

Sorafenib for the Treatment of Advanced Renal Cell Carcinoma

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Abstract **Purpose:** This report describes the U.S. Food and Drug Administration (FDA) review and approval of sorafenib (Nexavar, BAY43-9006), a new small-molecule, oral, multi-kinase inhibitor for the treatment of patients with advanced renal cell carcinoma (RCC).
Experimental Design: After meeting with sponsors during development studies of sorafenib, the FDA reviewed the phase 3 protocol under the Special Protocol Assessment mechanism. Following new drug application submission, FDA independently analyzed the results of two studies in advanced RCC: a large, randomized, double-blinded, phase 3 international trial of single-agent sorafenib and a supportive phase 2 study.
Results: In the phase 3 trial, 902 patients with advanced progressive RCC after one prior systemic therapy were randomized to 400 mg sorafenib twice daily plus best supportive care or to a matching placebo plus best supportive care. Primary study end points included overall survival and progression-free survival (PFS). A PFS analysis, pre-specified and conducted after a total of 342 events, showed statistically significant superiority for the sorafenib group (median = 167 days) compared with that for the controls (median = 84 days, log-rank $P < 0.000001$); the sorafenib/placebo hazard ratio was 0.44 (95% confidence interval, 0.35-0.55). Results were similar regardless of patient risk score, performance status, age, or prior therapy. The (partial) response rate to sorafenib was 2.1%. Overall survival results are preliminary. The principal toxicities in the sorafenib patients included reversible skin rashes in 40% and hand-foot skin reaction in 30%; diarrhea was reported in 43%, treatment-emergent hypertension was reported in 17%, and sensory neuropathic changes were reported in 13%. Grade 4 adverse events were uncommon. Grade 3 adverse events were hand-foot skin reaction (6%), fatigue (5%), and hypertension (3%). Laboratory findings included asymptomatic hypophosphatemia in 45% of sorafenib patients versus 11% in the placebo arm and elevation of serum lipase in 41% of sorafenib patients versus 30% in the placebo arm. Grade 4 pancreatitis was reported in two sorafenib patients, although both patients subsequently resumed sorafenib, with one at full dose.
Conclusions: Sorafenib received FDA regular approval on December 20, 2005 for the treatment of advanced RCC based on the persuasive magnitude of improvement in PFS with acceptable safety. The recommended dose is 400 mg (two 200-mg tablets) twice daily taken either 1 h before or 2 h after meals. Adverse events were accommodated by temporary dose interruptions or reductions.

On December 20, 2005, the Food and Drug Administration (FDA) granted regular marketing approval for sorafenib tosylate 200-mg tablets (Nexavar, BAY43-9006, Bayer Pharmaceuticals Corp., West Haven, CT and Onyx Pharmaceuticals Corp., Emeryville, CA), a new, small-molecular entity and oral multi-

kinase inhibitor for the treatment of patients with advanced renal cell carcinoma (RCC). This indication is based on the demonstration of substantially improved progression-free survival (PFS) in a large, randomized double-blinded, placebo-controlled phase 3 multinational study and a supportive phase 2 study. Overall survival results from the phase 3 study are preliminary.

The original Investigational New Drug application for sorafenib was submitted in 2000. Phase 1 and 2 studies suggested antitumor activity in RCC. In September 2003, a Special Protocol Assessment agreement was reached with Bayer and Onyx Pharmaceuticals regarding the design, patient enrollment, end points, and analysis plan for a phase 3 randomized trial in patients with advanced RCC. In March 2004, sorafenib received Fast Track designation for the RCC indication for sorafenib, and in September 2004, sorafenib was granted Orphan Drug Status. In April 2005, the sponsors met with the Agency to discuss the results of the PFS analysis and to

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Received 5/22/06; revised 9/19/06; accepted 10/4/06.

The views expressed herein are independent and do not necessarily represent the views of the U.S. Food and Drug Administration.

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doi:10.1158/1078-0432.CCR-06-1249

discuss the regulatory consequences of allowing control group patients to crossover to receive sorafenib. The sorafenib new drug application, submitted in July 2005, consisted of two principal clinical studies and received priority review.

Chemistry

Sorafenib tosylate (the tosylate salt form), chemical name 4-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-methylpyridine-2-carboxamide-4-methylbenzenesulfonate, is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$ and a molecular weight of 637.0. Sorafenib tosylate is manufactured via chemical synthesis, by coupling picolinamide phenyl ether, a key intermediate, with 4-chloro-3-trifluoromethylphenylisocyanate, followed by salt formation. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol, and soluble in PEG 400. The chemical structure of sorafenib tosylate is shown in Fig. 1.

