

ORIGINAL ARTICLE

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

Bernard Escudier, M.D., Tim Eisen, M.D., Walter M. Stadler, M.D., Cezary Szczylik, M.D., Stéphane Oudard, M.D., Michael Siebels, M.D., Sylvie Negrier, M.D., Christine Chevreau, M.D., Ewa Solska, M.D., Apurva A. Desai, M.D., Frédéric Rolland, M.D., Tomasz Demkow, M.D., Thomas E. Hutson, D.O., Pharm.D., Martin Gore, M.D., Scott Freeman, M.D., Brian Schwartz, M.D., Minghua Shan, Ph.D., Ronit Simantov, M.D., and Ronald M. Bukowski, M.D., for the TARGET Study Group*

ABSTRACT

BACKGROUND

We conducted a phase 3, randomized, double-blind, placebo-controlled trial of sorafenib, a multikinase inhibitor of tumor-cell proliferation and angiogenesis, in patients with advanced clear-cell renal-cell carcinoma.

METHODS

From November 2003 to March 2005, we randomly assigned 903 patients with renal-cell carcinoma that was resistant to standard therapy to receive either continuous treatment with oral sorafenib (at a dose of 400 mg twice daily) or placebo; 451 patients received sorafenib and 452 received placebo. The primary end point was overall survival. A single planned analysis of progression-free survival in January 2005 showed a statistically significant benefit of sorafenib over placebo. Consequently, crossover was permitted from placebo to sorafenib, beginning in May 2005.

RESULTS

At the January 2005 cutoff, the median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio for disease progression in the sorafenib group, 0.44; 95% confidence interval [CI], 0.35 to 0.55; $P < 0.01$). The first interim analysis of overall survival in May 2005 showed that sorafenib reduced the risk of death, as compared with placebo (hazard ratio, 0.72; 95% CI, 0.54 to 0.94; $P = 0.02$), although this benefit was not statistically significant according to the O'Brien–Fleming threshold. Partial responses were reported as the best response in 10% of patients receiving sorafenib and in 2% of those receiving placebo ($P < 0.001$). Diarrhea, rash, fatigue, and hand–foot skin reactions were the most common adverse events associated with sorafenib. Hypertension and cardiac ischemia were rare serious adverse events that were more common in patients receiving sorafenib than in those receiving placebo.

CONCLUSIONS

As compared with placebo, treatment with sorafenib prolongs progression-free survival in patients with advanced clear-cell renal-cell carcinoma in whom previous therapy has failed; however, treatment is associated with increased toxic effects. (ClinicalTrials.gov number, NCT00073307.)

From Institut Gustave Roussy, Villejuif, France (B.E.); Cambridge Research Institute, Cambridge, United Kingdom (T.E.); University of Chicago, Chicago (W.M.S., A.A.D.); Military School of Medicine, Warsaw, Poland (C.S.); Hôpital Européen Georges Pompidou, Paris (S.O.); Klinikum Grosshadern der Ludwig Maximilians Universität, Munich, Germany (M. Siebels); Centre Léon Bérard, Lyon, France (S.N.); Institut Claudius Regaud, Toulouse, France (C.C.); Wojewodzka Przychodnia Onkolog, Gdansk, Poland (E.S.); Centre René Gauducheau, Saint-Herblain, France (F.R.); Centrum Onkologii, Warsaw, Poland (T.D.); Baylor Charles A. Sammons Cancer Center, Dallas (T.E.H.); Royal Marsden Hospital, Surrey, United Kingdom (M.G.); Onyx Pharmaceuticals, Emeryville, CA (S.F.); Bayer Pharmaceuticals, West Haven, CT (B.S., M. Shan, R.S.); and Cleveland Clinic Taussig Cancer Center, Cleveland (R.M.B.). Address reprint requests to Dr. Escudier at the Department of Medicine, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France, or at escudier@igr.fr.

*Investigators in the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) are listed in the Appendix.

N Engl J Med 2007;356:125-34.

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THE 5-YEAR SURVIVAL RATE FOR PATIENTS with metastatic renal-cell carcinoma is less than 10%.¹ High-dose interleukin-2 therapy rarely induces a durable complete response, and interferon alfa provides only a modest survival advantage. Until recently, there have been no other treatments for patients with renal-cell carcinoma who are ineligible for, or unable to tolerate, these cytokines.²⁻⁶

Sorafenib, an orally active multikinase inhibitor with effects on tumor-cell proliferation and tumor angiogenesis, was initially identified as a Raf kinase inhibitor.⁷ It also inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3; platelet-derived growth factor receptor β (PDGFR β); FMS-like tyrosine kinase 3 (Flt-3); c-Kit protein (c-Kit); and RET receptor tyrosine kinases.^{7,8}

Sorafenib has antitumor activity in animal models.⁷ In the murine renal adenocarcinoma (Renca) model⁹ and the von Hippel-Lindau tumor-suppressor gene (*VHL*) knockout model,¹⁰ sorafenib prevented tumor growth, primarily by inhibiting angiogenesis.^{9,10} It also induced tumor-cell apoptosis and necrosis in the *VHL*-deficient xenograft model.¹⁰

In a phase 2, randomized discontinuation trial, sorafenib prolonged progression-free survival, as compared with placebo, in patients with metastatic renal-cell carcinoma in whom previous treatment had failed.¹¹ Most patients who had a response to sorafenib had clear-cell renal-cell carcinoma,¹¹ the most aggressive and prevalent type of this disease.¹

Increased production of vascular endothelial growth factor (VEGF) and transforming growth factor α (TGF- α) and the loss of the *VHL* tumor-suppressor gene are implicated in the progression of clear-cell renal-cell carcinoma. Sorafenib targets the pathways downstream of VEGF and TGF- α .¹ We conducted a phase 3 study, the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), to determine the effects of sorafenib on progression-free survival and overall survival in patients with advanced clear-cell renal-cell carcinoma in whom one previous systemic therapy had failed.

