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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Medical Review(s)

Division of Drug Oncology Products

Medical Team Leader's Review- Correction sheet

NDA:	21923
Sponsor:	Bayer
Drug Product:	Nexavar, Sorafenib, BAY93-4006
Projected Action Date:	December 15, 2005

I have a typographical error on page 7, replace the text which reads 0.0000001 with 0.000001.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Farrell
12/20/2005 11:12:41 AM
MEDICAL OFFICER

Division of Drug Oncology Products

Medical Team Leader's Review

NDA:	21923
Sponsor:	Bayer
Drug Product:	Nexavar, Sorafenib, BAY93-4006
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Summary

On July 6, 2005, Bayer Pharmaceuticals submitted this New Drug Application (NDA) for sorafenib, an oral multi-kinase inhibitor, a new molecular entity, for the treatment of patients (pts) with advanced renal cell cancer (RCC). The submission consisted of two studies for the proposed indication.

One study (Study 11213), the major study for the indication, is a large, international, double-blind, randomized, well-controlled phase 3 study in which results from single agent sorafenib therapy were compared to placebo therapy with best supportive care for patients with advanced RCC who had received one prior therapy. In the phase 3 study, sorafenib treatment resulted in an improvement PFS for RCC patients compared with control. The median PFS was improved from 84 days in the control group to 167 days for sorafenib; hazard ratio = 0.44; $p < 0.000001$.

This major study is supported by data from RCC patients enrolled in a randomized discontinuation study (Study 10039). In the phase 2 randomized discontinuation trial for the subset of patients with RCC, patients who entered the randomized discontinuation arm and were randomized to continued sorafenib therapy were compared with patients who entered the randomized discontinuation arm and were randomized to discontinue sorafenib therapy. The primary efficacy objective of the study was the progression-free rate at the end of the 12 week period post randomization. The study demonstrated that the progression-free rate at the end of the 12-week randomization period was statistically significantly different (i.e., higher) for the sorafenib group than that for the placebo group. Overall, 50.0% (16/32) of subjects randomized to sorafenib and 18.2% (6/33) of subjects randomized to placebo were progression-free at 12 weeks after randomization (*P* value = 0.0077). The median progression-free survival (PFS) was also statistically significantly different (i.e., longer) for subjects randomized to sorafenib (163 days) than for subjects randomized to placebo (41 days, *P* value = 0.0001).

The major toxicities observed with sorafenib treatment included: dermatologic (rashes, hand-foot syndrome), gastrointestinal (diarrhea), constitutional (fatigue, fever, weight loss, sweating, other), cardiovascular (hypertension), blood/bone marrow (decreased hemoglobin) and neurologic (neuropathy).

One scientific and regulatory issue to consider is whether this application should receive accelerated or regular approval. Regular approval is typically given when an agent has demonstrated an improvement in clinical benefit. The Agency has stated that clinical benefit is that which improves the quantity or quality of life. In this case, both studies show a statistically significant difference in PFS, which is primarily a radiographic endpoint. However, whether an improvement in PFS results in an improvement in the quantity or quality of life is debatable. The Cochrane Colloborative recently conducted a systematic review of immunotherapy trials for advanced RCC and determined that there was no relationship between remission rate and survival. The sponsor presented a review of the literature and listed 6 randomized trials which had positive overall survival results and the corresponding PFS result. Five out of six of these trials had a statistically significant improvement in PFS. This reviewer reviewed the 6 articles the sponsor presented and concurred with the sponsor's assessment. An effect on PFS resulting in prolongation over control appears to translate into a similar result for survival; thus, this application is recommended for regular approval.

Based on the results contained in this NDA submission, this reviewer recommends regular approval.

Bayer should continue to follow patients enrolled in study 11213 and provide the division with a final safety and survival analysis based on mature data for all patients enrolled in the major study.

Dr. Kane's review has several suggestions for additional study. These suggestions should be forwarded to the company.

Background:

Advanced Renal Cell Cancer

Renal cell carcinoma is serious and life threatening disorder most commonly seen in the 5th through 7th decade of life. The majority of patients with renal cell cancer present with apparently localized disease, which is curable surgically. However, approximately 30-50% of those presenting with localized disease will relapse later. Approximately 30-40% of patients will present with metastatic disease for which is there is no curative therapy. The only approved therapy for renal cell cancer is IL-2 which is associated with significant toxicity and for which the majority of patients with metastatic disease are not candidates because of co-morbidites.

United States Regulatory History
The IND was opened in May 2000. In September 2003, a Special Protocol Assessment agreement was reached with Bayer regarding the design, proposed patient enrollment and endpoints for the phase 3 randomized trial in patients with advanced RCC. In March 2004, Bayer received Fast Track designation. In September 2004, Bayer received Orphan Drug Status. In December 2004, the Agency met with Bayer for a pre-NDA meeting. In April 2005, the Agency met with Bayer to discuss the results from the analysis of PFS and to discuss the issue of allowing placebo treated patients to crossover to receive sorafenib. July 2005, the Agency has received a complete NDA submission to review.

For additional details, please see Dr. Kane's review.

Chemistry:

BAY43-9006, sorafenib, Nexavar™, manufactured by Bayer HealthCare AG, Leverkusen, Germany will be distributed by Bayer Pharmaceuticals and Onyx Pharmaceuticals.

For further details, please see Dr. Jee's and Dr. Liang's Chemistry, Manufacturing, and Control review of this NDA.

The reviewers did not identify any phase 4 commitments.

Nonclinical Pharmacology and Toxicology Information:

Mechanism of Action- multikinase inhibitor,

Bayer provide information to support that sorafenib inhibited the following kinases: CRAF, BRAF, V600E BRAF, FLT-3, c-KIT, VEGFR2, VEGFR3, and PDGFR-β.

From Dr. Mahloogi's review:
Sorafenib was genotoxic as demonstrated in the Chinese Hamster Ovary aberration test in the presence of S9. Sorafenib is teratogenic and can cause embryo-fetal toxicities at sub-therapeutic doses.

M-2 appears to be the major metabolite in human. The M-2 metabolite appears to be an active metabolite, since the pattern of toxicity obtained with M-2 is similar to that observed with the parent compound. The M-2 metabolite was not genotoxic in the Ames assay.

The main impurity of [redacted] was shown to be genotoxic in the Ames (+S9) assay. In vitro data indicate that sorafenib is metabolized by CYP3A4 and UGT1A9 pathways.

Sorafenib can cross the placental barrier, is teratogenic at sub-therapeutic doses, and can be excreted in milk. Therefore women of childbearing potential should be advised to avoid becoming pregnant while taking sorafenib. Women should be advised to avoid breast-feeding while taking the drug.
There is a potential for sorafenib to inhibit CYPs 2B6, 2C8, and 2C9 as well as to inhibit glucuronidation by UGT1A1 and UGT1A9. Therefore systemic exposure to substrates of CYP2B6, CYP2C8, 2B9, UGT1A1 and UGT1A9 may increase when co-administered with sorafenib.

Therefore the product is genotoxic and teratogenic and this information should clearly be in the label. The label will say Pregnancy D category.

For further details, please see the Pharmacology and Toxicology reviews of this NDA.

The reviewer did not identify any phase 4 commitments.

Human Pharmacology:

From Dr. Williams' review:
After administration of NEXAVAR tablets, the mean elimination half-life of sorafenib is approximately 25 - 48 hours. The clinical regimen (400 mg bid) results in a 2.5- to 7-fold accumulation compared to single dose administration and a peak to trough ratio of mean concentrations of less than 2. Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability was similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. Mean Cmax and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily. In vitro binding of sorafenib to human plasma proteins is 99.5%. Sorafenib is metabolized primarily in the liver undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady state...Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

Analyses of demographic data suggest that no dose adjustments are necessary for age or gender. There are no pharmacokinetic data in pediatric patients. In patients with mild (Child-Pugh A, n = 14) or moderate (Child-Pugh B, n = 8) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment. In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy

subjects, 19% of the administered dose of sorafenib was excreted in urine. In four Phase 1 clinical trials, sorafenib was evaluated in patients with normal renal function and in patients with mild renal impairment (CrCl > 50 – 80 mL/min, n = 24) or moderate renal impairment (CrCl 30 – 50 mL/min, n = 4). No relationship was observed between steady state sorafenib AUC and renal function at doses of 400 mg twice daily. The pharmacokinetics of sorafenib have not been studied in patients with severe renal impairment (CrCl < 30 ml/min) or patients undergoing dialysis.

Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days did not alter the mean AUC of a single oral 50 mg dose of sorafenib in healthy volunteers. Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4. Administration of NEXAVAR 400 mg twice daily for 28 days did not alter the exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), or omeprazole (CYP2C19 substrate). Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9. The possible effect of sorafenib on a CYP2C9 substrate was assessed indirectly in patients receiving warfarin. The mean changes from baseline in PT-INR were not higher in NEXAVAR patients compared to placebo patients. There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Substances that are inducers of CYP3A4 activity are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations…

In Phase 1 clinical studies, NEXAVAR has been administered with the anti-neoplastic agents gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67 - 120% increase in the AUC of SN-38 and a 26 - 42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown. Sorafenib inhibits CYP2B6 and CYP2C8 in vitro. Although not studied clinically, systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when coadministered with NEXAVAR. Similarly, sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways and, although not studied clinically, systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with NEXAVAR. 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.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) identified 5 phase 4 commitments.

