points included the objective response rate, overall survival, patient-reported outcomes, and safety.

We assessed the tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST).²¹ We performed tumor assessments with the use of imaging studies at baseline, at day 28 of cycles 1 through 4, and every two cycles thereafter until the end of treatment. We also used such assessments to confirm a response (at least 4 weeks after initial documentation) and whenever disease progression was suspected. The response was assessed by RadPharm, an independent third-party radiology group (independent central review), and by treating physicians (investigators' assessments). The third-party radiologists were unaware of assignments to study groups. Safety was assessed at regular intervals by documentation of adverse events, physical examination, radiography, and multigated acquisition scanning. Laboratory assessments (hematologic and serum chemical measurements) were performed throughout the study by a central laboratory. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0.

Health-related quality of life was assessed with the use of the Functional Assessment of Cancer Therapy — General (FACT-G) and FACT-Kidney Symptom Index (FKSI) questionnaires, ^{22,23} which were administered before randomization, on days 1 and 28 of each cycle, and at the end of treatment.

STATISTICAL ANALYSIS

Retrospective studies have shown that the median progression-free survival was 4.7 months for nearly 500 patients with advanced renal-cell carcinoma who received interferon alfa as first-line therapy. For our study, we determined that 471 events (disease progression or death from any cause) would be required for 90% power to detect a clinically relevant increase in progression-free survival from 4.7 to 6.2 months in patients treated with sunitinib, with the use of a two-sided, unstratified log-rank test with an overall significance level of 0.05. With a 1:1 randomization of assignment to study groups, we estimated that we would need to enroll 690 patients to observe 471 events.

The primary end point was analyzed in all patients assigned to a study group, according to the intention-to-treat principle. A blinded central review of radiologic images was used to assess the primary end point and the objective response rate. Safety analyses were performed on the basis of the treatment actually received. Time-to-event analyses were performed with the use of the Kaplan-Meier method. We explored the potential influences of the baseline characteristics of the patients — such as age, sex, and known risk factors^{20,24} — on progression-free survival with the use of a stratified log-rank test25 and a Cox regression model.²⁶ The proportion of patients who had an objective tumor response in each treatment group was compared by the Pearson chi-square method. For the analyses of health-related quality-of life data, we used repeated-measures mixedeffects models to test overall differences between the two treatment groups.^{27,28} All reported P values are two-sided and were not adjusted for multiple testing.

The cutoff date for data for the planned interim analysis was November 15, 2005. We planned for three scheduled analyses; this report provides the results of the second analysis. The nominal significance level for the interim analysis was determined with the use of the Lan–DeMets procedure with an O'Brien–Fleming stopping rule.²⁹ After the interim analysis had been performed and discussed with the data and safety monitoring committee, patients in the interferon alfa group with progressive disease were allowed to cross over to the sunitinib group.

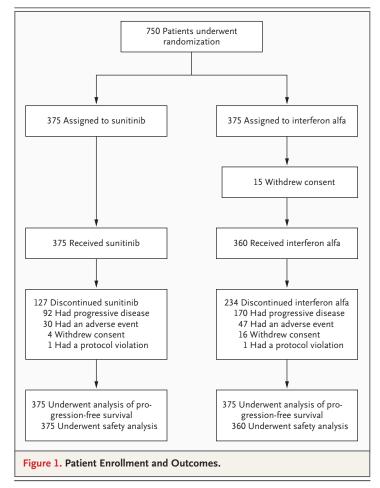
The academic authors and the sponsor were jointly responsible for the trial design and the de-

velopment of the protocol. Data were collected by means of case-report forms and were analyzed by the sponsor. The decision to publish the trial data and final decisions with regard to the content of the manuscript were made by the academic principal investigator in consultation with the other authors. All authors had access to the primary data and take responsibility for the veracity and completeness of the data reported.

RESULTS

PATIENTS

Between August 2004 and October 2005, 750 patients were enrolled at 101 centers in Australia, Brazil, Canada, Europe, and the United States, with 375 patients in each treatment group (Fig. 1). All 375 patients in the sunitinib group received at least one dose of the study drug. Fifteen patients (4%) in the interferon alfa group withdrew consent before starting treatment; the remaining 360 patients



received at least one dose of interferon alfa. The treatment groups were balanced with respect to baseline demographic and disease characteristics (Table 1).