Sorafenib is formulated as a red, round, biconvex, film-coated tablet; each tablet contains 274 mg sorafenib tosylate equivalent to 200 mg sorafenib and the inactive ingredients cellulose microcrystalline, croscarmellose sodium, hypromellose, magnesium stearate, and sodium lauryl sulfate. The coating material consists of hypromellose, macrogol (synthetic polyethylene glycol), titanium dioxide, and ferric oxide-red (E172).

Nonclinical Pharmacology-Toxicology

Sorafenib (BAY43-9006) is a multi-kinase inhibitor. It inhibits C-RAF, B-RAF, a mutant B-RAF, VEGFR-2, VEGFR-3, PDGFR β , Flt3, and C-Kit with IC₅₀s in the nanomolar ranges (1). Several of these kinases are involved in angiogenesis.

Repeat-dose animal toxicology was generally predictive of the toxicities observed in humans as indicated by the clinical adverse events. In the repeat-dose toxicology studies, findings included cirrhotic changes, glomerulopathy and renal tubular dilation, gastrointestinal hemorrhage, adrenal necrosis and hemorrhage, hypothyroidism, pancreatitis, and changes in serum α -amylase. Osteodystrophy of the jaw was noted in rats. Young animals showed incomplete epiphyseal closure, thickening of growth plates, and dentin alteration. Potential

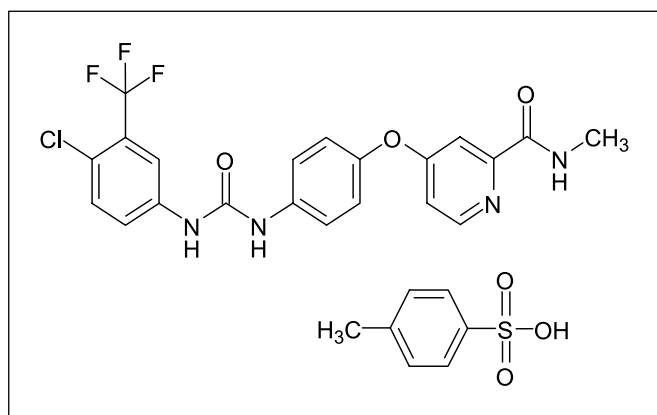


Fig. 1. Chemical structure of sorafenib tosylate.

cardiotoxicity was evidenced by positive findings in the *in vitro* hERG and action potential assays and inflammation/congestion/hemorrhage in the heart and increased creatine kinase in the chronic dog toxicity study. Changes in coagulation values were inconclusive. Sorafenib can cross the blood-brain barrier. Based on a safety pharmacology study, sorafenib may cause sensory neuropathy.

Sorafenib is teratogenic. Embryo-fetal toxicities, observed in rats and rabbits, occurred at subtherapeutic exposures and included increased post-implantation loss, fetal malformations, and necrotic placentas. Although fertility and early developmental studies were not conducted, adverse findings in the reproductive organs in the repeat dose toxicity studies suggest that sorafenib has the potential to impair reproductive function and fertility in males and females. Pharmacokinetic studies in rats with radiolabeled sorafenib indicated that sorafenib is excreted into the milk.

Clinical Pharmacology

After administration of sorafenib-containing tablets, the drug's mean elimination half-life is between 25 and 48 h. Sorafenib reaches peak plasma levels ~ 3 h after oral administration. With a high-fat meal, sorafenib bioavailability was reduced 29% compared with fasting bioavailability. *In vitro* binding of sorafenib to human plasma proteins is 99.5%.

Sorafenib is metabolized primarily in the liver; oxidative metabolism is mediated by CYP3A4, and glucuronidation is mediated by UGT1A9. Sorafenib accounts for $\sim 70\%$ to 85% of the circulating analytes in plasma at steady state. Following oral administration of a 100 mg sorafenib dose in a solution formulation, 77% of the dose was excreted in feces, and 19% was excreted in urine as glucuronidated metabolites. Unchanged sorafenib, which accounted for 51% of the dose, was found in feces but not in urine.

Analyses of demographic data suggest that no dose adjustments are necessary based on patient age or gender. No pharmacokinetic data exist for pediatric patients. In patients with mild (Child-Pugh A, $n = 14$ patients) or moderate (Child-Pugh B, $n = 8$) hepatic impairment, drug exposure values were within the range observed in patients with no hepatic impairment. Sorafenib's pharmacokinetics has not been studied in patients with severe (Child-Pugh C) hepatic impairment. In four phase 1 clinical trials, sorafenib was evaluated in patients with normal renal function, mild renal impairment (creatinine clearance >50 - 80 mL/min, $n = 24$), and moderate renal impairment (creatinine clearance = 30 - 50 mL/min, $n = 4$). No relationship was observed between renal function and steady-state sorafenib area under the curve at doses of 400 mg twice daily. The drug's pharmacokinetics has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or in patients undergoing dialysis.