From Dr. William's review they are:

1. Explore alternative dosing regimens in Asian patients, with the goal of arriving at a regimen that will produce the concentration time profile seen in non-Asians. First, modeling and simulation should be to identify an alternative dosage regimen that is predicted to result in Asian patients having a similar exposure as non-Asians. This regimen should then be administered to Asian patients in a multiple-dose pharmacokinetic study to determine if it performs as predicted.
2. Complete the ongoing study of the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375.
3. Complete the ongoing investigation of the ability of biomarkers to identify patients who respond to sorafenib.
4. Complete the ongoing study examining the ability of rifampin to alter the pharmacokinetics of sorafenib.
5. Complete the ongoing study examining the pharmacokinetics of sorafenib in patients with renal impairment.

Clinical Studies Summary:

Study 11213 is an international, multicenter, double-blind, randomized, phase 3, controlled study comparing sorafenib plus best supportive care (BSC) to placebo plus BSC in subjects with advanced RCC who received 1 prior regimen of chemotherapy or immunotherapy. The trial randomized (1:1), using a blinded computer generated central list stratified by Motzer category and country, patients to receive sorafenib (400 mg twice daily, total daily dose 800 mg) or placebo in an uninterrupted daily schedule. In the original protocol all patients were to be followed for survival.

For details on enrollment criteria, please see Dr. Kane's review.

Nine hundred seventy-six subjects with advanced RCC were enrolled; 769 were randomized (efficacy, intent-to-treat [ITT] population) and 768 were treated with at least 1 dose of study drug (safety population). The majority of patients enrolled were white and male. The median age was 58. Demographics and disease characteristics were relatively well-balanced between treatment arms. The mean duration of disease prior to study enrollment was approximately 3 years and the mean duration of metastatic disease was 1.3 years. Ninety-three percent had received prior nephrectomy. Eighty-two percent of patients had received prior cytokine therapy. Seventeen percent of patients received one prior therapy as part of neoadjuvant or adjuvant therapy.

For other details on demographics and disease characteristics as well as analysis populations, please see Dr. Kane's review.

Results

The table below demonstrates the efficacy results from the PFS analysis.

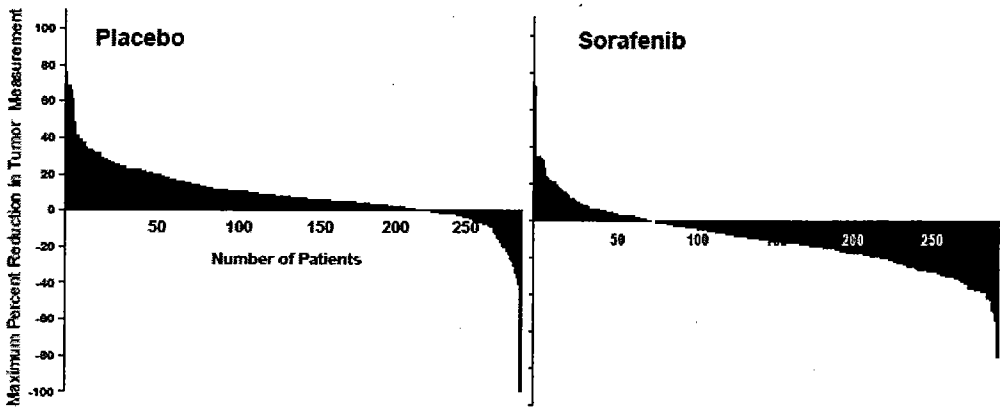
Trial 11213 PFS results

	Placebo	sorafenib
	N = 385	N = 384
Total failed (n = 342)	195 (50.6%)	147 (38.3%)
Total censored (n = 427)	190 (49.4%)	237 (61.7%)
Median PFS (days)	84	167
95% CI for median	(78, 91)	(139, 174)
Hazard ratio (sorafenib/placebo) (95% confidence interval)	0.44 (0.35,0.55)	
95% CI for hazard ratio	(0.35, 0.55)	
P-value	p<0.0000001	

The improvement in PFS for all subgroups was seen in all subgroups (men, women, those < 65 years, those ≥ 65 years

The overall best confirmed response rate for the sorafenib treatment was 2.1% compared to 0% for the placebo group (independent assessment). The overall best confirmed response rate for sorafenib treatment was 9% compared to 1.5% for the placebo group (independent assessment). All responses were partial responses. However the sponsor noted that a number of the responses were less than partial. Please see the sponsor's depiction of responses by treatment arm below (sponsor's figure 11-5) from the clinical study report.

Figure 11-5: Maximum Percent Reduction of Target Lesions by Subject, Using Independent Review of Scans



Reviewer's Comment: Although sorafenib treatment was not associated with many partial responses, the figure above suggests that tumor responses did occur.

In the sponsor's table below the maximum percent reduction in target lesion is summarized by treatment group in the 11213 study.

11213: Max % Reduction in Target SLD from BL
(Independent Review Data)

Population: Patients valid for response analysis

	Placebo		Sorafenib	
Max % Reduction in Target SLD (sum of longest diameter) from Baseline	N	%	N	%
% reduction>30%	5	1.5	29	8.7
% reduction>20% but <=30%	6	1.8	40	11.9
% reduction>10% but <=20%	7	2.1	77	23.0
% reduction>0% but <=10%	39	11.6	69	20.6
% growth>=0%	223	66.2	77	23.0
Missing	57	16.9	43	12.8

Sponsor's Table

Survival Analysis

Due to the termination of the randomized design, the sponsor agreed to perform an interim survival analysis on the blinded data. At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for sorafenib

arm than the placebo arm with a hazard ratio (Nexavar over placebo) of 0.72 (95% CI: 0.55, 0.95; p=0.018). This analysis did not meet the prespecified criteria of p<0.0005 for statistical significance. A final analysis is planned in the future.

The phase 2 study enrolled 202 patients with advanced RCC, all initially treated with sorafenib for 12 weeks and then entered into a randomized discontinuation design where patients with advanced RCC who had less than a 25% tumor response but no evidence of progression were randomized to either continued sorafenib treatment or to discontinue sorafenib treatment. The progression-free rate at the end of the 12-week randomization period was statistically significantly different (i.e., higher) for the sorafenib group than that for the placebo group. Overall, 50.0% (16/32) of subjects randomized to sorafenib and 18.2% (6/33) of subjects randomized to placebo were progression-free at 12 weeks after randomization (*P* value = 0.0077). The median progression-free survival (PFS) was also statistically significantly different (i.e., longer) for subjects randomized to sorafenib (163 days) than for subjects randomized to placebo (41 days, *P* value = 0.0001). Sorafenib was restarted in 26 patients who were randomized to the discontinuation arm and subsequently progressed. For these 26 patients the time from restating sorafenib to end of treatment (toxicity/progression) was 24 weeks.

For details regarding other secondary endpoints and the randomized discontinuation trial, please see Dr. Kane's review.

Sponsor's Review of the Literature
The sponsor performed a literature analysis for randomized controlled trials in patients with advanced renal cell cancer which reported both progression-free survival (PFS) and overall survival (OS) results.

Sponsor's Literature Review of Randomized Controlled Trials (RCT) in Patients with Advanced and/or Metastatic Renal Cell Cancer Reporting PFS and OS

Study/Author	Design	Results
Atzpodien J et al.[1]	RCT 341 patients with metastatic disease randomized to one of 3 treatment arms	3 year PFS Arm A vs. B and – no statistically significant difference, Arm B vs. C p=0.0248 OS median Arm A 25 months, Arm B – 27 months, Arm C -16 months, Arm B vs. C p=0.02
Atzpodien J et al.[2]	RCT 78 patients with metastatic disease randomized to one of 2 treatment arms	PFS median 7 vs. 0 months (p<0.0001) OS PFS median 24 vs. 13 months (p=0.03)
McDermott et. al.[3]	RCT 192 patients with metastatic disease randomized to one of 2 treatment arms	No statistically significant difference in PFS or OS between treatment arms
Medical	RCT 350 patients	PFS (hazard ratio 0.72 95% CI 0.56,0.92,

Research Council Renal Cancer Collaborators[4]	randomized to Interferon versus medroxyprogesterone acetate	p=0.01) OS (hazard ratio 0.72 95% CI 0.55,0.94, p=0.02)
Mickisch G H J et al.[5]	RCT 85 patients randomized to radical nephrectomy plus interferon-α versus interferon-α alone	PFS median 5 vs. 3 months (hazard ratio 0.60 95% CI 0.36,0.97, p=0.04) OS median 17 vs. 7 months (hazard ratio 0.54 95% CI 0.31,0.94, p=0.03)
Pyrhonen et al.[6]	RCT 160 patients randomized to Interferon alfa-2a plus vinblastine versus vinblastine alone	PFS median 13 weeks vs. 9 weeks, p=0.0001 OS median 68 vs. 38 weeks p=0.0049

Reviewer's Table

Overall Safety Assessment

Adverse Events (AEs)
Treatment emergent AEs seen in 5% or more of the sorafenib treated patients enrolled in the major study included: Blood/Bone Marrow (decrease hemoglobin), Cardiovascular (hypertension), Constitutional (fatigue, fever, constitutional symptoms-other, weight loss, sweating), Dermatologic (rash, hand-foot syndrome, alopecia, pruritis, dermatologic-other, dry skin, flushing), Gastrointestinal (diarrhea, nausea, anorexia, vomiting, constipation, gastrointestinal-other, mucositis), Infection, Lymphatics (edema), Musculosketetal, Neurology (sensory neuropathy), Pain (multiple sites), and Pulmonary (cough, dyspnea, other).