TREATMENT DURATION

At the time of analysis, the median duration of treatment was 6 months (range, 1 to 15) in the sunitinib group and 4 months (range, 1 to 13) in the interferon alfa group. Treatment was ongoing among 248 patients in the sunitinib group (66%) and 126 patients in the interferon alfa group (34%). Reasons for discontinuing treatment were progressive disease (in 25% of the patients in the sunitinib group and 45% in the interferon alfa group, P<0.001), adverse events (8% and 13%, respectively; P=0.05), withdrawal of consent (1% and 8%, respectively; P<0.001), and protocol violation (<1% in each group).

ADVERSE EVENTS

Most general adverse events of all grades occurred more frequently in the sunitinib group than in the interferon alfa group (Table 2). The proportion of patients with grade 3 or 4 adverse events was relatively low in both groups. Treatment-related grade 3 or 4 fatigue was significantly higher among patients in the interferon alfa group than in the sunitinib group (12% vs. 7%, P<0.05). Patients in the sunitinib group, as compared with those in the interferon alfa group, had higher rates of grade 3 diarrhea (5% vs. no cases), vomiting (4% vs. 1%), hypertension (8% vs. 1%), and the hand–foot syndrome (5% vs. no cases, P<0.05 for all comparisons).

The incidence of a grade 3 decline in the left ventricular ejection fraction was similar in the sunitinib group and the interferon alfa group (2% and 1%, respectively). In the sunitinib group, this decline was not associated with clinical sequelae and was reversible after a modification of the dose or discontinuation of treatment. No grade 4 events were reported in this category.

As expected, adverse events that are typically associated with interferon alfa — such as pyrexia, chills, myalgia, and influenza-like symptoms — were all reported more frequently in the interferon alfa group than in the sunitinib group, but the symptoms were generally mild to moderate in severity.

Grade 3 or 4 leukopenia, neutropenia, and thrombocytopenia occurred more often in the

sunitinib group than in the interferon alfa group (P<0.05 for all comparisons). Grade 3 or 4 neutropenia was observed in 12% of patients in the sunitinib group and in 7% of those in the interferon alfa group; the condition was associated with fever in two patients receiving sunitinib. Grade 3 lymphopenia occurred with greater frequency in patients treated with interferon alfa (P<0.05).

A total of 38% of patients in the sunitinib group and 32% in the interferon alfa group had a dose interruption because of adverse events, whereas 32% and 21%, respectively, had a dose reduction.

EFFICACY

Objective Response Rate

Sunitinib treatment was associated with a higher objective response rate than was interferon alfa, as assessed by blinded central review of imaging studies: 31% in the sunitinib group (95% confidence interval [CI], 26 to 36) and 6% in the interferon alfa group (95% CI, 4 to 9; P<0.001) (Table 3). The results of investigator assessment were similar (37% and 9%, respectively; P<0.001).

Progression-free and Overall Survival

Median progression-free survival (as assessed by central review of imaging studies) was 11 months in the sunitinib group (95% CI, 10 to 12) and 5 months in the interferon-alfa group (95% CI, 4 to 6), corresponding to a hazard ratio of 0.42 (95% CI, 0.32 to 0.54; P<0.001) (Fig. 2). The results were similar in the analyses using the investigators' assessments: 11 months (95% CI, 8 to 14) and 4 months (95% CI, 4 to 5), respectively, with a hazard ratio of 0.42 (95% CI, 0.33 to 0.52; P<0.001).

At the time of the analysis, median overall survival had not been reached in either group; 13% of patients in the sunitinib group and 17% in the interferon alfa group had died. Although there was a trend toward improved survival with sunitinib (hazard ratio for death, 0.65; 95% CI, 0.45 to 0.94; P=0.02), the comparison did not meet the prespecified level of significance for this interim analysis. A final survival analysis will be reported when the data become mature.

Outcome According to Risk Factors

We analyzed the influence of baseline clinical features and previously identified prognostic fac-

tors²⁰ on the treatment effect with the use of a Cox proportional-hazards model, controlling for each factor at a time. The benefit of sunitinib over interferon alfa was observed across all subgroups of patients (Fig. 3).