Steady-state dosing of ketoconazole (400 mg), a potent inhibitor of cytochrome P450 3A4 (CYP3A4) did not alter the mean area under the curve of an oral dose of sorafenib. Administration of sorafenib tablets did not alter the exposure of concomitantly given midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), or omeprazole (CYP2C19 substrate). The possible effect of sorafenib on the CYP2C9 substrate warfarin was assessed indirectly by measuring the PT-INR. Mean changes from baseline in PT-INR were not higher

in patients administered sorafenib tablets compared with patients given a placebo. Although not studied clinically, inducers of CYP3A4 activity are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations.

Sorafenib tablets have been given with the antineoplastic agents gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Concomitant treatment with sorafenib resulted in a 21% increase in the area under the curve of doxorubicin. When given with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, sorafenib produced a 67% to 120% increase in the area under the curve of SN-38 and a 26% to 42% increase in the area under the curve of irinotecan. Because sorafenib inhibits CYP2B6 and CYP2C8 *in vitro*, systemic exposure to substrates of CYP2B6 and CYP2C8 might be expected to increase when co-administered with sorafenib. Similarly, although not studied clinically, sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways, and systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with sorafenib. CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4 *in vivo*.

Clinical Studies

In a phase 2 study (2), 202 patients with advanced RCC (a subgroup) were treated with 400 mg sorafenib twice daily p.o. continuously for 12 weeks and then had follow-up radiologic assessment. Patients with bidimensional radiologic tumor shrinkage $\geq 25\%$ (79 of 202) continued sorafenib, whereas patients with tumor growth $\geq 25\%$ discontinued treatment. Of the remaining patients, 65 with $< 25\%$ change in bidimensional tumor measurements from baseline were randomized to sorafenib or placebo for an additional 12 weeks to assess the effect of continuation of sorafenib therapy on duration of tumor control. The study's primary efficacy end point was the proportion of patients not showing radiologic progression at the end of this 12-week interval following the randomization. Among the 65 randomized patients, the progression-free rate was statistically significantly higher for the sorafenib group compared with the placebo group. Overall, 50% (16 of 32) of patients randomized to sorafenib versus 18% (6 of 33) randomized to placebo remained progression-free at 12 weeks after randomization ($P = 0.0077$). PFS also was statistically significantly longer for patients randomized to sorafenib (median = 163 days) than for patients given placebo (median = 41 days; log-rank $P = 0.0001$; hazard ratio, 0.29). These results suggested antitumor activity and led to a definitive phase 3 efficacy trial.

The phase 3 trial is a large, randomized, double-blind, controlled international, multicenter study comparing sorafenib plus best supportive care with placebo plus best supportive care in patients with advanced RCC and with disease progression after receiving one systemic regimen of chemotherapy, immunotherapy, or chemo-immunotherapy. Eligibility criteria included pathologic evidence of advanced (unresectable or metastatic) RCC, an Eastern Cooperative Oncology Group performance status of 0 or 1, a prognostic risk score of "low" or "intermediate" according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk score (3), at least

one measurable lesion, and a typical clear cell histologic pattern. Exclusion criteria included advanced cardiac disease [arrhythmias requiring therapy, symptomatic coronary disease, or myocardial infarction within 6 months, or congestive heart failure of class > 2 (New York Heart Association classification)], brain or meningeal metastases, ongoing viral or bacterial infections, or "high" MSKCC prognostic risk score.

Patients gave written informed consent to be randomized to oral sorafenib, 400 mg twice daily (800 mg total daily dose) in an uninterrupted schedule or to a matching placebo. No subsequent crossover upon disease progression from placebo to sorafenib was provided in the protocol. Eligible patients were stratified by MSKCC risk score and country and then centrally randomized (1:1) to sorafenib or placebo. The primary study end point is overall survival, and the primary analysis is a log-rank comparison of the intention-to-treat population (all randomized) with a two-sided type one error allocation (α) of 0.04, to occur upon reaching 540 events. The trial was designed to detect a clinically meaningful survival improvement, defined as a 33.3% increase in overall survival, and assumed a 10-month median survival in the control group. Two interim analyses and one final overall survival analysis were pre-specified per protocol.

PFS was analyzed as a co-primary end point, with a two-sided α allocation of 0.01 and a single planned stratified log-rank comparison to be done on the ITT population at ~ 363 events. Stratification factors were MSKCC prognostic risk category and country. PFS was defined as the time from randomization to progression of disease or to death from any cause, whichever occurred earlier. Progression of disease and tumor response rate were determined by independent blinded radiologic review of computed tomography scans using the Response Evaluation Criteria in Solid Tumors (RECIST) according to a pre-specified radiologic charter. In determining PFS, clinical progressions based on investigator assessment were included only if radiologically shown progression (based on independent radiologic review) was not documented on or before the date of the clinical progression. Scheduled tumor assessments were planned at 6-week intervals for the first 6 months and then at 8-week intervals thereafter. All patients who received any treatment were included in the safety assessment population.