Grade 3-4 AEs
Thirty-one percent of sorafenib treated patients had grade 3 treatment emergent AEs compared with twenty-two percent of placebo treated patients. Seven percent of sorafenib treated patients had grade 4 treatment emergent AEs compared with six percent of placebo treated patients. These treatment emergent AEs seen in 2% or more of the sorafenib treated patients enrolled in the major study included: Blood/Bone Marrow (decrease hemoglobin), Cardiovascular (hypertension), Constitutional (fatigue), Dermatologic (hand-foot syndrome), Gastrointestinal (diarrhea), Pain (tumor), and Pulmonary (dyspnea).

Serious Adverse Events (SAES)
Thirty-four percent of sorafenib treated patients had treatment emergent SAEs compared with twenty-four percent of placebo treated patients. These treatment emergent SAEs seen in 1% or more of the sorafenib treated patients enrolled in the major study included: Blood/Bone Marrow (decrease hemoglobin), Cardiovascular (cardiac ischemia/infarction, cardiopulmonary arrest, hypertension), Constitutional (fatigue, other), Death –not associated with

progression, Gastrointestinal, Muculoskeletal (fracture), Pain (tumor), Pulmonary (dyspnea) and Renal (failure).

Discontinuations
Ten percent of sorafenib treated patients had AEs leading to permanent discontinuation compared with eight percent of placebo treated patients. These AEs seen in the sorafenib treated patients enrolled in the major study included: Blood/Bone Marrow (decrease hemoglobin), Cardiovascular (cardiac ischemia/infarction, cardiopulmonary arrest, hypertension), Constitutional (fatigue, other), Death –not associated with progression, Dermatologic (hand-foot syndrome), Gastrointestinal (diarrhea, vomiting), Metabolic (amylase), Muculoskeletal (fracture), Neurology, Pain (tumor), Pulmonary (other, dyspnea, effusion, pneumonitis) Renal (failure) and Vascular (thrombosis/embolism). The most common reasons for dose interruption were hand-foot reaction, hypertension, and diarrhea. When these sorafenib treated patients resumed treatment, they were usually given dose reductions.

For further details, please see Dr. Kane's review of this NDA.

Division of Scientific Investigations

For additional details, please see the Division of Scientific Investigations report.

Discussion

Conclusions and Recommendations
On July 6, 2005, Bayer Pharmaceuticals submitted this New Drug Application (NDA) for sorafenib, an oral multi-kinase inhibitor, a new molecular entity, for the treatment of patients (pts) with advanced renal cell cancer (RCC). The submission consisted of two studies for the proposed indication in this population.

In the phase 3 study, sorafenib treatment resulted in an improvement PFS for RCC patients compared with control. The median PFS was improved from 84 days in the control group to 167 days for sorafenib; hazard ratio = 0.44; $p < 0.000001$. In the phase 2 randomized discontinuation trial for the subset of patients with RCC. The study demonstrated that the progression-free rate at the end of the 12-week randomization period was statistically significantly different (i.e., higher) for the sorafenib group than that for the placebo group. Overall, 50.0% (16/32) of subjects randomized to sorafenib and 18.2% (6/33) of subjects randomized to placebo were progression-free at 12 weeks after randomization (*P* value = 0.0077). The median progression-free survival (PFS) was also

statistically significantly different (i.e., longer) for subjects randomized to sorafenib (163 days) than for subjects randomized to placebo (41 days, *P* value = 0.0001).

The major toxicities observed with sorafenib treatment included: dermatologic (rashes, hand-foot syndrome), gastrointestinal (diarrhea), constitutional (fatigue, fever, weight loss, sweating, other), cardiovascular (hypertension), blood/bone marrow (decreased hemoglobin) and neurologic (neuropathy).

The sponsor presented a review of the literature and listed 6 randomized trials which had positive overall survival results and the corresponding PFS result. Five out of six of these trials had a statistically significant improvement in PFS. This reviewer reviewed the 6 articles the sponsor presented and concurred with the sponsor's assessment. An effect on PFS resulting in prolongation over control appears to translate into a similar result for survival; thus, this application is recommended for regular approval.

Based on the results contained in this NDA submission, this reviewer recommends regular approval.

Bayer should continue to follow patients enrolled in study 11213 and provide the division with a final safety and survival analysis based on mature data for all patients enrolled in the major study.

Dr. Kane's review has a number of suggestions for additional study. These suggestions should be forwarded to the company.

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[1] Atzpodien J, Kirchner H, Jonas U, Bergmann L, Schott H, Heynemann H, Fornara P, Loening SA, Roigas J, Mu¨ller SC, Bodenstein H,Pomer S, Metzner B, Rebmann U, Oberneder R, Siebels M, Wandert T, Puchberger T, and Reitz M. *Interleukin-2– and Interferon Alfa-2a–Based Immunochemotherapy in Advanced Renal Cell Carcinoma: A Prospectively Randomized Trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN)* Journal of Clinical Oncology 2004, 22(7):1188-94.

[2] Atzpodien J, Kirchner H, Illiger HJ, Metzner B, Ukena D, Schott H, Funke PJ, Gramatzki M; von Jurgenson S, Wandert T, Patzelt T, Reitz M and *(DGCIN) German Cooperative Renal Carcinoma Chemoimmunotherapy Group. IL-2– in combination with IFN-α and 5-FU versus Tamoxifen in Metastatic Renal Cell Carcinoma: Long-Term Results of a Controlled Randomized Trial.* British Journal of Cancer 2001, 85(8):1130-36.

[3] McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, Kirkwood JM, Gordon MS, Sosman JA, Ernstoff MS, Tretter CPG, Urba WJ, Smith JW, Margolin KA, Mier JW, Gollob JA, Dutcher JP, and Atkins MB. *Randomized Phase III Trial of High-Dose Interleukin-2 Versus Subcutaneous Interleukin-2 and Interferon in Patients With Metastatic Renal Cell Carcinoma.* Journal of Clinical Oncology 2005, 23(1):133-141.

[4] Medical Research Council Renal Cancer Collaborators. Interferon-α and Survival in Metastatic Renal Carcinoma: Early Results of a Randomised Controlled Trial. Lancet 1999, 353:14-17.

[5] Mickisch G H J, Garin A, van Poppel H, de Prijck L, Sylvester R, and members of the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. *Radical Nephrectomy plus Interferon-alfa-based Immunotherapy Compared with Interferon alfa Alone in Metastatic Renal-cell Carcinoma: a Randomised trial.* Lancet 2001, 358:966-70.

[6] Pyrhonen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, Juusela H, Rintala E, Hietanen P, and Kellokumpu-Lehtinen P-L. *Prospective Randomized Trial of Interferon Alfa-2a Plus Vinblastine Versus Vinblastine Alone in Patients With Advanced Renal Cell Cancer.* Journal of Clinical Oncology 1999, 17:2859-67.

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/s/

Ann Farrell
12/14/2005 12:33:02 PM
MEDICAL OFFICER

ADDENDUM TO
CLINICAL REVIEW

Application Type	NDA	Sorafenib
Submission Number	21-923	
Submission Code	000	
Letter Date	July 6, 2005	
Stamp Date	July 8, 2005	
PDUFA Goal Date	January 8, 2006	
Reviewer Name	Robert C. Kane, MD	
Date	December 13, 2005	

Addendum to Medical officer NDA review for Sorafenib - Nexavar
Addenda and clarifications 12/13/05

Since submission of the clinical NDA review to DFS, additional notes and changes are included here.

I. Phase 4 commitments for Nexavar

New text - revised:

1.2.2 Required Phase 4 Commitments

Bayer should continue to follow all patients in study 11213 "A phase 3 randomized study of BAY43-9006 in patients with unresectable and/or metastatic renal cell cancer" for the survival outcome and provide those results to the FDA. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted upon a finding of statistically significant improvement in overall survival or upon the completion of the survival analysis provided there is no finding of an adverse survival effect of sorafenib. The study also should continue to follow all patients to provide further experience regarding duration of exposure for sorafenib safety and tolerance.

Clinical- Required post-marketing commitments:

1) Provide the results of the statistical analyses of overall survival after approximately 270 events and after approximately 540 events as described in the "modified analysis plan for overall survival for study 11213" dated August 18, 2005

2) Provide the complete study report within 6 months of the time that the definitive statistical analysis of overall survival is performed on the following study:
Study 11213: "A phase 3 randomized study of BAY43-9006 in patients with unresectable and/or metastatic renal cell cancer"

1.2.3 Other Phase 4 Requests

A: Hemorrhage has been reported in association with sorafenib, in particular involving the skin, nails, and GI tract. The applicant should perform a study of platelet function [redacted] or similar assay) in patients before and during sorafenib therapy to ascertain if platelet function is impaired by sorafenib.