Patients were grouped according to prognostic risk category on the basis of Memorial Sloan-Kettering Cancer Center (MSKCC) criteria.²⁰ The three prognostic risk categories (favorable, intermediate, and poor) were assigned on the basis of the baseline clinical features (Table 1). In all three prognostic risk groups, the median progression-free survival was longer for patients treated with sunitinib than for those treated with interferon alfa. In patients with favorable risk features, the

Table 1. Baseline Demographic and Clinical Characteristics.*					
Variable	Sunitinib (N=375)	Interferon Alfa (N = 375)			
Sex — no. (%)					
Male	267 (71)	269 (72)			
Female	108 (29)	106 (28)			
Median age — yr (range)	62 (27–87)	59 (34–85)			
ECOG performance status — no. (%)					
0	231 (62)	229 (61)			
1	144 (38)	146 (39)			
Previous nephrectomy — no. (%)	340 (91)	335 (89)			
Previous radiation therapy — no. (%)	53 (14)	54 (14)			
Common sites of metastases — no. (%)					
Lung	292 (78)	298 (79)			
Liver	99 (26)	90 (24)			
Bone	112 (30)	112 (30)			
Lymph nodes	218 (58)	198 (53)			
No. of disease sites — no. (%)					
1	55 (15)	72 (19)			
2	106 (28)	112 (30)			
≥3	214 (57)	191 (51)			
MSKCC risk factors — no. (%)†					
0 (favorable)	143 (38)	121 (34)			
1–2 (intermediate)	209 (56)	212 (59)			
≥3 (poor)	23 (6)	25 (7)			

^{*} ECOG denotes Eastern Cooperative Oncology Group.

[†] Data were missing for 17 patients in the interferon alfa group. Risk factors associated with shorter survival according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification²⁰ are a low serum hemoglobin level, an elevated corrected serum calcium level, an elevated serum lactate dehydrogenase level, a poor performance status, and an interval of less than 1 year between diagnosis and treatment.

Variable	Suni	tinib (N=3	75)	Interfer	Interferon Alfa (N=360)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade -	
	percent						
Adverse event							
Diarrhea†	53	5	0	12	0	0	
Fatigue†	51	7	0	51	11	1	
Nausea	44	3	0	33	1	0	
Stomatitis	25	1	0	2	1	0	
Vomiting†	24	4	0	10	1	0	
Hypertension†	24	8	0	1	1	0	
Hand-foot syndrome†	20	5	0	1	0	0	
Mucosal inflammation	20	2	0	1	1	0	
Rash	19	1	1	6	1	0	
Asthenia	17	4	0	20	4	0	
Dry skin	16	1	0	5	0	0	
Skin discoloration	16	0	0	0	0	0	
Changes in hair color	14	0	0	1	0	0	
Epistaxis	12	1	0	1	0	0	
Pain in a limb	11	1	0	3	0	0	
Headache	11	1	0	14	0	0	
Dry mouth	11	0	0	6	1	0	
Decline in ejection fraction	10	2	0	3	1	0	
Pyrexia	7	1	0	34	0	0	
Chills	6	1	0	29	0	0	
Myalgia	5	1	0	16	1	0	
Influenza-like illness	1	0	0	7	1	0	
Laboratory abnormality							
Leukopenia†	78	5	0	56	2	0	
Neutropenia†	72	11	1	46	7	0	
Anemia	71	3	1	64	4	1	
Increased creatinine	66	1	0	49	1	0	
Thrombocytopenia†	65	8	0	21	0	0	
Lymphopenia†	60	12	0	63	22	0	
Increased lipase†	52	13	3	42	5	1	
Increased aspartate aminotransferase	52	2	0	34	2	0	
Increased alanine aminotransferase	46	2	1	39	2	0	
Increased alkaline phosphatase	42	2	0	35	2	0	
Increased uric acid	41	0	12	31	0	8	
Hypophosphatemia	36	4	1	32	6	0	
Increased amylase†	32	4	1	28	2	1	
Increased total bilirubin	19	1	0	2	0	0	

^{*} Listed are all treatment-related adverse events of interest and those occurring in at least 10% of patients in the sunitinib group. All severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

[†] The comparison between the sunitinib group and the interferon alfa group was significant (P<0.05) with the use of Fisher's exact test applied to the sum of grade 3 and 4 adverse events. The significance of the comparison between treatment groups for "all grades" of adverse events is not shown.