METHODS

PATIENTS

Eligible patients were at least 18 years of age and had histologically confirmed metastatic clear-cell renal-cell carcinoma, which had progressed

after one systemic treatment within the previous 8 months. Additional eligibility criteria were a performance status of 0 or 1 on the basis of Eastern Cooperative Oncology Group criteria; an intermediate-risk or low-risk status, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score¹²; a life expectancy of at least 12 weeks; adequate bone marrow, liver, pancreatic, and renal function; and a prothrombin time or partial-thromboplastin time of less than 1.5 times the upper limit of the normal range. Patients with brain metastases or previous exposure to VEGF pathway inhibitors were excluded.

All patients provided written informed consent. The study was approved by the institutional review board at each center and complied with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

STUDY DESIGN

We conducted the study at 117 centers in 19 countries. Patients were stratified according to country and MSKCC prognostic score (low or intermediate) and randomly assigned to study groups in a 1:1 ratio with a block size of four. The patients received either continuous treatment with oral sorafenib (at a dose of 400 mg twice daily) or placebo in a double-blind fashion, administered in 6-week cycles for the first 24 weeks and in 8-week cycles thereafter. We assessed safety every 3 weeks for the first 24 weeks and every 4 weeks thereafter. Doses were delayed or reduced if patients had clinically significant hematologic or other adverse events that were considered to be related to sorafenib, as measured with the use of version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute. In such cases, doses were reduced to 400 mg once daily and then to 400 mg every other day. If further reductions were required, patients were withdrawn from the trial. If adverse events resolved to a grade of 1 or less, the dose could be escalated to the previous level at the investigator's discretion. Evaluations of tumor responses were performed within the last 10 days of each cycle. We followed the patients, who continued to receive sorafenib until either disease progression or withdrawal from the study because of adverse events, until death. Investigators were unaware of the study group assignments, but disclosure was permitted after documented progression on the basis of radiologic evaluation. Patients receiving sora-

fenib who had a response were eligible to continue receiving open-label treatment with the drug.

From November 2003 to April 2005, the sponsor and investigators were unaware of the study-group assignments in the evaluation of data. An independent data and safety monitoring committee reviewed the data regarding safety and efficacy. In April 2005, on the basis of the first progression-free survival analysis by this committee, a decision was made to reveal the study-group assignments and to offer sorafenib to patients who were assigned to receive placebo. The investigators and the sponsor remained unaware of the study-group assignments with regard to survival data. Since crossover may compromise the end point of overall survival, the protocol was amended to allow a first analysis of overall survival at the start of the treatment crossover, in May 2005.

STUDY END POINTS

We measured the primary end point (overall survival) from the date of randomization until the date of death and the secondary end point (progression-free survival) from the date of randomization until the date of progression. Progression of disease was determined on the basis of findings on computed tomography (CT) or magnetic resonance imaging (MRI), clinical progression, or death, with the use of the Response Evaluation Criteria in Solid Tumors (RECIST). Investigators and independent radiologists who were unaware of the study-group assignments assessed progression-free survival. Another secondary end point was the best overall response rate (on the basis of RECIST) within the last 10 days of each drug cycle. Assessments of responses required confirmatory findings on CT or MRI 4 or more weeks after the initial determination of a response. Adverse events were graded with the use of the CTCAE.

STATISTICAL ANALYSIS

We calculated the number of patients who would need to be enrolled in order to detect a 33.3% increase in overall survival among patients with sorafenib, as compared with those receiving placebo. Assuming a two-sided type I error of 0.04, the study would have 90% power to detect a 33.3% difference in survival between the two groups after a total of 540 patients had died. The duration of the study was estimated to be 29 months on the basis of the following assumptions: a monthly enrollment rate of 50 patients, an expo-

entially distributed event time, a median time of 12 months in the placebo group, and a 17-month-long enrollment for a total of 856 patients in the two groups (428 per group). Assuming that 3% of patients would be lost to follow-up, approximately 884 patients had to be randomly assigned to study groups. According to these assumptions, approximately 270 deaths were expected in approximately 17 months.

We analyzed planned interim findings (when approximately 270 of the patients had died) and the final intention-to-treat findings regarding overall survival (when approximately 540 patients had died) with a stratified log-rank test. The O'Brien-Fleming spending function was used prospectively to ensure that the overall false positive rate (alpha) was no more than 0.04 (in a two-sided analysis). In the first analysis of overall survival, which was performed in May 2005, the information fraction — the total number of deaths (regardless of crossover) at the cutoff date divided by the total number of deaths specified by the protocol (540) — was used to calculate the O'Brien-Fleming threshold for significance ($P=0.0005$). In November 2005 (6 months after crossover was allowed), when we performed the second analysis of overall survival, the O'Brien-Fleming threshold was $P=0.0094$. The final, planned analysis of overall survival was undertaken after 540 patients had died.