B: Hypophosphatemia occurs commonly and is an unusual adverse event of anti-neoplastic therapy. The applicant should study further the mechanism of hypophosphatemia. If renal tubular re-absorptive function is altered by sorafenib, other substances in plasma may have altered renal handling as well.

C: Thyroid changes and hypothyroidism were observed in some nonclinical studies of sorafenib and are associated with inhibition of tyrosine kinase activity. Although only 2 sorafenib-treated patients were diagnosed with clinical hypothyroidism in the phase 3 study, this was not prospectively assessed in the study. The sponsor should conduct a prospective study to assess changes in thyroid function in a cohort of sorafenib-treated patients over time.

D. Sorafenib is the first in the class of raf-kinase inhibitors to receive FDA approval. It is also a VEGF-R inhibitor. Bevacizumab, a monoclonal antibody VEGF inhibitor, has been associated with thrombosis, hemorrhage, and surgical wound healing delays. In the controlled studies of sorafenib to date, only a modest number of patients have been at risk for such complications. The applicant should propose and implement a plan: (1) to monitor arterial thrombosis and hemorrhage in a larger population of patients and (2) to monitor wound healing in patients requiring surgical procedures while receiving sorafenib.

Original text:

1.2.2 Required Phase 4 Commitments

Bayer should continue to follow all patients for the survival outcome and provide those results to the FDA. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted upon a finding of statistically significant improvement in overall survival or upon the completion of the survival analysis provided there is no finding of an adverse survival effect of sorafenib. The study also should continue to follow all patients to provide further experience regarding duration of exposure for sorafenib safety and tolerance.

Sorafenib is a new molecular entity, small molecule, and it would be the first in the class of raf-kinase inhibitors to receive FDA approval. It is also a VEGF-R inhibitor. Bevacizumab, a monoclonal antibody VEGF inhibitor, has been associated with thrombosis, hemorrhage, and surgical wound healing delays. In the controlled studies of sorafenib to date, only a modest number of patients have been at risk for such complications. The applicant should propose and implement (with FDA concurrence on the details) a plan: (1) to monitor arterial thrombosis and hemorrhage in a larger population of patients and (2) to monitor wound healing in patients requiring surgical procedures while receiving sorafenib.

1.2.3 Other Phase 4 Requests

Hemorrhage has been reported in association with sorafenib, in particular involving the skin, nails, and GI tract. The applicant should perform a study of platelet function (C J or similar assay) in patients before and during sorafenib therapy to ascertain if platelet function is impaired by sorafenib.

Hypophosphatemia occurs commonly and is an unusual AE of anti-neoplastic therapy. The applicant should study further the mechanism of hypophosphatemia. If renal tubular re-absorptive function is altered by sorafenib, other substances in plasma may have altered renal handling as well.

Thyroid changes and hypothyroidism were observed in some nonclinical studies of sorafenib and are associated with inhibition of tyrosine kinase activity. Although only 2 sorafenib-treated patients were diagnosed with clinical hypothyroidism in the phase 3 study, this was not prospectively assessed in the study. The sponsor should conduct a prospective study to assess changes in thyroid function in a cohort of sorafenib-treated patients over time.

The applicant should inform physicians specifically of the unusual AE findings associated with sorafenib therapy, in particular the expected elevations in lipase, reductions in phosphate, and the elevations in blood pressure which may occur.

Reviewer Comments regarding the post-marketing commitments and text changes:

1.2.2:
Overall survival is a primary study endpoint and is being followed by Bayer. The first interim survival analysis has been completed and submitted. Additional survival information in the form of a (second) pre-specified interim survival analysis is anticipated within the next 2 – 3 months. The text revisions in section 1.2.2 restate the commitment in a more standard format.

1.2.3:
A: As of the safety update, bleeding events were reported in 69 (15.3%) sorafenib patients and 37 (8.2%) placebo patients. The large majority were grade 1 and 2. The most common AE term was hematoma, all Grade 1, which was reported in 19 (4.2%) sorafenib patients and 5 (1.1%) placebo patients. The second most common bleeding event was categorized in CTCAE as "Hemorrhage-other." The 19 cases of "Hemorrhage-other" in the sorafenib group included 9 cases of Grade 1 subungual hemorrhage (8 of the 9 reported in France), 3 cases of hemoptysis (one of which was Grade 2 and two of which were Grade 1), 2 cases of gastrointestinal bleeding (one of which was Grade 1 and one was Grade 2), 1 case each of gum bleeding, hemorrhoidal bleeding, hematuria, and epistaxis, and 1 case of Grade 5 esophageal bleeding associated with progression patients. In addition, there were two other patients in single-agent sorafenib studies with SAEs in the Hemorrhage category: a case of recurrent hemoptysis, ultimately fatal, in a patient with squamous cell NSCLC and a case of Grade 4 hematemesis, which resolved, in a patient with hepatocellular carcinoma. The pattern of hemorrhage, involving skin and mucosal surfaces, is suggestive of a platelet function defect. This can be examined by a lab procedure, the [ ] assay.

B: Hypophosphatemia occurred in 40% of the sorafenib-treated patients compared to 7% of the placebo patients. Changes in renal tubular function would most likely be the cause of this

alteration. Although the applicant did not observe clinical consequences of this finding, more information is needed to understand its pathogenesis.

C: Two sorafenib-treated patients and no placebo-treated patients were diagnosed with hypothyroidism during the trial. In non-clinical studies, hypothyroidism and thyroid gland histopathological changes were observed sufficiently for the pharm-tox reviewer to note this pathology.

D. This commitment to examine thrombosis, hemorrhage, and wound healing related to surgical procedures has been moved to this section to allow additional discussion with the applicant regarding settings in which these concerns may be assessed most efficiently. The applicant may be able to address this commitment through scenarios such as adjuvant or neo-adjuvant use of sorafenib in RCC or in other conditions or in current studies.

Sorafenib is a new molecular entity, small molecule, and it would be the first in the class of raf-kinase inhibitors to receive FDA approval. It is also a VEGF-R inhibitor. Bevacizumab, a monoclonal antibody VEGF inhibitor, has been associated with thrombosis, hemorrhage, and surgical wound healing delays. In the controlled studies of sorafenib to date, only a modest number of patients have been at risk for such complications. The applicant should develop a plan: (1) to monitor arterial thrombosis and hemorrhage in a larger population of patients and (2) to monitor wound healing in patients requiring surgical procedures while receiving sorafenib.

Among the 385 sorafenib-patients, 40 had a procedure during the study, most of which were biopsies or endoscopies. Two had a laparotomy, and one each had a lower lip biopsy, hernia repair, oral surgery, small bowel resection, laminectomy, bone pinning, clavicle repair, and hip fixation. There were no cases of post-operative wound dehiscence or other wound complications. No formal studies of the effect of sorafenib on wound healing have been conducted. Regarding arterial thrombosis, as of the safety update, cardiac ischemia/infarction occurred in 13/451 sorafenib patients versus 2/452 controls. CNS ischemic events were reported in 1 sorafenib patient and 4 controls; arterial thrombosis/embolism was reported in 6 sorafenib patients and 6 controls; and phlebitis was reported in 2 sorafenib patients and no controls. Almost all patients with cardiac events had an antecedent history of risk factors such as coronary artery disease and/or hypertension and/or diabetes; however, the difference in incidence between the sorafenib and the placebo groups is concerning.

II. Other addenda/corrections to the clinical NDA review:

In section 2.2, other FDA approved products for treatment of renal cell carcinoma:

> Medroxyprogesterone acetate injectable suspension (Depo-Provera) also has received FDA approval for "adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic ... renal cell carcinoma in doses of 400 mg to 1000 mg intramuscularly weekly.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Kane
12/14/2005 11:51:59 AM
MEDICAL OFFICER

Ann Farrell
12/14/2005 12:04:18 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA Sorafenib
Submission Number	21-923
Submission Code	000
Letter Date	July 6, 2005
Stamp Date	July 8, 2005
PDUFA Goal Date	January 8, 2006
Reviewer Name	Robert C. Kane, MD
Review Completion Date	December 1, 2005
Established Name	Sorafenib
(Proposed) Trade Name	Nexavar
Therapeutic Class	Anti-neoplastic
Applicant	Bayer
Priority Designation	P
Formulation	Tablet
Dosing Regimen	400 mg twice daily
Indication	Advanced renal cell carcinoma
Intended Population	Adults with unresectable and/or metastatic disease

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Table 1: Abbreviations used in the review

AE	Adverse Event (CTCAE criteria)
BAY43-9006	Sorafenib tosylate, Nexavar™
BID	bis in die – twice daily
CMH	Cochrane Mantel Haenszel Chi square test
CR	Complete response (RECIST criteria)
CSR	Clinical study report
CTCAE	Common Toxicity Criteria, version 3, NCI
DLT	Dose-limiting toxicity
DSMB	Data safety monitoring committee
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intention to treat population (all patients' randomized)
IV	Intravenous
LDH	Lactate dehydrogenase
NCI	National Cancer Institute
NOS	Not otherwise specified
NS	not statistically significant
PD	Pharmacodynamic
PFS	Progression-free survival (a composite of time to progression and death)
PK	Pharmacokinetic
PO	per os, orally
PR	Partial response (RECIST or WHO criteria)
PS	Performance status
RECIST	response evaluation criteria in solid tumors
RCC	Renal cell carcinoma
advanced RCC	Unresectable or metastatic RCC
SAE	Serious adverse event (CTCAE criteria)
TEAE	Treatment-emergent adverse event
TTP	Time to tumor progression
ULN	Upper limit of normal
VEGF	vascular endothelial growth factor
VEGF-R	vascular endothelial growth factor receptor

1 Executive Summary

Advanced renal cell carcinoma (RCC) is a serious and life-threatening malignancy for which there is no systemic therapy currently of general benefit to patients. While interleukin-2 has received FDA approval for this condition and interferon has been used off-label, these agents have considerable toxicity and have not shown convincing evidence for a survival benefit or an improvement in measures of disease progression in controlled studies. No traditional chemotherapy agents have shown clinical benefit in a controlled study.