Results

The phase 3 trial opened in November 2003. The data cutoff date for the PFS analysis was in February 2005. In the interval, 769 patients (385 in the placebo group and 384 in the sorafenib group) were randomized and available for the PFS analysis. The country with the highest enrollment was France (186 patients); 146 patients were enrolled from the United States.

The baseline demographic and disease characteristics of the study population, summarized in Table 1, seemed to be well balanced between the two groups. The majority of patients were male, consistent with the disease pattern of RCC. Prognostic risk categories were evenly distributed in both study arms; $> 80\%$ of the patients had received prior interleukin-2 (IL-2) or IFN. More than 90% of patients had stage IV (metastatic) RCC disease, and $> 90\%$ had had a nephrectomy.

Protocol deviations, which occurred in 23% of the patients, were mostly minor and equally distributed on both study arms.

Table 1. Baseline demographic and disease characteristics in the phase 3 trial

Characteristics	Sorafenib (%) (n = 384)	Placebo (%) (n = 385)
Gender		
Male	267 (70)	287 (75)
Female	116 (30)	98 (25)
Race		
White	276 (72)	278 (73)
Black/Asian/Hispanic/other	11 (3)	10 (2)
Not reported*	97 (25)	97 (25)
Age group, y		
<65	255 (67)	280 (73)
≥65	127 (33)	103 (27)
ECOG performance status at baseline		
0	184 (48)	180 (47)
1	191 (50)	201 (52)
2	6 (2)	1 (<1)
Not reported	3 (<1)	3 (<1)
MSKCC prognostic risk category		
Low	200 (52)	194 (50)
Intermediate	184 (48)	191 (50)
Prior nephrectomy	356 (93)	362 (94)
Prior cytokine: IL-2 and/or IFN		
Yes	319 (83)	313 (81)
No	65 (17)	72 (19)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*Race information was not collected from the 186 patients enrolled in France due to local regulations. In eight other patients, race was not available at the time of analysis.

The most common deviations were related to inclusion and exclusion criteria, especially receipt of more than one prior therapy; the use of local laboratories instead of the designated central laboratory; and continuation of double-blind treatment after disease progression. An analysis excluding these patients did not alter the efficacy results.

Overall, 91% of patients in the placebo group and 84% in the sorafenib group received >90% of the planned dose of study drug. For the 384 patients receiving sorafenib, the mean duration of therapy was 136 days (SD, 1 ± 13 days), and the range to data cutoff for the PFS analysis was 5 to 399 days.

The independent, blinded radiologic review of serial computed tomography scans was the data source for determining radiological progression. The actual timing of progression of disease assessments was highly symmetrical between the two groups. The median time from randomization to first follow-up scan was 41 days for the placebo group and 42 days for the

Table 2. Disease progression event categories for the PFS analysis in the phase 3 trial

Progressions	Placebo	Sorafenib	Total
Radiologic	164	117	281
Clinical	8	7	15
Death	23	23	46
Total PFS events	195	147	342
Censored	190	237	427

Table 3. Results of the PFS analysis for the phase 3 trial

	Placebo (n = 385)	Sorafenib (n = 384)
Total events (n = 342)	195 (50.6%)	147 (38.3%)
Total censored (n = 427)	190 (49.4%)	237 (61.7%)
Median PFS (95% CI), d	84 (78-91)	167 (139-174)
Stratified log-rank test	<i>P</i> < 0.000001	
Hazard ratio (95% CI), sorafenib/placebo	0.44 (0.35-0.55)	

Abbreviation: CI, confidence interval.

sorafenib group; for the second scan, the median time for both arms was 84 days. Variation in the timing of scheduled assessments occurred in <10% of visits and was balanced between the two groups.

Table 2 shows the disease progression event categories at the time of the single, planned formal PFS analysis. In all, 82% (281 of 342) of the events were radiologically determined. Deaths accounted for an additional 6% in each group, and clinical progressions accounted for 2% in each group. Baseline scans were not available for 4.5% of patients, and subsequent scans at various intervals were missing for about 1% of assessments on both study arms.