We performed the planned, independently reviewed analysis of progression-free survival on January 28, 2005, after disease had progressed in approximately 363 patients. The analysis had a power of 90% to detect a 50% increase in progression-free survival in the sorafenib group (two-sided alpha of 0.01). Progression-free survival was compared by the log-rank test (stratified by prognostic group and country). All patients in the study groups were included in the efficacy analyses. Treatment-related differences in response were evaluated by the Cochran-Mantel-Haenszel test. All patients receiving at least one dose of sorafenib were eligible for the safety analysis. All reported P values are two-sided and unadjusted for interim analyses.

Bayer Pharmaceuticals and Onyx Pharmaceuticals designed the trial, in conjunction with the principal academic investigators and two members of the steering committee. Data were collected and tracked by LabCorp. The academic investigators and an independent panel of radiologists from Perceptive Informatics performed the radio-

logic assessments. Axio Research performed the statistical analysis for the data and safety monitoring committee. Data were managed in parallel by the sponsor and the academic investigators. The academic investigators were responsible for the decision to publish the results of the study and had unrestricted access to the final data. Drs. Escudier, Simantov, and Shan vouch for the completeness and accuracy of the data.

MSKCC criteria. Most of the patients had undergone previous nephrectomy and had received cytokine-based treatment. As of May 31, 2005, a total of 282 patients in the sorafenib group and 338 in the placebo group had discontinued treatment or died (Fig. 1). Eighteen patients in the sorafenib group and 17 in the placebo group discontinued the study drug because of adverse events. The median follow-up was 6.6 months for both groups.

RESULTS

From November 24, 2003, when we screened the first patient, until March 31, 2005, when we closed enrollment, we enrolled 903 patients and randomly assigned them to receive either sorafenib or placebo. There were 451 patients in the sorafenib group and 452 in the placebo group (Fig. 1).

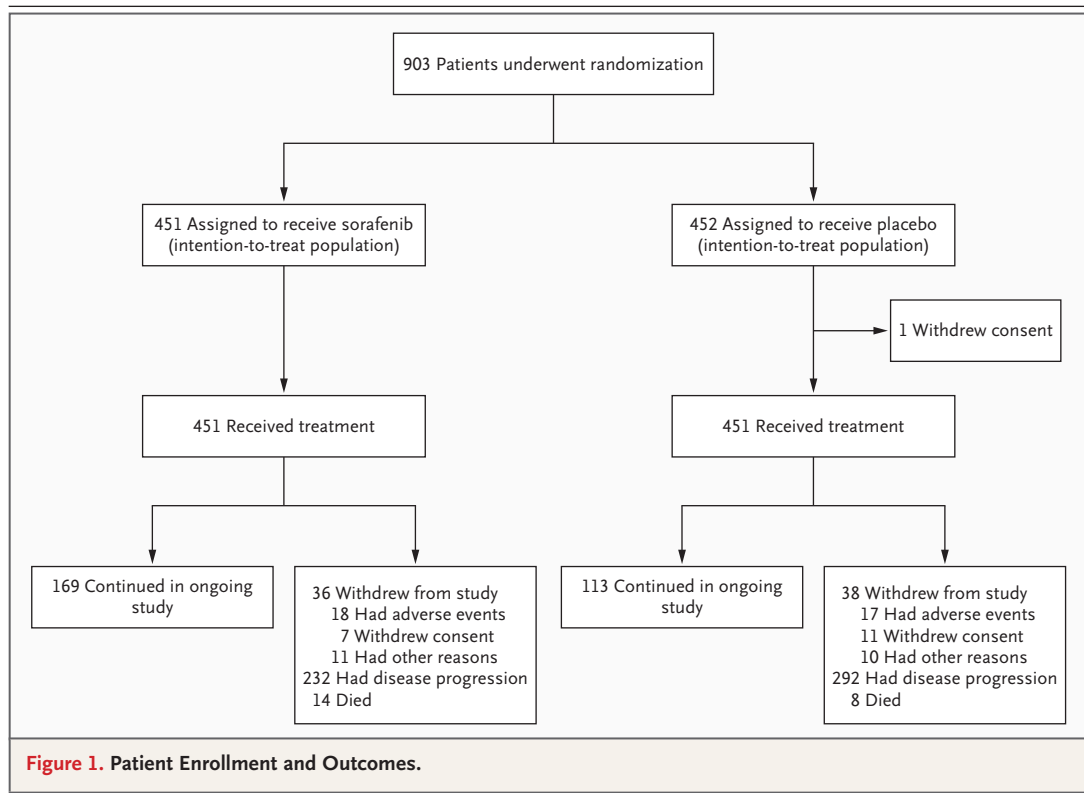
BASELINE CHARACTERISTICS

Baseline characteristics were well balanced between the study groups (Table 1). Most of the patients (99%) had clear-cell renal-cell carcinoma. Of those patients, 51% had low-risk disease, and 49% had intermediate-risk disease, according to

EFFICACY

Overall Survival

In the first analysis of overall survival, which was performed in May 2005 immediately before crossover was allowed, 220 deaths (41% of the protocol-defined 540 deaths) had occurred: 97 of 451 patients (22%) in the sorafenib group and 123 of 452 patients (27%) in the placebo group died. At a median follow-up of 6.6 months, the median actuarial overall survival was 14.7 months in the placebo group but had not yet been reached in the sorafenib group (hazard ratio, 0.72; 95% confidence interval [CI], 0.54 to 0.94; $P=0.02$) (Fig. 2A). Overall survival was assessed 6 months later (in November 2005), after 216 of 452 patients receiving placebo had switched to sorafenib and after



367 deaths had occurred (68% of the protocol-defined 540 events). Of these deaths, 171 occurred in the sorafenib group (38%) and 196 in the placebo group (43%). The median overall survival was 19.3 months for patients in the sorafenib group and 15.9 months for patients in the placebo group (hazard ratio, 0.77; 95% CI, 0.63 to 0.95; $P=0.02$) (Fig. 2B). The analyses did not reach prespecified O'Brien–Fleming boundaries for statistical significance.