In this context, Bayer has submitted a single, large, double-blind, randomized, well-controlled phase 3 study in which sorafenib therapy is compared to a control group receiving placebo with best supportive care for patients with advanced RCC. Sorafenib is a new molecular entity that appears to target and inhibit certain cellular proliferative pathways. Patients were not selected on the basis of test results for these pathway biomarkers. Efficacy is based on statistically compelling and clinically convincing evidence of improvement in progression-free survival (PFS) for RCC patients treated with sorafenib (after one prior therapy). The median PFS was improved from 84 days in the placebo control group to 167 days for sorafenib; hazard ratio = 0.44; logrank $p < 0.000001$. Progression was based on a blinded, independent radiologic review of all patients. Safety is demonstrated in the context of this efficacy benefit by the low frequency and/or low severity of adverse effects, dose reductions, and withdrawals for drug-related toxicity. The magnitude and severity of adverse events observed with sorafenib are modest and credible when compared to the placebo arm of the study. Unusual adverse events and toxicities associated with sorafenib therapy include hypertension, hand-foot skin reaction, hypophosphatemia, elevation of serum lipase levels, and a non-cumulative sensory neuropathy.

Following the applicant's report of the PFS improvement, in consultation with the FDA and other regulatory agencies, the study was prematurely terminated and all placebo patients were offered the opportunity to receive sorafenib. The applicant was encouraged to prepare an NDA submission and an expanded access protocol. While the magnitude of PFS improvement in this study is substantial, the clinical benefit conveyed by this PFS improvement is not well defined in renal cell cancer. PFS improvements have been a basis for the regular approval of hormonal therapy for advanced breast cancer as well as for accelerated approval in other disease states. In oncology, PFS is often evaluated in conjunction with response rate for confirmatory evidence of drug effect.

The objective response rate in the study is low (2.1%), as assessed by the usual oncology (RECIST) criterion (30% reduction in the sum of tumor diameters), although lesser degrees of tumor shrinkage did occur for the majority of patients as assessed by the applicant. Tumor shrinkage may not be an appropriate indicator of its effect since sorafenib is proposed to act as a cytostatic agent to reduce tumor proliferation.

Overall survival, a primary study endpoint, is premature at this time to analyze but may be available in the next 3-6 months. The survival results may be able to confirm that a clear clinical benefit is conveyed by the PFS benefit achieved by sorafenib.

1.1 Recommendation on Regulatory Action

I recommend approval of sorafenib under subpart H of 21 CFR 314, accelerated approval, for the applicant's proposed indication, the treatment of patients with advanced renal cell carcinoma (RCC), on the basis of substantial evidence of effectiveness and safety derived from a single, large, adequate and well-controlled, double-blind study comparing sorafenib with placebo for this patient population. Confirmatory evidence is provided by a supportive phase 2 study also submitted for the NDA.

Advanced renal cell carcinoma (including unresectable and metastatic disease) is a serious and life-threatening disease for which there is no standard therapy of general benefit to patients. Effectiveness is demonstrated by statistically compelling and clinically convincing evidence of prolongation in progression-free survival (PFS) for sorafenib treated patients after receiving one prior therapy as well as for a patient group who had not received previous treatment specifically directed toward metastatic disease (the prior therapy occurred pre- or post-operatively). While PFS has been shown to convey clinical benefit in other disease states, this relationship has not been established for advanced RCC. A hazard ratio of 0.44, indicating a relative improvement for PFS of 56%, is substantial and likely to convey clinical benefit. Notably, the response rate is low – 2.1% – when measured using traditional RECIST criteria.

Safety is demonstrated in the context of this therapy by the low frequency and/or low severity of adverse effects, dose reductions, and withdrawals for drug-related toxicity. The applicant examined one fixed dose schedule, 400 mg twice daily by mouth, and found it to be well tolerated by a large majority of the patients. Hand-foot skin reaction, blood pressure elevation, and sensory neuropathy may require interruption of therapy. Temporary dose interruptions occurred in 14% of sorafenib patients, and dose reductions were employed in 10% of sorafenib patients for AEs. The label adequately conveys the clinical information and directions for use.

Bayer should continue to follow all patients for the survival outcome results. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted based on the completion of the survival analysis as pre-specified and provided there is no finding of an adverse survival effect of sorafenib.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Blood pressure should be monitored weekly during the first 6 weeks of treatment with sorafenib to allow detection and management of the 10% of patients who may experience hypertension on sorafenib therapy. This monitoring is described in the label. No unique risk management actions are evident at present.

1.2.2 Required Phase 4 Commitments

Bayer should continue to follow all patients for the survival outcome and provide those results to the FDA. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted upon a finding of statistically significant improvement in overall survival or upon the completion of the survival analysis provided there is no finding of an adverse survival effect of sorafenib. The study also should continue to follow all patients to provide further experience regarding duration of exposure for sorafenib safety and tolerance.

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Thyroid changes and hypothyroidism were observed in some nonclinical studies of sorafenib and are associated with tyrosine kinase inhibitory activity. The sponsor should conduct a prospective study to assess changes in thyroid function in a cohort of sorafenib-treated patients over time. Although only 2 sorafenib-treated patients were diagnosed with clinical hypothyroidism in the phase 3 study, this was not prospectively assessed in the study.

The applicant should inform physicians specifically of the unusual AE findings associated with sorafenib therapy, in particular the expected elevations in lipase, reductions in phosphate, and the elevations in blood pressure which may occur.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Renal cell carcinoma, typically a disease of the 5th through 7th decade, is curable surgically if localized. For metastatic disease, which develops in 40-50% of patients, there is no standard treatment of clinical benefit for most patients.

BAY43-9006, sorafenib, Nexavar™, manufactured by Bayer HealthCare AG, Leverkusen, Germany and to be distributed by Bayer Pharmaceuticals and Onyx Pharmaceuticals, has been studied as a single agent administered orally in one phase 2 study and one phase 3 trial submitted and reviewed for the indication: treatment of patients with advanced renal cell carcinoma (RCC). The phase 2 study comprised 202 patients with advanced RCC, all initially treated with sorafenib for 12 weeks and then entered into a randomized discontinuation design described below (section 10, individual study reports). The phase 3 trial is a randomized, double blind, placebo controlled comparison with sorafenib in a total of 769 patients with advanced (unresectable or metastatic) RCC who had received one prior therapy. Notably, for 133 patients, the prior therapy exposure occurred in a pre-operative and/or an adjuvant setting and not for extant metastatic disease. All treated patients are in the safety population.

1.3.2 Efficacy

In this large, single, multi-national, double-blind, placebo-controlled, well-designed and conducted phase 3 trial, the two treatment groups (sorafenib and placebo) were well balanced for baseline disease and demographic characteristics. Over 90% of patients had stage 4 (metastatic) RCC disease, and all had received one prior therapy. For 17% of patients, the prior therapy occurred before the metastatic disease was documented, thus they could be considered treatment-naïve from the perspective of their metastatic disease. All patients were good performance status with low or intermediate Motzer risk prognosis. The placebo control is appropriate and necessary since there is no alternative therapy of recognized benefit available for RCC patients either first-line or following cytokine therapy. The PFS endpoint is acceptable to encompass the risk of early deaths or discontinuations related to therapy as well as to reflect those patients experiencing some degree of disease control. Survival information will be available later for this study.

Sorafenib therapy resulted in a statistically significant prolongation in the time to progression and progression-free survival endpoints compared to a control group receiving a matching placebo and best supportive care. All patient subgroups appeared to benefit from sorafenib. PFS was doubled from a median of about 3 months on placebo to 6 months with sorafenib, statistically highly persuasive ($p<0.000001$; HR 0.44).

Response, based on RECIST criteria, was documented only in 2.1% of patients. Although a majority of patients had some amount of shrinkage, the amount was smaller than the 30% shrinkage required for declaring an objective response by RECIST criteria. The objective response proportion is notably small but may be related to the proposed "cytostatic" mechanism of sorafenib in contrast to chemotherapy agents perceived as having cytotoxic effects. There are

fewer tumor shrinkages in the placebo group; tumor shrinkage on placebo therapy for RCC has been observed historically also.

The study accrued over 900 patients in 14 months' time, of which 769 were eligible after screening. Patients (who had received one prior therapy) were informed that they would be randomized to receive either an experimental pill or supportive care with a placebo pill. No cross-over to sorafenib was provided in the protocol. The blinding procedure was credible based on the types, frequencies, and severities of AEs reported on the placebo arm.