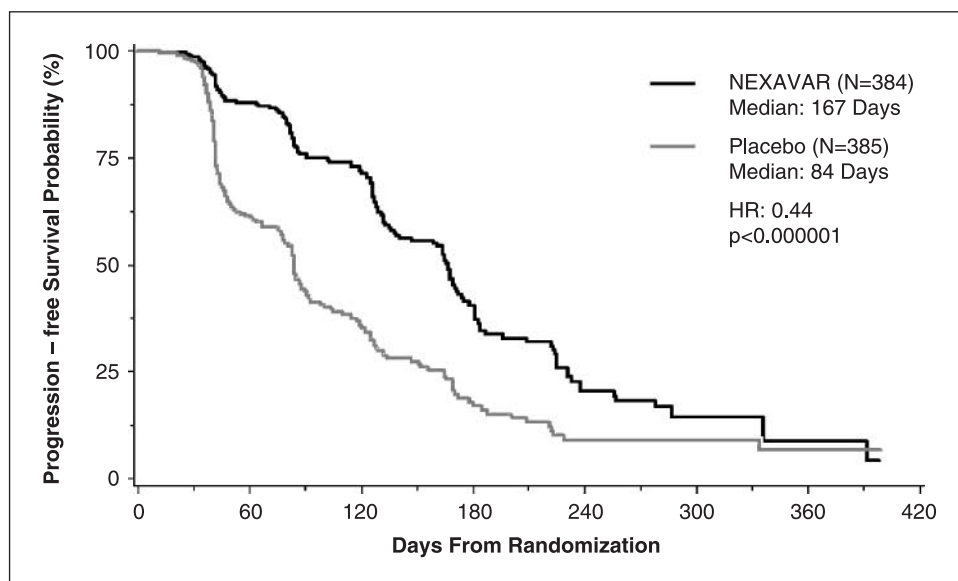
Efficacy. The Kaplan-Meier PFS curves for the phase 3 trial are shown in Fig. 2. The pre-specified PFS analysis was based on a total of 342 events; the results are presented in Table 3. PFS in the sorafenib arm was significantly superior (median = 167 days) to that in the placebo arm (median = 84 days, *P* < 0.000001). The hazard ratio for disease progression or death in the sorafenib arm, compared with the placebo arm, was 0.44 (95% confidence interval, 0.35-0.55; see Table 4).

Exploratory univariate analyses of PFS subsets examined patient age above or below 65 years, Eastern Cooperative Oncology Group performance status of 0 or 1, Memorial Sloan-Kettering Cancer Center prognostic risk category of low or intermediate, whether the prior therapy was for progressive metastatic disease or for an earlier disease setting (adjuvant or neoadjuvant), and time from diagnosis of <1.5 or >1.5 years. The effect of sorafenib on PFS was consistently superior in all these subsets. In addition, in patients with no prior therapy with IL-2 or IFN (*n* = 137: 65 patients receiving sorafenib and 72 on placebo), the median PFS was 172 days with sorafenib and 85 days with placebo.

Response rate also was determined by blinded, independent radiologic review using RECIST (including a second confirmatory scan). Among 672 patients (337 on placebo and 335 on sorafenib) eligible for response assessment, there were 7 (2.1%) partial responders on the sorafenib arm and none on placebo. In an exploratory analysis, the sponsor examined all tumor measurement changes observed for patients in the response population (see Fig. 3 and Table 4). In Fig. 3, the greatest magnitude of tumor measurement change from baseline is shown, ordered from largest increase to largest decrease, for each patient in each group. As Fig. 3 and Table 4 indicate, many more patients achieved some tumor shrinkage at some point in time with sorafenib than with placebo.

A planned interim survival analysis was conducted based on 220 deaths observed at the end of the double-blind treatment

Fig. 2. Kaplan-Meier curves for PFS in the phase 3 trial. Hazard ratio (*HR*) is from the Cox regression model with the following covariates: MKSCC prognostic risk category and country. *P* value is from two-sided log-rank test stratified by MKSCC prognostic risk category and country.



phase. Overall survival was found to be longer in the sorafenib patients than in placebo patients with hazard ratio of 0.72 (95% confidence interval, 0.55-0.95); however, this result did not meet the pre-specified criteria for statistical significance. Additional analyses are planned as the survival data mature.

Safety. Earlier in the development of sorafenib, doses above 400 mg twice daily led to dose-limiting diarrhea and hand-foot syndrome; thus, a 400 mg twice-daily dose was selected for further study. In the phase 3 trial, safety was assessed in a total of 902 study patients, including 451 who had received at least one dose of sorafenib. Because the trial was placebo controlled, sorafenib-associated toxicities occurring at higher frequency could be distinguished from events associated with underlying advanced RCC in the placebo group. Adverse events were defined and reported using version 3 of the National Cancer Institute's Common Terminology Criteria for Adverse Events.¹ Treatment-emergent adverse events reported in at least 10% of sorafenib patients are presented in Table 5. Some confidence in the success of blinding is suggested by the reported treatment-emergent adverse events in the placebo arm. The treatment-emergent adverse event totals for any events were only slightly lower for placebo than for sorafenib.