Progression-free Survival

In January 2005, a protocol-defined independent review of the status of 769 patients — 384 in the sorafenib group and 385 in the placebo group — was conducted. In this analysis, the median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group ($P<0.001$), based on 147 events (in 38% of patients) in the sorafenib group (23 deaths, 117 radiologic progression events, and 7 clinical progression events) and 195 events (51% in the placebo group (23 deaths, 164 radiologic progression events, and 8 clinical progression events). Investigator-assessed median progression-free survival was 5.9 months in the sorafenib group and 2.8 months in the placebo group ($P<0.001$), based on 136 events (in 35% of patients) in the sorafenib group and 211 events (55%) in the placebo group. Sorafenib was associated with a reduction of 56% in the independently assessed risk of progression (hazard ratio, 0.44; 95% CI, 0.35 to 0.55) (Fig. 2C). The investigator-assessed progression-free survival in 903 patients at the time of crossover was also significantly prolonged with sorafenib treatment (5.5 vs. 2.8 months, $P<0.001$), with a 49% reduction in the risk of progression (hazard ratio, 0.51; 95% CI, 0.43 to 0.60) (Fig. 2D). This benefit in progression-free survival was independent of age, MSKCC score, previous use or nonuse of cytokine therapy, presence or absence of lung or liver metastases, and the time since diagnosis (<1.5 or ≥ 1.5 years) (Fig. 3).

Overall Response

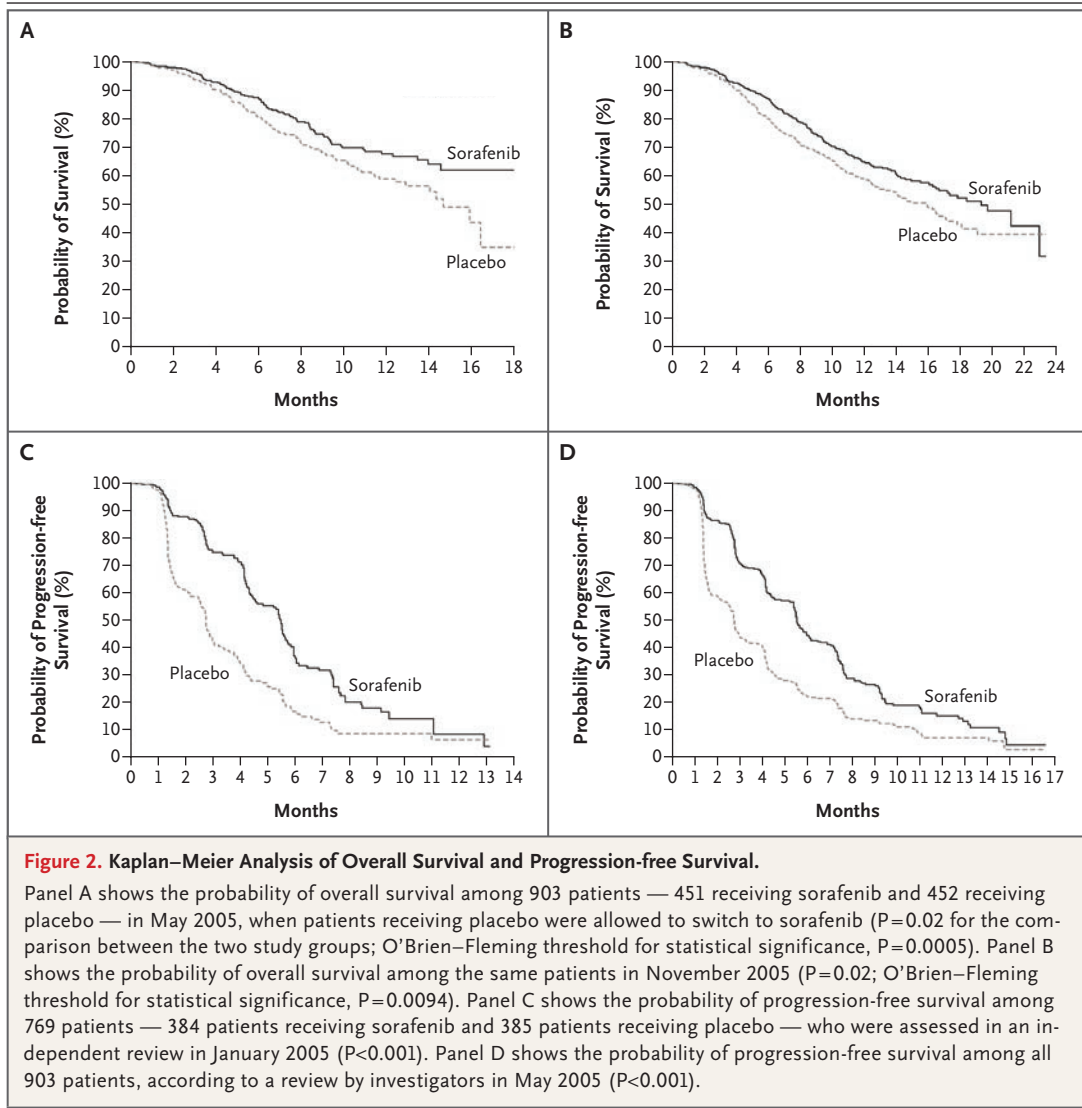
At the January 2005 cutoff, independent reviewers assessed the best responses among 672 patients: 335 in the sorafenib group and 337 in the placebo group. The sorafenib group had 7 patients with a partial response (2%), 261 patients with stable disease (78%), and 29 patients with disease progression (9%); data were missing for 38 patients (11%). The placebo group had no patients with a