While the drug mechanism of action is presumed to be mediated by inhibition of molecular targets, evidence for such inhibition or correlation of inhibition with outcomes is not currently available. Patients were not stratified by biomarker status. The applicant has attempted to obtain patient samples and expects to perform a retrospective analysis to explore correlations.

There is no regulatory precedent in RCC to judge the magnitude of the PFS endpoint as a clinical benefit or as likely to predict one (see section 6.1.2). No other drugs have demonstrated an improvement in PFS or a survival improvement in controlled studies of RCC. The magnitude and duration of the improvement in PFS are statistically compelling and clinically convincing as a meaningful benefit that patients would seek if available to them. Interim overall survival results are anticipated in the next 6 months. Early termination of the study may confound the final survival outcome but is clinically appropriate to expedite the availability of this therapy, given the lack of alternatives.

1.3.3 Safety

In the phase 3 study, 384 RCC patients received sorafenib and comprise the principal safety population for analysis. The previous phase 1 experience comprised 197 patients with various tumor types that led to the selection of the subsequent fixed dose schedule of 400 mg orally twice daily. In the phase 2 randomized discontinuation study, 202 RCC patients received sorafenib. In the phase 3 study, 384 patients received sorafenib; the mean duration of therapy is 136 days (SD 13 days) and the range is 5-399 days to the time of data cutoff. Among all studies, 253 patients received sorafenib for at least 6 months and 42 patients received more than 12 months of therapy. The median treatment duration was 9.2 weeks for placebo and 18.0 weeks for sorafenib; thus there was longer exposure of the sorafenib arm. The median daily dose taken in the sorafenib group was 791 mg/day based on pill counts and compliance estimates. In the placebo group, the median number of pills taken per day was 3.9 (4 pills per day equals 100%). Dosing with study drug was reduced or interrupted for toxicity in 25 subjects (6%) in the placebo group and 95 (24%) in the sorafenib group.

AEs tended to appear in the early weeks of therapy; there were no toxicities that appeared to be cumulative or progressive over time. AEs were defined and reported on case report forms in accordance with the standard oncology reporting system, NCI CTCAE version 3, by the site investigators who were blinded to the therapy.
The principal AEs of concern include:

- Dermatologic: reversible skin rashes, most often described as a maculopapular erythematous eruption on the scalp, face, and trunk (34%), and hand-foot skin reaction in 27% are common on sorafenib therapy, probably are related to the kinase-inhibiting activity, and are dose-limiting
- Hypertension: At baseline, 7.5% of both study arms had systolic BP values of 160 mm Hg or greater; medication therapy for increased blood pressure was instituted during study in 14% of sorafenib patients compared to 3% of placebo patients
- Diarrhea: although a common AE (33% with sorafenib versus 10% with placebo), management was usually successful without dose reduction
- Neuropathy: sensory neuropathic changes were reported for 10% of sorafenib patients versus 3.6% on placebo
- Alopecia, pruritis, oral mucositis, and hemorrhage also were observed more frequently on the sorafenib treatment arm

Grade 3 and 4 AEs were unusual; only one occurred at 5% or greater frequency, hand-foot skin reaction.

Notable laboratory findings include asymptomatic hypophosphatemia in 40% of sorafenib patients versus 7% in the placebo arm, elevation of serum lipase in 39% of sorafenib patients versus 24% in the placebo arm, and lymphopenia in 8% of sorafenib patients versus 5% of placebo patients. Grade 4 pancreatitis, defined by CTCAE as "life-threatening," was reported in 2 sorafenib patients although both patients subsequently resumed sorafenib, one at full dose. Sorafenib did not cause important reductions in blood counts or infectious complications when compared to placebo.

The elevated lipase findings are unusual and unexplained. Amylase elevations occurred approximately equally on both study arms. Pancreatic involvement by tumor (assessed primarily by CT scans) was not the explanation where this considered for several patients. In a patient with abdominal pain, making a diagnosis of pancreatitis could be confounded by these "spurious" enzyme elevations; laboratory findings of elevated lipase and/or amylase should at least be considered as possibly occurring independently of a clinical process such as pancreatitis. Of three patients diagnosed as having pancreatitis in the phase 3 study, one, who was described as asymptomatic, likely had only the laboratory findings; this occurred relatively early in the study, before the frequency of these abnormal "pancreatic enzyme" findings were appreciated.

Please see the summary table in section 7.4.3 expressing safety from the perspective of causality.

1.3.4 Dosing Regimen and Administration

Phase 1 studies identified 400 mg BID as a well-tolerated dose; at 600 mg BID, resulting dermatitis and diarrhea were judged as unacceptable toxicities (see section 5). In the combined phase 1 experience, the incidence of grade 3 or greater skin toxicity (hand-foot syndrome and skin reaction) was 3.2% at 400 mg BID and 32% at 600 mg BID dosing. This single, fixed 400 mg BID dose was chosen for all subsequent studies. Dose response explorations are not available

except from the perspective of dose reductions to mitigate toxicity. In phase 3, all patients started therapy with sorafenib, 200 mg tablets, taking 2 tablets each morning and evening (800 mg daily) or identical matching placebo. Dose adjustments specified for toxicity were: first reduction to 400 mg daily (one tablet every 12 hours), second reduction to 400 mg every other day, third level was to discontinue therapy. A reduced dose could be re-escalated following reduction of toxicity to grade 1 or less. Dose reductions were relatively uncommon (20% of patients) and not associated with particular demographic or disease characteristics.

Sorafenib should not be taken with a high-fat meal. Bioavailability is similar with a moderate fat meal or in the fasted state but is reduced by 29% if taken with a high fat meal.

1.3.5 Drug-Drug Interactions

None were observed in this experience. CYP-3A4 inhibitors were not to be given concomitantly in the phase 2 and 3 studies. Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism by CYP3A4 as well as glucuronidation mediated by UGT1A9. In a PK inhibitor study with ketoconazole given 400 mg daily for 7 days prior to sorafenib, inhibition of CYP3A4 did not alter the metabolism of sorafenib.

Sorafenib is an inhibitor of UGT1A1. Sorafenib increases the exposure of irinotecan and its active metabolite, SN-38, which is primarily metabolized via the UGT1A1 pathway. Doxorubicin exposure was increased by 21% in a small study in combination with sorafenib. Its effects on warfarin dosing are not well characterized.

1.3.6 Special Populations

No data are available in pediatric patients. RCC is primarily a disease of older adults. In this study, the median age is 59 years and one-third of patients receiving sorafenib were age 65 or older. There is no evidence for a differential effect of gender or age on the efficacy or safety of the drug. Non-white racial groups were insufficiently represented to assess differences in results of therapy. There appears to be a difference in AUC for Asian patients (see clinical pharmacology review) of uncertain clinical significance.

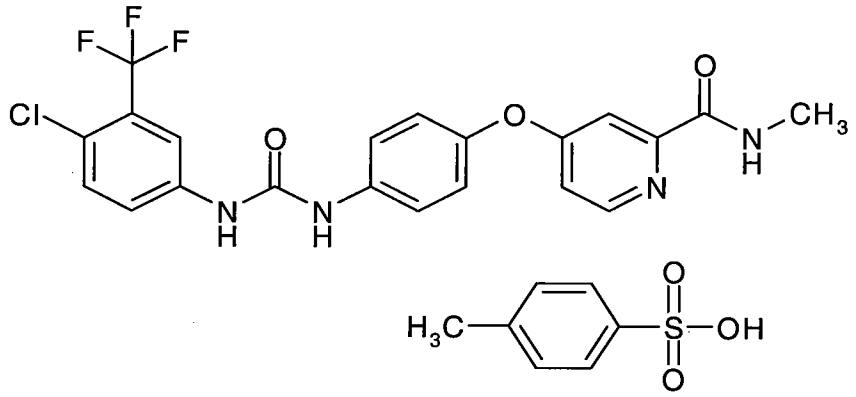
Renal function was reduced in almost all patients (> 90%) by virtue of prior nephrectomy for RCC but did not deteriorate further on sorafenib. Metabolism is principally via hepatic transformations. Patients with severe renal or hepatic impairments were excluded from eligibility and therefore were not evaluated, and the label reflects these precautions. See section 8.3, special populations, for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

BAY 43-9006, sorafenib tosylate, Nexavar™ is a new molecular entity, small molecule anti-neoplastic. The tablet is immediate-release, film-coated, round, and salmon in color containing 200 mg of the free base, BAY 43-9006, and the excipients croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, and magnesium stearate. The filmcoat consists of hydroxypropylmethyl cellulose, polyethylene glycol, titanium dioxide and red iron oxide.

Molecular Formula: C12H16CIF3N4O3 X C7H8O3S
M.W.: BAY 43-9006 tosylate: 637 Daltons; BAY 43-9006 (free base): 465 Daltons .



Sorafenib is a multi-kinase inhibitor with effects on tumor proliferation and angiogenesis. Sorafenib inhibits the activity of targets present inside tumor cells, including members of the Raf family of serine/threonine kinases. In addition, sorafenib inhibits cell surface receptor tyrosine kinases, including Flt-3, kit, Ret, vascular endothelial growth factor receptor-2 (VEGFR-2), vascular endothelial growth factor receptor-3 (VEGFR-3), and platelet-derived growth factor receptor (PDGFR). The *ras* oncogene, through its signaling pathway, is considered an important element in some human cancers. Ras activity leads to activation of Raf kinase, then sequentially the pathway leads via MAP kinase, Erk, to actions of transcription factors in the cell nucleus. Raf kinase activity is inhibited by nanoMolar amounts of sorafenib. Sorafenib also targets angiogenesis through direct inhibition of VEGF-R2 and other receptor tyrosine kinases as well. Sorafenib exposure caused inhibition of renal cell cancer growth in animal models.