Response	Independent Central Review;		Investigator Assessment		
	Sunitinib (N=335)	Interferon Alfa (N = 327)	Sunitinib (N=374)	Interferon Alfa (N = 373)	
	no. of patients (%)				
Objective response‡	103 (31)	20 (6)	137 (37)	33 (9)	
Complete response	0	0	1 (<1)	0	
Partial response	103 (31)	20 (6)	136 (36)	33 (9)	
Stable disease	160 (48)	160 (49)	176 (47)	213 (57)	
Progressive disease or disease could not be evaluated	72 (21)	147 (45)	61 (16)	127 (34)	

^{*} Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Listed are the numbers of patients with measurable disease at baseline. Differences in the numbers of patients for independent central review and for investigator assessment were predominantly due to the availability of imaging studies.

median progression-free survival had not been reached at the time of the analysis for 143 patients in the sunitinib group, as compared with a median survival of 8 months for 121 patients in the interferon alfa group (hazard ratio for disease progression, 0.37; 95% CI, 0.21 to 0.64). In the intermediate-risk group, respective median values for 209 patients in the sunitinib group and 212 patients in the interferon alfa group were 11 months and 4 months, with a hazard ratio in the sunitinib group of 0.39 (95% CI, 0.28 to 0.54). In the poor-risk group, the respective median values for 23 patients in the sunitinib group and 25 patients in the interferon alfa group were 4 months and 1 month, with a hazard ratio of 0.53 (95% CI, 0.23 to 1.23). These results highlight the efficacy of sunitinib, as compared with interferon alfa, regardless of the patients' baseline features or prognostic factors.

QUALITY OF LIFE

Health-related quality of life was significantly better in the sunitinib group than in the interferon alfa group (P<0.001), as reported by patients in post-baseline assessments with the use of both FACT-G and FKSI questionnaires (see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). The higher scores (indicating better quality of life) in the sunitinib group for kidney cancer—related symptoms and overall quality of life were clinically meaningful, on the basis of established guidelines.^{22,23,30}

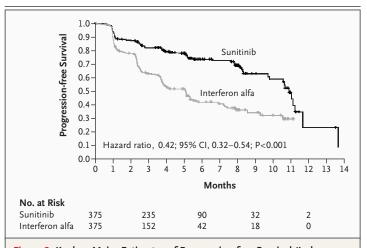


Figure 2. Kaplan-Meier Estimates of Progression-free Survival (Independent Central Review).

DISCUSSION

This randomized, phase 3 trial shows that previously untreated patients with metastatic renalcell carcinoma who received sunitinib had longer progression-free survival than did patients who received interferon alfa. Median progression-free survival in the sunitinib group (11 months) was 6 months longer than that in the interferon alfa group (5 months). This improvement was greater than the expected improvement that we used for calculating the number of patients needed for the trial, thereby meeting the trial's primary end point in the interim analysis.

This trial also demonstrates a higher objec-

[†] Imaging studies for 88 patients had not been sent or were available but had not been assessed by central review at the time of the analysis. ‡ P<0.001 for the comparison between the sunitinib group and the interferon alfa group in both assessments.

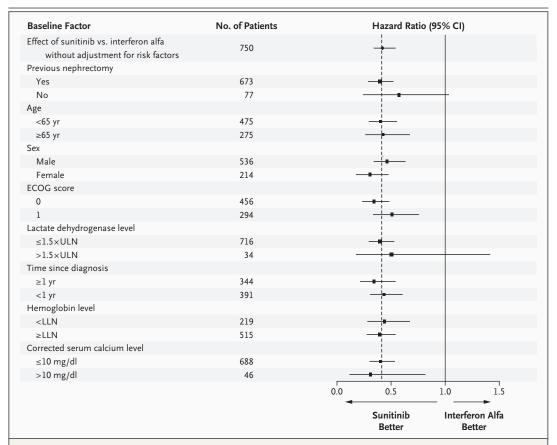


Figure 3. Progression-free Survival in Subgroups, According to Baseline Factors (Independent Central Review).

Data are missing for time since diagnosis for 15 patients and for hemoglobin level and corrected serum calcium level for 16 patients. To convert values for calcium to millimoles per liter, multiply by 0.25. ECOG denotes Eastern Cooperative Oncology Group, ULN upper limit of the normal range, and LLN lower limit of the normal range.

tive response rate and better patient-reported outcomes in the sunitinib group than in the interferon alfa group. Response rates in the range of 30 to 40% have been observed in three trials of sunitinib as first-line and second-line therapy. 10,11 These rates are substantially higher than the rates reported for other cytokines or chemotherapeutic agents.31 The consistently higher scores for patient-reported outcomes in the sunitinib group indicated an improved sense of well-being, which is influenced by factors related to the adverseevent profile and efficacy of sunitinib. Hypertension, the hand-foot syndrome, vomiting, and diarrhea were observed with sunitinib treatment, as reported previously.^{10,11} The proportion of grade 3 or 4 adverse events with sunitinib ranged from 1 to 13% for all categories (Table 2). Most sunitinib-related adverse events were ameliorated by interruption or modification of the dose;

treatment was discontinued in less than 10% of patients because of adverse events.