Table 1. Demographic and Baseline Characteristics (Intention-to-Treat Population).*

Variable	Sorafenib (N=451)	Placebo (N=452)
Male sex — no. (%)	315 (70)	340 (75)
Median age — yr (range)	58 (19–86)	59 (29–84)
ECOG performance status — no. (%)		
0	219 (49)	210 (46)
1	223 (49)	236 (52)
2	7 (2)	4 (1)
Data missing	2 (<1)	2 (<1)
No. of metastatic sites — no. (%)		
1	62 (14)	63 (14)
2	131 (29)	129 (29)
>2	256 (57)	258 (57)
Missing data	2 (<1)	2 (<1)
Metastatic sites — no. (%)		
Lung	348 (77)	348 (77)
Liver	116 (26)	117 (26)
Previous systemic therapy — no. (%)		
Cytokine-based	374 (83)	368 (81)
Interleukin-2	191 (42)	189 (42)
Interferon	307 (68)	314 (69)
Both interleukin-2 and interferon	124 (27)	135 (30)
Radiotherapy	124 (27)	108 (24)
Nephrectomy	422 (94)	421 (93)
Median duration of disease — yr (range)	2 (<1–19)	2 (<1–20)
MSKCC prognostic risk — no. (%)		
Low	233 (52)	228 (50)
Intermediate	218 (48)	223 (49)
Missing data	0	1 (<1)

* There were no significant differences between the sorafenib group and the placebo group at baseline. ECOG denotes Eastern Cooperative Oncology Group, and MSKCC Memorial Sloan-Kettering Cancer Center.

partial response, 186 patients with stable disease (55%), and 102 patients with disease progression (30%); data were missing for 49 patients (15%). At the May 2005 cutoff, 903 patients in the intention-to-treat population were eligible for evaluation of best response by investigators (Table 2). Among the 451 patients in the sorafenib group, 1 patient had a complete response (<1%), 43 had a partial response (10%), and 333 had stable disease (74%). Among the 452 patients in the placebo group, no patient had a complete response, 8 had



a partial response (2%), and 239 had stable disease (53%). Significantly more patients in the sorafenib group than in the placebo group had partial responses or stable disease ($P<0.001$) (Table 2). After 3 months of treatment, 255 patients receiving sorafenib (57%) had a complete or partial response or stable disease, as compared with 152 patients receiving placebo (34%). Among the 44 patients in the sorafenib group who had a complete or partial response, the median time to response was 80 days (range, 35 to 275), and the median duration of response was 182 days (range, 36 to 378).

ADVERSE EVENTS

The median duration of treatment was 23 weeks in the sorafenib group and 12 weeks in the placebo group. The proportion of patients who discon-

tinued the study drug owing to adverse events was similar in the two groups (10% in the sorafenib group and 8% in the placebo group), and discontinuation was mostly due to constitutional, gastrointestinal, dermatologic, or pulmonary–upper respiratory tract symptoms. Doses were reduced in 13% of patients in the sorafenib group, as compared with 3% in the placebo group ($P<0.001$), and doses were interrupted owing to adverse events in 21% of patients in the sorafenib group, as compared with 6% in the placebo group ($P<0.001$). The median duration of the dose interruptions was 7 days in the sorafenib group and 6 days in the placebo group. Dose interruptions were mostly due to dermatologic events (mainly hand–foot skin reactions or rash) and gastrointestinal events, including diarrhea.

Adverse events occurring during treatment were predominantly of grade 1 or 2. The most common events were diarrhea, rash, fatigue, hand-foot skin reactions, alopecia, and nausea (Table 3). Hypertension was more frequent in the sorafenib group but led to permanent discontinuation in less than 1% of patients; the condition generally occurred during the first treatment cycle. Cardiac ischemia or infarction occurred in 12 patients in the sorafenib group (3%) and 2 patients in the placebo group (<1%) ($P=0.01$). Of these events, 11 (including 2 deaths in the sorafenib group and 1 death in the placebo group) were considered to be serious adverse events associated with treatment.

Bleeding (predominantly grade 1 in severity) was more frequent in the sorafenib group (15%) than in the placebo group (8%). The incidence of serious hemorrhage was similar in the two groups (3% in the sorafenib group and 2% in the placebo group). Febrile neutropenia or grade 4 thrombocytopenia did not occur in the sorafenib group. Grade 3 or 4 anemia occurred in 3% of patients in the sorafenib group and 4% in the placebo group.

Serious adverse events leading to hospitalization or death were reported in 154 patients receiving sorafenib (34%), including 46 deaths (10%), and in 110 patients receiving placebo (24%), including 25 deaths (6%) ($P<0.01$). Serious adverse events affecting at least 2% of patients included the above-mentioned cardiac ischemia or infarction, other constitutional symptoms (2% in both groups), dyspnea (2% in both groups), and death owing to progressive disease (2% in both groups). The most frequent drug-related serious adverse event was hypertension (in 1% of patients in the sorafenib group and none in the placebo group).