The applicant's proposed indication is "Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma."

2.2 Currently Available Treatment for Indications

The only drug with FDA approval for advanced and metastatic RCC is Interleukin-2 (IL-2).

Elements of the IL-2 approval are outlined here:

1. IND filed in 1984
2. BLA filed in 1988
3. Clinical results – 7 phase 2 studies, total 255 pts, most (65%) were PS = 0; median age 52
4. CRs = 9 (3.5%); PRs = 28 (11%); ORR = 15%
5. Median survival for CRs – not reached
6. Median duration of PRs – 20 months
7. Toxic deaths 4%; other AEs: Acute MI – 2%; renal dialysis – 2%
8. Approval in 1992 for a high-dose, IV schedule for selected patients

Only a small minority of patients are candidates for IL-2 therapy due to its considerable toxicity; it is typically infused in an intensive care unit in-patient setting. Of those, 15% showed responses, a few of which have been long-term complete responses to therapy. However, most RCC patients are not benefited or are unable to tolerate IL-2. Attempts to give IL-2 in lower doses or by subcutaneous infusion have not been successful.

Interferon alphas have shown response rates of about 15% in advanced RCC with rare complete or durable responses.[1, 2] Doses have ranged from 5 million units (MU) to 20 MU three times weekly subcutaneously. Responses are usually limited to good performance status patients with low bulk disease in nodal or lung sites. Toxicity for Interferon therapy, as for IL-2, is considerable. While two studies[3,4] have reported survival benefits with interferon therapy of advanced disease, the studies are not definitive and many others have failed to confirm a benefit. Interferon alpha is an approved treatment for advanced RCC in Europe and Canada. Use of the alternative cytokine after failure of the initial one is futile.[5]

An informative Canadian study comparing Interferon gamma (IFNγ) with placebo was reported in 1998.[6] Previous phase 2 data of this drug had shown an average response rate of 11% (range of 0 – 33%). All patients who progressed had the code broken and the option to cross-over to IFNγ. This Phase 3 trial showed a response rate (determined by an independent review committee)) of 4.4% in IFNγ group and 6.6% in placebo group. The complete response rate was 3.3% in IFN group and 3.3% in placebo group. Median TTP for both groups was 2 months. Median survival was 12 months on IFN and 15.7 months on the placebo arm. Notably, 15.7 months was the median survival for the various IL-2 series.

In 2005, the French Immunotherapy Group reported the largest multicenter prospective randomized trial in untreated patients with metastatic RCC comparing 4 regimens: medroxyprogesterone alone (control group), alpha interferon subcutaneous (SC) alone, Interleukin-2 SC alone, and the combination of SC interferon and interleukin-2.[7] Among almost 500 total patients, response rates were 2.5, 4.4, 4.1, and 10.9% respectively. Median overall survival was 15 months and did not differ among the groups (all p values > 0.5). The benefits of cytokine therapy in RCC remain in doubt.

RCC is an component of the von Hippel-Lindau (VHL) syndrome, an autosomal dominant disease occurring in about 1 per 40,000 births. The study of VHL has helped to explain the genetics of RCC. A gene, the VHL gene, which has a key role in regulation of angiogenesis, is inactivated (by mutation or hypermethylation) in VHL patients and in about 70% of sporadic cases of kidney cancer. In von Hippel–Lindau disease, an inactivated copy of the VHL gene is inherited. Later, inactivation of the remaining allele results in the loss of an (HIF) inhibitor and is linked to the development of vascular tumors (haemangioblastomas) in the central nervous system and retina and to the development of RCC. Inactivation of the VHL gene also leads to the overproduction of VEGF protein. VEGF has been identified as a crucial regulator of both normal and pathologic angiogenesis. In sporadic RCC, the source of the VEGF is the cancer itself.

Based on the findings of the role of VEGF in angiogenesis, Bevacizumab was developed as a specific monoclonal antibody inhibitor of the VEGF molecule. This antibody inhibitor in turn prevents VEGF binding with its cell surface receptor and prevents the subsequent downstream signaling. As a single agent therapy for RCC, Bevacizumab showed a low response rate (10%), a significant improvement in TTP, but no overall survival benefit in advanced RCC. [8] AE-941 (Neovastat™), Thalidomide®, CCI-779, bortezomib, and several other putative anti-angiogenic agents are also being studied in RCC.

In summary, there is no standard, established therapy generally applicable for advanced or metastatic RCC. The response rates observed for Interferon and Interleukin have not conveyed clinical benefits to a population of patients, although occasional individual patients have had long disease remissions. No comparative study has confirmed a benefit of combining Interferon alpha with Interleukin-2. No comparative study has found a benefit of combining chemotherapy with Interferon alpha or IL-2. A meta-analysis of 83 chemotherapy trials for the treatment of metastatic RCC between 1983 and 1993 showed a response rate of 6% (1.3% CR and 4.7% PR).[9] Similar findings were reported through the 1990s. No study has shown a benefit of any adjuvant treatment, including radiotherapy. No drugs have shown efficacy following initial cytokine therapy for RCC.

2.3 Availability of Proposed Active Ingredient in the United States

Sorafenib is an investigational drug available through IND and an expanded access treatment protocol for RCC. It is not marketed in any country at this time.

2.4 Important Issues With Pharmacologically Related Products

There are no structurally closely-related products in development. As a class effect, VEGF inhibitors produce hypertension in 10 to 30% of patients. The blood pressure changes do not appear to provide a pharmacodynamic marker for anti-tumor effect.

2.5 Presubmission Regulatory Activity

The initial sorafenib IND 60453 was submitted on May 30, 2000.

An EOP2 meeting on August 6, 2003 reported on the results of the randomized discontinuation design phase 2 study (RDD study) in renal cell carcinoma (RCC), following which the phase 3 RCC study was submitted as a special protocol assessment. Survival and progression-free survival (PFS, with radiographic determination of time to progression or death) were identified as acceptable primary study endpoints.

A single analysis of PFS by logrank test was proposed to be performed when approximately 50% of progression events occurred with the consideration of accelerated approval based on the magnitude and duration of the effect. Regular approval could be considered based on subsequent survival results. Fast track status was granted March 8, 2004 for RCC and rolling review was accepted. Orphan drug designation was granted in September 2004.

Following a report of the substantial difference in PFS findings, FDA discussed with Bayer the possibility of terminating the study so that all patients could be offered sorafenib treatment and submitting their findings for NDA review. A treatment protocol for treatment use (expanded access) under the IND was reviewed by FDA and approved in May 2005.

2.6 Other Relevant Background Information

The Motzer prognostic risk categories are used to classify RCC patients:
Low risk = no risk factors
Intermediate risk = 1 or 2 risk factors
High risk = more than 2 factors
The relevant risk factors are:

- ECOG performance status ≥ 2
- high LDH > 1.5 X ULN
- low serum hemoglobin (< lower limit of normal)
- high corrected serum calcium (> 10 mg/dL)
- absence of prior nephrectomy (i.e., removal of primary was not performed)

A dermatologic condition described variously as "hand-foot skin reaction," hand-foot syndrome, or palmar-plantar dysesthesia occurs with a number of cancer chemotherapy products including fluorouracil or doxorubicin when given by infusion, liposomal doxorubicin, capecitabine, sorafenib, and occasionally with other kinase inhibitors. The pathophysiology is unknown. The symptoms are progressive until therapy is stopped and involve uniquely the palms and soles with pain, dysesthesia, erythema, ulceration and desquamation of the skin in these areas. A grading scale of severity is based on the combination of pain, dysesthesia, and desquamation. Kinase inhibitors commonly also cause maculopapular and/or acneiform rashes in a substantial minority of patients, presumably related to inhibition of molecular targets in skin and apocrine glands.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see the CMC review by Dr. Josephine Jee. The applicant has made some modifications to the manufacturing process and controls which are under CMC review.

3.2 Animal Pharmacology/Toxicology

Acute toxicity studies determined the GI tract and the liver to be target organs/tissues of toxicity. In the repeat-dose toxicology studies, conducted in rats and dogs, clear signs of toxicities were observed in the following organs/tissues: liver, kidneys, hematopoietic system, skin, bone, teeth, reproductive system, GI tract, and pancreas. In addition, hypothyroidism was noted in the chronic dog toxicity study. Adverse cardiovascular effects were not seen in the dog telemetry studies (no relevant changes in the QTc intervals, blood pressure, and heart rate at toxic doses).

Please see the pharm-tox review by Dr H. Saber-Mahloogi. A summary of findings is provided here.

Based on the safety pharmacology studies, sorafenib has the potential to cause cardiac toxicity by blocking the K-channel and the Ca- inward channel, sensory neuropathy, and hypoglycemia.