Most adverse events were grade 1 or 2. Grade 3 adverse events were reported in 31% of patients receiving sorafenib versus 22% of placebo patients. Grade 4 adverse events were reported in 7% of sorafenib patients versus 6% of placebo patients. The only individual category grade 3 adverse events observed at an incidence of $\geq 5\%$ were hand-foot skin reaction (6%) and fatigue (5%), both on the sorafenib arm. Grade 3 adverse events reported at an incidence $\geq 2\%$ higher in sorafenib patients than in placebo patients were hand-foot skin reaction, fatigue, and hypertension (see Table 5). Serious adverse events were reported in 153 (33.9%) sorafenib patients and 110 (24.4%) placebo patients. The rates of drug discontinuation due to adverse events were similar for the two groups (10%,

sorafenib; 8%, placebo). Dose interruptions related to an adverse event occurred in 14% of sorafenib patients and in 4% of the placebo patients.

The most common adverse events attributed to sorafenib were dermatologic events. Skin rashes were most often described as maculopapular erythematous eruptions on the scalp, face, and trunk (40% with sorafenib versus 16% with placebo); hand-foot skin reactions were reported in 30% of sorafenib patients versus 7% of placebo patients. Although these events frequently led to temporary discontinuation or dose reduction of study drug, dermatologic events led to permanent discontinuation of sorafenib in only two cases. Hair thinning or patchy hair loss was reported in 27% of sorafenib-treated patients, although complete alopecia was uncommon. Pruritis and dry skin also were reported more frequently in sorafenib patients. Dermatologic toxicities were usually reversible.

Diarrhea, although common (43% with sorafenib versus 13% with placebo), was usually managed successfully using antidiarrheal measures without dose reduction or interruption. Constipation, anorexia, nausea, fatigue, and anemia were

Table 4. Maximum % reduction in target SLD from baseline in the phase 3 trial

Max % reduction in target SLD from baseline	Placebo (%)	Sorafenib (%)
% Reduction >30%	5 (1.5)	29 (8.7)
% Reduction >20% but $\leq 30\%$	6 (1.8)	40 (11.9)
% Reduction >10% but $\leq 20\%$	7 (2.1)	77 (23.0)
% Reduction >0% but $\leq 10\%$	39 (11.6)	69 (20.6)
% Growth $\geq 0\%$	223 (66.2)	77 (23.0)
Missing	57 (16.9)	43 (12.8)
Total	337	335

(response analysis population)

NOTE: These data are from the independent radiologic review without a second confirmatory scan, which was required in the protocol definition of responder.
Abbreviation: SLD, sum of longest diameters of tumors.

¹ <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.