Laboratory abnormalities of grade 3 or 4 that were reported in the sorafenib group and the placebo group included lymphopenia (in 13% and 7% of patients, respectively), hypophosphatemia (13% and 3%), and elevated lipase levels (12% and 7%). An elevated lipase level of any grade was a frequent laboratory abnormality in both groups (occurring in 41% and 30% of patients, respectively) but was rarely associated with clinical manifestations of pancreatitis (1% and <1%).

DISCUSSION

The prognosis for patients with metastatic renal-cell carcinoma has not improved appreciably during the past 25 years. Renal-cell carcinoma is highly resistant to both chemotherapy and radia-

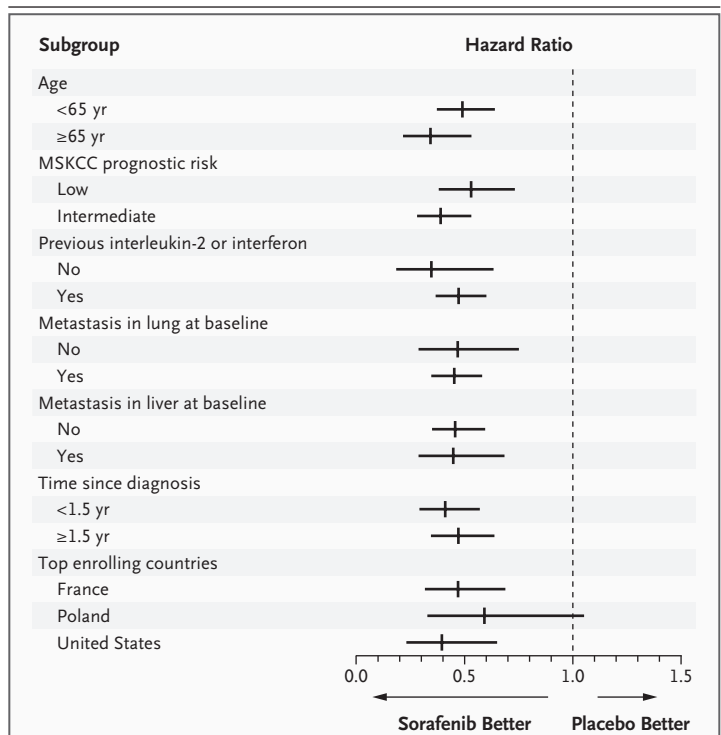


Figure 3. Hazard Ratios for Progression-free Survival among Subgroups of Patients.

The graph shows hazard ratios (with 95% confidence intervals) among subgroups of patients receiving continuous oral sorafenib (at a dose of 400 mg twice daily) or placebo. The 769 patients — 384 patients receiving sorafenib and 385 patients receiving placebo — were assessed by an independent reviewer in January 2005. MSKCC denotes Memorial Sloan-Kettering Cancer Center.

Table 2. Best Response Rates.*

Response	Sorafenib (N=451)		Placebo (N=452)	
	no. of patients	% (95% CI)	no. of patients	% (95% CI)†
Complete response	1	<1 (0–1)	0	0 (0–1)
Partial response	43	10 (7–13)	8	2 (1–4)
Stable disease‡	333	74 (70–78)	239	53 (48–58)
Progressive disease	56	12 (10–16)	167	37 (33–42)
Not evaluated	18	4 (2–6)	38	8 (6–11)
Disease control rate‡‡	279	62 (57–66)	167	37 (33–42)

* Investigators performed their evaluation on the basis of Response Evaluation Criteria in Solid Tumors (RECIST). All 95% CIs are based on the Cochran-Mantel-Haenszel test.

† Stable disease was defined as disease that remained unchanged for at least 28 days.

‡‡ This rate is the sum of the percentages of patients with a complete response, a partial response, and stable disease for at least two cycles.