The group of patients in our trial consisted of a relatively unselected population of patients with metastatic clear-cell renal-cell carcinoma. The median age and sex distributions were typical for this type of cancer, and patients with coexisting conditions (e.g., hypertension and diabetes) were allowed to enter the study as long as such conditions were controlled medically. Moreover, when we examined the outcome according to known prognostic factors and risk groups, the benefit of sunitinib extended across all clinical prognostic subgroups studied, although the number of patients in the poor-risk group was small.

Cytokine treatment has been standard therapy for metastatic renal-cell carcinoma for the past 20 years. Interferon alfa monotherapy has been associated with an improvement in survival among

patients with advanced renal-cell carcinoma, as compared with a variety of controls.32-34 However, previous trials have not shown the superiority of one cytokine treatment (interferon alfa or interleukin-2) over another.8,35 Interferon alfa was chosen as the comparator for this trial on the basis of these data and the widespread use of this agent, which is the least toxic of the available cytokine treatments. In 1992, the Food and Drug Administration approved the use of high-dose interleukin-2 for the treatment of renal-cell carcinoma on the basis of phase 2 data, which showed prolonged complete remission in approximately 7% of treated patients.^{9,36} The use of high-dose interleukin-2 has been limited because of significant cardiorespiratory adverse events.32,37 The question of the relative merits of high-dose interleukin-2 and sunitinib for patients who are eligible for high-dose interleukin-2 treatment has not been settled, since the two agents have been shown to be beneficial according to different end points. Additional data on the durability of the response to sunitinib and the long-term outcome may further clarify the survival benefit associated with each treatment.

Renal-cell carcinoma of the clear-cell type overexpresses many cellular receptors related to angiogenesis and the maintenance of the tumor microvascular environment. Sunitinib is one of several agents (including sorafenib and bevacizumab) that target the activity of angiogenic growth factors and show favorable results in clinical trials involving patients with metastatic clear-cell renal-cell carcinoma. The data from these trials^{9,38} indicate that inhibition of angiogenesis is a promising strategy for the treatment of clear-cell renal-cell carcinoma. Further studies are warranted to assess the relationships among the response to sunitinib, genetic abnormalities, and the expression of angiogenic growth factors in metastatic renal-cell carcinoma.

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APPENDIX

In addition to the authors, the following investigators participated in the study: Australia — A. Boyce, I. Davis, P. Mainwaring, N. Pavlakis, K. Pittman, G. Toner, S. Troon; Brazil — C. Barrios, D. Herchenhorn, M. Zereu; Canada — G. Bjarnason, S. Ernst, C. Kollmannsberger, A. Lavoie, H. Martins, D. Ruether, F. Saad, J. Sutherland, I. Tannock, P. Venner; France — L. Geoffrois, B. Laguerre, F. Rolland; Germany — W. Eberhardt, V. Gruenwald, G. Jakse, M. Ringhoffer; Italy — G. Carteni, P. Conte, G. Gasparini, C. Porta, E. Ruggeri, C. Sternberg; Poland — T. Demkow, J. Lorenz, M. Mazurkiewicz, A. Pluzanska, J. Rolski, E. Solska; Russia — O. Gladkov, A. Kaprin, P. Karlov, O. Karyakin, M. Lichinitser, V. Moiseyenko, I. Rusakov, E. Slonimskaya; Spain — D. Castellano, X. Garcia del Muro, J.L. Gonzalez-Larriba, J.A. Moreno-Nogueira, J.L. Perez-Gracia; United Kingdom — J. Barber, T. Eisen, P. Harper, R. Hawkins, P. Nathan; United States — R. Amato, J.C. Barrett, R. Belt, P. Benedetto, J. Clark, M. Cooney, T. Cosgriff, C. Croot, H. Drabkin, A. Dudek, J. Dutcher, M. Ernstoff, M. Fishman, G. Hudes, R. Hauke, K. Karamlou, P. Kaywin, A. Keller, T. Kuzel, J. Lacy, F. Millard, D. Minor, M. Monte, R. Pill, L. Puneky, D. Richards, C. Ryan, W. Samlowski, L. Schwartzberg, J. Sosman, J. Thompson, U. Vaishampayan, J. Vuky, G. Wilding. Data and Safety Monitoring Committee: A. Tolcher, Cancer Therapy and Research Institute, San Antonio, TX; S. Bates, National Cancer Institute, Bethesda, MD; and S.L. George, Duke University Medical Center, Durham, NC.

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