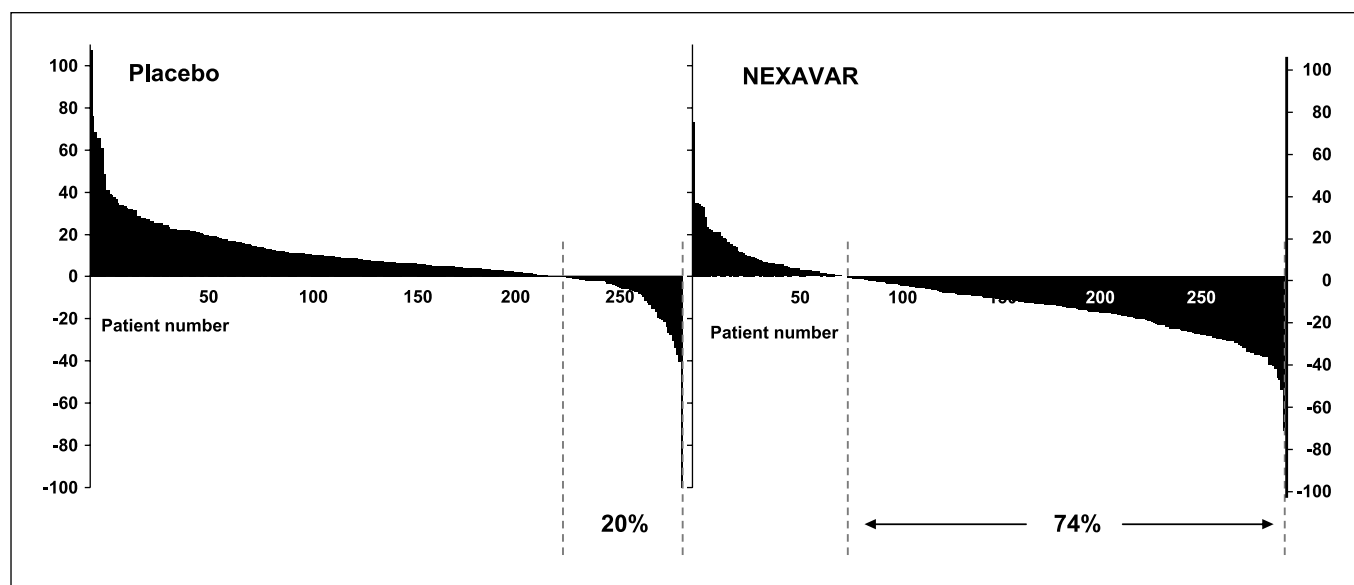


Fig. 3. Maximum percent reduction of target lesions by patient in the phase 3 trial (based on independent review). In the phase 3 trial, maximum percentage reduction in tumor burden from baseline for individual patients in each study arm, each of whom is represented by a vertical line (bar) drawn from the X axis on the graph. Bars pointing in the positive direction of the Y axis represent patients whose tumors grew, whereas bars pointing in the negative direction represent patients with tumor shrinkage. The point of "no change" in size is represented by the vertical dashed line. Some amount of reduction in size was observed for 20% of placebo patients compared with 74% of sorafenib (Nexavar) patients.

relatively common adverse events; these occurred with similar frequency in the placebo and sorafenib groups.

Hypertension of all grades was observed in 17% of sorafenib-treated patients versus 2% of placebo patients. The increases in blood pressure usually were noted during the first 4 to 6 weeks of therapy. At baseline, 7.5% of patients in both study arms had systolic blood pressure ≥ 160 mm Hg. Medication for treatment-emergent increases in blood pressure was instituted during the study in 14% of sorafenib patients and 3% of placebo patients.

Among other adverse events, hemorrhage/bleeding was reported in 15% of sorafenib-treated patients and 8% of placebo patients. Most of this difference was due to subungual, splinter-type hemorrhages observed in the sorafenib group (4). A noncumulative sensory neuropathy, generally paralleling the hand-foot skin reaction, was observed more commonly in sorafenib-treated patients (13%) than in placebo patients (6%). Grade 4 pancreatitis, defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events as life-threatening, was reported in two sorafenib patients, although both subsequently resumed sorafenib, with one at full dose. The incidence of cardiac ischemia and infarction events was higher in the sorafenib group (2.9%) than in the placebo group (0.4%). Central nervous system ischemic events were reported in 0.2% of sorafenib patients and in 0.9% of placebo patients.

Notable laboratory findings included asymptomatic hypophosphatemia (45% of sorafenib patients versus 11% in the placebo arm), elevation of serum lipase (41%, sorafenib; 30%, placebo), and lymphopenia (23%, sorafenib; 13%, placebo).

Discussion

RCC is a serious and life-threatening disease most commonly occurring in the fifth through seventh decades of life. The majority of patients present with apparently localized disease,

which may be curable surgically. However, ~30% to 50% of those later experience relapse, and ~30% to 40% of RCC patients will initially present with metastatic disease.

Systemic therapy has been inadequate for most patients with RCC; metastatic RCC has not responded to cytotoxic chemotherapy. Two drugs previously have received FDA approval for the treatment of advanced RCC. Medroxyprogesterone acetate injectable suspension is FDA approved for adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic RCC in doses of 400 to 1,000 mg i.m. weekly.² Aldesleukin, a recombinant DNA product possessing the biological properties of human IL-2, was licensed in 1992 for the treatment of metastatic RCC.³ The biological license was granted based on a response rate end point in a total of 255 patients from seven phase 2 studies combined, in which the overall response rate was 15%, including 3.5% (9 of 255) complete responses and 11% partial responses. For the patients experiencing a partial response, the median duration of response was 20 months. For patients experiencing complete response, the median survival exceeds several years (5). However, the IL-2 regimen is suitable for only a minority of patients due to its requirement for excellent baseline organ function and its considerable toxicity, which requires administration in an intensive care unit.

IFN- α cytokines, although reported to produce response rates of about 15% in advanced RCC with rare complete or durable responses, are not FDA approved for treatment of RCC (6, 7). As with IL-2, responses are usually associated with good performance status and low bulk disease in nodal or lung sites. Toxicity for IFN therapy, as with IL-2, is considerable. Although two studies have reported survival benefits using IFN

² Depo-Provera (package insert). Kalamazoo (MI): Pharmacia & Upjohn Company. November 2004.

³ http://www.proleukin.com/hcp_choice/prescribing_information.pdf.

Table 5. Treatment-emergent adverse events reported in at least 10% of sorafenib-treated patients in the phase 3 trial

Adverse event*	Sorafenib (n = 451), %			Placebo (n = 451), %		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any event	95	31	7	86	22	6
Cardiovascular, general						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand-foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage, all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

*According to version 3 of the National Cancer Institute's Common Terminology Criteria for Adverse Events.

therapy for advanced RCC, the studies are not definitive and many other studies have failed to confirm the findings (8, 9). No advantage has been shown for combining IL-2 with IFN or for cytokine-chemotherapy combinations. Use of the alternative cytokine after failure of the initial one also has been shown to be futile (10). A recently reported randomized study casts doubt on any role for cytokine-based therapy compared with medroxyprogesterone in advanced RCC (11).