Table 3. Adverse Events.*

Adverse Event	Sorafenib (N=451)			Placebo (N=451)			P Value (Grade 3 or 4)†	P Value (Grade 2)‡
	Any Grade	Grade 2	Grade 3 or 4	Any grade number (percent)	Grade 2	Grade 3 or 4		
Cardiac — hypertension§	76 (17)	44 (10)	16 (4)	8 (2)	3 (<1)	2 (<1)	0.001	<0.001
Hematologic — decreased hemoglobin	34 (8)	14 (3)	12 (3)	33 (7)	8 (2)	20 (4)	0.21	0.28
Constitutional								
Fatigue	165 (37)	54 (12)	22 (5)	125 (28)	39 (9)	16 (4)	0.41	0.12
Other symptoms	46 (10)	9 (2)	6 (1)	27 (6)	8 (2)	6 (1)	1.00	1.00
Weight loss	46 (10)	23 (5)	3 (<1)	25 (6)	8 (2)	0	0.25	0.009
Gastrointestinal								
Diarrhea	195 (43)	56 (12)	11 (2)	58 (13)	13 (3)	3 (1)	0.06	<0.001
Nausea	102 (23)	27 (6)	3 (<1)	87 (19)	21 (5)	3 (1)	1.00	0.46
Anorexia	73 (16)	24 (5)	3 (<1)	57 (13)	16 (4)	5 (1)	0.73	0.26
Vomiting	73 (16)	25 (6)	4 (1)	53 (12)	20 (4)	6 (1)	0.76	0.54
Constipation	68 (15)	22 (5)	3 (1)	49 (11)	19 (4)	3 (1)	1.00	0.75
Neurologic — sensory neuropathy	59 (13)	13 (3)	2 (<1)	29 (6)	4 (1)	3 (1)	1.00	0.05
Pain								
Abdominal	49 (11)	22 (5)	7 (2)	41 (9)	16 (4)	9 (2)	0.80	0.41
Headache	47 (10)	18 (4)	1 (<1)	27 (6)	7 (2)	2 (<1)	1.00	0.04
Joint	45 (10)	13 (3)	7 (2)	29 (6)	14 (3)	1 (<1)	0.07	1.00
Bone	34 (8)	18 (4)	3 (1)	35 (8)	12 (3)	15 (3)	0.007	0.35
Tumor	29 (6)	9 (2)	13 (3)	24 (5)	11 (2)	8 (2)	0.38	0.82
Pulmonary								
Cough	60 (13)	21 (5)	1 (<1)	64 (14)	19 (4)	1 (<1)	1.00	0.87
Dyspnea	65 (14)	25 (6)	16 (4)	52 (12)	18 (4)	11 (2)	0.44	0.35
Dermatologic								
Rash or desquamation	180 (40)	59 (13)	4 (1)	70 (16)	9 (2)	1 (<1)	0.37	<0.001
Hand-foot skin reaction	134 (30)	55 (12)	25 (6)	30 (7)	5 (1)	0	<0.001	<0.001
Alopecia	122 (27)	17 (4)	1 (<1)	15 (3)	2 (<1)	0	1.00	<0.001
Pruritus	85 (19)	21 (5)	1 (<1)	29 (6)	2 (<1)	0	1.00	<0.001

* Listed are adverse events of any grade occurring in at least 10% of patients (with a breakdown of grade 2 events) and adverse events of grade 3 or 4 occurring in at least 2% of patients.
 † P values are for the comparison between the sorafenib group and the placebo group with respect to grade 3 or 4 adverse events.
 ‡ P values are for the comparison between the sorafenib group and the placebo group with respect to grade 2 adverse events.
 § Cardiac ischemia or infarction occurred in 12 patients (3%) in the sorafenib group and 2 patients (<1%) in the placebo group (P=0.01).

tion therapy.¹³ Interleukin-2 and interferon alfa have been used for metastatic disease, but these agents have limited efficacy and are associated with considerable toxic effects. A recent study did not support first-line cytokine treatment in patients with intermediate-prognosis metastatic renal-cell carcinoma.¹⁴ Until recently, patients who did not have a response to first-line cytokine therapy had no other viable options for treatment.

Progression-free survival is a credible end point in oncology trials.¹⁵ Our trial demonstrated a significant prolongation of progression-free survival in sorafenib-treated patients with advanced clear-cell renal-cell carcinoma in whom previous therapy had failed. In April 2005, the robustness of the data regarding progression-free survival led to a decision to offer sorafenib to patients who were receiving placebo. A planned analysis of overall survival at this time demonstrated a 28% reduction in the risk of death among patients receiving sorafenib, as compared with those receiving placebo. The hazard ratio of 0.72 and the P value of 0.02 were not considered to be statistically significant, since the study's protocol called for a P value of 0.0005 for the comparison between treatment groups at this analysis. The median actuarial overall survival among patients in the placebo group was 14.7 months. In a trial of AE-941 (Neovastat) an angiogenesis inhibitor, the median overall survival was 12.6 months in patients with metastatic renal-cell carcinoma in whom immunotherapy had failed.¹⁶

Our first estimate of overall survival was unlikely to have been affected significantly by modification of the trial because at that time only 12 patients had crossed over to receive sorafenib. An analysis of overall survival 6 months after crossover showed a continued trend toward improved survival, with a 23% reduction in the risk of death (hazard ratio, 0.77; $P=0.02$), but the comparison between study groups did not meet the prespecified O'Brien-Fleming significance threshold of $P=0.0094$.

We used RECIST to grade tumor responses. These criteria were originally developed to assess responses to cytotoxic drugs and may not be an appropriate indicator of activity for sorafenib or other targeted agents, which are associated with prolonged stable disease and moderate tumor shrinkage.¹⁷

The continuous administration of sorafenib in this trial had a profile of adverse events that was

similar to that observed in the phase 2 trial; the most commonly reported toxic effects were dermatologic symptoms and diarrhea.¹¹ There was a significant difference between the sorafenib group and the placebo group in the frequency of serious adverse events (34% and 24%, respectively; $P<0.01$). Cardiovascular adverse events were more frequent in the sorafenib group than in the placebo group (3% and <1%, respectively; $P=0.01$). However, the overall rate of these events was low, and the risk-benefit ratio was acceptable in the context of an apparent clinical benefit in patients with a fatal disease. As compared with standard chemotherapies — which have been associated with alopecia, anemia, and neutropenia — sorafenib had moderate and easily manageable toxic effects. Nevertheless, 21% of sorafenib-treated patients required an interruption in treatment owing to adverse events. Sorafenib was not associated with grade 3 or 4 renal or neurologic adverse events, which limit cytokine therapy.¹⁸