In this large phase 3 controlled trial, the PFS improvement on the sorafenib arm is statistically highly persuasive ($P < 0.000001$; hazard ratio, 0.44; 95% confidence interval, 0.33-0.55) and clinically meaningful. A majority of sorafenib patients had some tumor shrinkage on at least one follow-up scan. Although the magnitude of these responses is less than that required by the Response Evaluation Criteria in Solid Tumors criteria, these response findings resulted from a blinded radiologic review of a double-blinded study and depict response as a continuous variable rather than a dichotomous one. The findings also may be reflecting a cytostatic effect.

Hand-foot skin reaction, blood pressure elevation, and sensory neuropathy may require reduction or interruption of therapy. Blood pressure should be monitored closely during the first several weeks of therapy for all antiangiogenic class compounds because blood pressure elevations are common and may require antihypertensive therapy. Likewise, when antiangiogenic drugs are discontinued, blood pressure should be monitored for possible declines that may require reductions in antihypertensive medication. The elevated lipase findings are unusual and unexplained clinically, although some nonclinical pancreatic toxicity was observed. Laboratory findings of elevated

lipase or amylase should be considered as possibly occurring independent of a clinical process such as pancreatitis.

Regulatory basis for approval. PFS, the primary basis for the marketing approval of sorafenib, was a co-primary end point with a single pre-specified analysis. The magnitude of improvement in PFS is statistically persuasive and judged clinically substantial in this well-designed and well-conducted phase 3 trial. There is no regulatory precedent in RCC for judging the magnitude of the PFS end point as a clinical benefit or as likely to predict one. In previous studies of RCC that have examined correlates of survival outcome, response rate has not been found to be predictive of overall survival benefit (12) most likely because response rates have been low and of modest duration. In contrast, there is some evidence linking improvement in PFS to an improvement in overall survival (Table 6). For example, in the Medical Research Council and the Pyrhonen studies, improvements of 1 to 2 months in PFS were associated with survival improvements of 2.5 to 7.5 months. The sorafenib phase 3 trial is the largest and most informative analysis to date in advanced RCC. Of particular note, if the sponsor had pursued a single-arm study with a response rate end point, it is likely that sorafenib would have been considered as "not effective."

An April 2005 FDA draft guidance⁴ for industry on clinical trial end points for the approval of cancer drugs and biologics notes that prolongation of PFS might be an accepted surrogate end point for clinical benefit to support full approval of a drug.

⁴ <http://www.fda.gov/cder/guidance/6592dft.doc>.

Table 6. Randomized trials in advanced RCC reporting both overall survival and PFS

Author(s)	Regimens	No. patients	Median PFS (mo)	P	Median OS (mo)	P
Atzpodien et al. (13)	IFN- α /VBL	63	5.0	0.0248	16.0	0.0227
	IL-2/IFN- α /5-FU	132	6.0		25.0	
	IL-2/IFN- α /CRA/5-FU	146	7.0		27.0	
Atzpodien et al. (14)	IL-2/IFN- α /5-FU	41	7	NA	24	0.032
	Tamoxifen	37	6		13	
McDermott et al. (15)	High-dose IL-2	95	3.1	0.018	17.0	0.211
	IL-2/IFN- α	91	3.1		13.0	
Mickisch et al. (16)	IFN- α	43	3.0	0.04	7.0	0.03
	Nephrectomy/IFN- α	42	5.0		17.0	
MRCC study (8)	IFN- α	174	4	0.009	8.5	0.017
	MPA	176	3		6	
Pyrhonen et al. (9)	IFN- α Plus VBL	79	3.0	0.001	15.7	0.0049
	VBL	81	2.1		8.2	

Abbreviations: OS, overall survival; VBL, vinblastine; CRA, 13-*cis*-retinoic acid; 5-FU, 5-fluorouracil; MPA, medroxyprogesterone acetate; MRCC, Medical Research Council Renal Cancer Collaborators; NA, not available.

In the guidance, important considerations include "the magnitude of the effect, the toxicity profile of the treatment and the clinical benefits and toxicities of other available therapies. For the assessment of PFS, randomized blinded studies with a blinded (independent) review are recommended."

The FDA-approved sorafenib for advanced RCC on the basis of a statistically compelling and clinically meaningful improvement in PFS showed in a large, well-designed, and conducted study powered for a survival end point. Compared with the

toxicities of traditional cytotoxic drugs and other available therapy in this setting, the toxicity profile of sorafenib, an oral formulation, is modest.

Acknowledgments

We thank Diane S. Hackett (Research Fellow, Center for Drug Evaluation and Research, Food and Drug Administration) for assistance in editing this article. This fellowship program is given by Oak Ridge Associated Universities through a contract with the Food and Drug Administration.

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