Sorafenib is one of several new agents that inhibit proangiogenic kinases. It may act against renal-cell carcinoma by disrupting the tumor vasculature. In a phase 2 trial, bevacizumab, an antagonist of VEGF, improved progression-free survival and led to a 10% objective rate of tumor response in patients with renal-cell carcinoma.⁶ Promising antitumor activity has also been shown with the oral VEGFR and PDGFR inhibitors sunitinib and AG-013736. The 10% investigator-assessed partial response rate in our study with sorafenib was similar to that reported for high-dose bevacizumab.⁶ In two phase 2 trials of sunitinib, the partial response rates (as assessed by investigators and by independent review) were 40% and 34%, respectively.^{19,20} A partial response rate of 46% was reported in patients receiving AG-013736.²¹ Reported toxic effects of these agents include diarrhea, hypertension, fatigue, hand-foot skin reaction, and rash, although the incidences and severity have varied.^{6,19-22}

In conclusion, oral sorafenib therapy prolonged progression-free survival in patients with advanced clear-cell renal-cell carcinoma in whom first-line therapy had failed. This improvement was associated with an increased number of adverse events, as compared with placebo.

Supported by Bayer Pharmaceuticals and Onyx Pharmaceuticals.

Drs. Escudier, Eisen, Stadler, Szczylik, Negrier, Hutson, Gore, and Bukowski report receiving consulting fees from Bayer HealthCare; Drs. Escudier, Eisen, Hutson, Gore, and Bukowski,

receiving lecture fees from Bayer HealthCare; Dr. Freeman, being a former employee of Onyx Pharmaceuticals and having equity ownership in the company; Dr. Stadler, having equity ownership in Abbott; Drs. Gore and Bukowski, receiving grant support from Bayer HealthCare; Dr. Schwartz, being a former employee of Bayer HealthCare; and Drs. Shan and Simantov, being employees of Bayer HealthCare. No other potential conflict of interest relevant to this article was reported.

We thank the patients who participated in this study and their

families; the medical, nursing, and research staff at the study centers; the data managers, statisticians, and programmers at Bayer HealthCare and Pharmaceutical Research Associates; the clinical-trial management team; and the following members of the independent data and safety monitoring committee: Dr. John MacDonald (chair), Dr. Sophia Fossa, Dr. Beverly Drucker, Dr. KyungMann Kim, Dr. Lynn Shemansky (Axio Research), and Anna Zourabian (Perceptive Informatics); and Dr. Kavita Maung for scientific review of the manuscript.

APPENDIX

The following investigators participated in the TARGET study group: *Argentina* — C. Blajman, L. Fein, C. Martín, R. Taber; *Australia* — M. Boyer, I. Davis, H. Gurney, E. Hovey, D. Leong, C. Steer; *Belgium* — J. DeGreve, T. Gil; *Brazil* — C. Barrios, W. David, N.G. Skare, A. Notari, G. Schwartzmann, N. Gunnar; *Canada* — S. Ernst, S. Hotte, W. Miller, M. Moore, S. North; *Chile* — M. Fodor; *France* — A. Caty, C. Chevreau, B. Duclos, G. Gravis, S. Negrier, S. Oudard, A. Ravaud, F. Rolland, E. Sevin; *Germany* — M.O. Grimm, J. Gschwend, H. Heinzer, E. Jäger, S. Krause, M.-S. Michel, D. Rohde, M. Siebels, M. Siegsmund, M. Staehler, M. Wirth; *Hungary* — M. Baki, I. Bodrogi, J. Cseh, A. Ruzsa, C. Toth; *Israel* — R. Ben-Yosef, E. Gez; *Italy* — E. Bajetta, C. Boni, S. Bracarda, F. Cognetti, P. Conte, C. Porta; *the Netherlands* — D.J. Spronsen; *Poland* — M. Blasinka-Morawiec, T. Demkow, J. Lorenz, M. Mazurkiewicz, J. Rolski, A. Sikorski, E. Solska, P. Tomczak; *Russia* — L. Bolotina, P. Karlov, O. Karyakin, R. Khasanov, M. Lichinitser, V. Lubennikov, V. Moiseenko, N. Sherman; *South Africa* — R. Abratt, L. Coetzee, G. Cohen, C. Heyns, J. Jordaan, P. Ruff, S. Wentzel; *Spain* — J. Bellmunt, M.A. Climent, J.L. González, G. López; *Ukraine* — V. Bashtan, Y. Dumamsky, I. Klimenko, N. Pilipenko, Y. Shparik; *United Kingdom* — R. Hawkins, R. McMenemin, P. Nathan, E. Porfiri, P. Savage, J. White; *United States* — C. Anderson, Y. Bains, E. Bleickardt, J. Bradof, D. Brooks, G. Cardí, A. Cervera, N. Davis, A. Desai, H. Drabkin, A. Dudek, J. Dutcher, G. Formanek, N. Gabrail, H. Gross, Y. Haung, C. Henderson, T. Hutson, E. Jonasch, P. Lara, J. McCracken, D. McDermott, R. Mena, R. Middleton, D. Petrylak, J. Picus, D. Quinn, P. Rausch, D. Rinaldi, C. Ryan, N. Tchekmedyan, J. Vuky.

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CORRECTION

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma . The last footnote of Table 2 (page 131) should have read “This rate is the sum of the percentages of patients with a complete response, a partial response, and stable disease for at least two cycles” rather than “This rate is the sum of the percentages of patients with a complete response, a partial response, and stable disease.” The table has been corrected on the *Journal's* Web site at www.nejm.org. We regret the error.