Acute toxicity studies determined the GI tract and the liver to be target organs/tissues of toxicity. In the repeat-dose toxicology studies, conducted in rats and dogs, clear signs of toxicities were observed in the following organs/tissues:

- Skin: alopecia, pustules, red/blue spots on skin, atrophy/degeneration of hair follicles, acanthosis, dermatitis
- GI: vomiting, liquid feces, red/bloody feces, inflammation, hemorrhage/ necrosis
- Hematopoietic system: depletion/atrophy/cellular necrosis of lymphatic tissues; bone marrow hypocellularity; thymus and spleen atrophy, ↑iron deposition in spleen (possibly due to hemolytic anemia)
- Liver (hepato/hepatobiliary): ↑ALT, AST, GLDH, ALP, GGT; ↑cholesterol, ↓albumin, cirrhotic changes, liver hypertrophy, bile duct proliferation
- Kidneys: hypertrophy; glomerulopathy, tubular dialation, ↑urinary protein, ↑NAG, proteinaceous casts
- ♂ reproductive system: ↑weights of testes/prostate/epididymis; degeneration and tubular dilation of testes; oligospermia
- ♀ reproductive system: retardation of ovaries/ arrested follicular development, necrosis of corpora lutea
- Bone: incomplete epiphyseal closing; thickening of the growth plate (chondrodystrophy), ↑marrow fat (appears to be secondary to hypocellularity)
- Teeth: dentin alteration (in juvenile animals), osteodystrophy of jaw (rats only)
- Adrenal glands: necrosis and hemorrhage

- Thyroid and parathyroid: hypothyroidism (↓T3, ↓T4, ↑TSH), fibrosis of parathyroid, hypophosphatemia
- Pancreas: hypertrophy/ atrophy, degeneration/ regeneration, changes in serum alpha-amylase
- Heart: inflammation/ congestion, ↑CK (no findings in ECG, heart rate, blood pressure)

Although clear adverse cardiovascular effects were not seen in the dog telemetry studies (no relevant changes in the QTc intervals, blood pressure, and heart rate at toxic doses in the 52 week dog toxicology study), there is a potential for cardiovascular toxicity, based on the limited histopathological findings in few toxicology studies, the positive finding in the in vitro hERG and action potential assays, the ↑CK in the chronic dog toxicity study, and the general knowledge on the family of compounds directly or indirectly targeting tyrosine kinase receptors, e.g. VEGF/R and EGF/R inhibitors.

Growth plate suppression, as was seen with sorafenib, is a characteristic of many receptor kinase inhibitors, including VEGFR, PDGFR, and FGFR inhibitors.

Sorafenib was genotoxic in the CHO chromosome aberration test, in the presence of S9. Sorafenib is teratogenic and can cause embryo-fetal toxicities at sub-therapeutic doses.

Sorafenib can cross the blood-brain barrier. In addition, the single dose safety pharmacology revealed the potential for sorafenib to cause sensory neuropathy. Sensory neuropathy (mostly low grade) was observed in the clinical trials conducted with sorafenib.

Mechanism of action:
Sorafenib is a multi-kinase inhibitor. Sorafenib can potently inhibit the following kinases (at nM concentrations):
CRAF, BRAF, V600E BRAF, FLT-3, c-KIT, VEGFR2, VEGFR3, and PDGFR-β

Sorafenib did not inhibit the following kinases at concentrations as high as 10 μM:
MEK-1, ERK-1, EGFR, HER2/neu, c-MET, PKA, PKB, IGFR-1Cdk-1/cyclinB, PIM-1, GSK3-b, CK-2, PKC-α, PKC-β, or PKC-γ.

Drug activity related to proposed indication:
RAS functions downstream of several receptor tyrosine kinases (RTKs), such as vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and platelet-derived growth factor receptor (PDGFR). Once in the active GTP-bound state, Ras interacts with several effector proteins such as Raf and phosphoinositide-3-kinase (PI-3 kinase). Activation of Raf will in turn result in the activation of MAP-kinase-kinase (MAPKK, MEK) and MAPK (ERK). These conserved signaling cascades are involved in cell survival and proliferation.

In several human cancers, the processes of tumor progression and metastasis are initiated by activation of RTKs and the signaling cascades. Therefore, receptor tyrosine kinases and proteins involved in their downstream events have been the target of several anticancer drugs.

The therapeutic target(s) of sorafenib in RCC remains unclear. BRAF mutations are found not to play an important role in renal cell tumors ; however, overall activation of the signaling cascade (RAS/RAF/MEK pathway) has been observed .

Sorafenib was shown to have antitumor activity in several human tumor models, including antitumor activity in RENCA murine renal cell cancer model. Oral doses of 7.5 to 90 mg/kg/day in mice resulted in 30% to 84% tumor growth inhibition.

Sorafenib can cross the placental barrier, is teratogenic at sub-therapeutic doses, and can be excreted in milk. Therefore women of childbearing potential should be advised to avoid becoming pregnant while taking sorafenib. Women should be advised to avoid breast-feeding while taking the drug.

There is a potential for sorafenib to inhibit CYPs 2B6, 2C8, and 2C9 as well as to inhibit glucuronidation by UGT1A1 and UGT1A9. Therefore systemic exposure to substrates of CYP2B6, CYP2C8 , 2B9, UGT1A1 and UGT1A9 may increase when co-administered with sorafenib.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The NDA was submitted electronically but not as an eCTD. Also, a paper copy was submitted in 99 volumes. Clinical study reports for studies 100391 (part A, MRR-00157, randomized discontinuation study, all patients), 100391 (part B, MRR00158, renal cancer patients) and 11213 (MRR-00170, phase 3 trial) were also provided in paper form in 36 volumes. A single phase 2 and a phase 3 study provide the efficacy data for this review.

4.2 Tables of Clinical Studies

Table 2: clinical efficacy studies

Study #	Dates open	Trial Design; Indication; Objective; Primary Endpoint	Treatment/ Dosed	RCC [a] Patients Entered n	Mean Age (Range) in Years	% M/Fe % B/W/O [d]
11213	23Nov 2003 - 28 Jan 2005	Randomized, blinded, placebo-controlled, metastatic RCC; safety and efficacy; survival	Sorafenib 400 mg bid [c]	384	59.0 (19-86)	69.5/30.2 0.5/71.9/27.6
			Placebo	385	58.3 (29-84)	74.5/25.5 0.3/72.2/27.5

10039 [b] US,UK	10 Oct 2002 - 28 Sept 2004	12-week induction followed by a 12-week randomized, placebo-controlled period for stable patients; solid tumors; safety and efficacy; progression free rate at 24 weeks	Open-label Sorafenib 400 mg bid	202	57.8 (23 -83)	74/26 5/90/5
			Randomized Sorafenib 400 mg bid	32	58.4 (32 - 76)	81/19 3/91/6
			Randomized placebo	33	56.7 (23 - 74)	64/36 9/88/3

Applicant's table 6-1, Module 2, section 2.7.3
a RCC = Renal Cell Carcinoma.
b Data provided for Study 100391 applies to RCC patients only.
c mg = milligram, bid = bis in die (twice a day).
d M/F = Male/Female; B/W/O = Black/White/Other.

Table 3: Phase 1 studies of sorafenib - single agent

Study #	Country	Tumor Type	# Patients Valid for Safety
10164	Belgium	Advanced, refractory solid tumors	42
10658	Japan	Advanced, refractory solid tumors	18
100277	Canada	Advanced, refractory solid tumors	39
100283	Germany	Advanced, refractory solid tumors	65
100313	US	Advanced, refractory solid tumors	6
100342	US	Advanced, refractory solid tumors	18
10922	Belgium, Canada, Germany, US	Advanced, refractory solid tumors	9

Sponsor's table 1-1, module 2.5, page 11

4.3 Review Strategy

The single phase 2 and phase 3 studies of Nexavar treatment of RCC submitted for the NDA were the information sources for this review. Phase 1 studies (197 patients) were reviewed in summary form for dose-limiting toxicities and safety. Two major strengths of the phase 3 trial

are the double-blind placebo control and the independent blinded radiological review of tumor response and progression. The clinical and statistical reviewers together verified that the two study groups were balanced for eligibility and prognostic factors. Dropouts, early deaths, narratives, and selected AEs were examined for toxicity issues and adequacy of the safety assessments. Radiologic audit was not planned because of the blinded, independent review performed by the applicant.

4.4 Data Quality and Integrity

DSI audits have been requested for the largest enrolling sites that are in France, Poland, and two U.S. sites. Also audits are planned for the sponsor, Bayer, and the CRO, — Preliminary findings are favorable. If the European sites are audited, the results are not anticipated in time for the PDUFA deadline.

4.5 Compliance with Good Clinical Practices

The applicant affirmed that all clinical work conducted in this study was conducted according to standards under the guiding principals detailed in the Declaration of Helsinki. The study was also carried out in keeping with applicable local law(s) and regulation(s). The informed consent was provided to and judged as satisfactory by FDA. The study protocol and the 6 amendments were reviewed by the appropriate Independent Ethics Committees /Institutional Review Boards. Consent form approval and written consent for each patient was required of any site before any patient enrollment.

4.6 Financial Disclosures

The applicant provided a detailed financial disclosure for the site investigators. In only one instance was sponsor financial support in excess of $50,000. This investigator, [ ] [ ] for the [ ] study. However, this [ ] study is only supportive of the [ ] findings and not the primary basis for the NDA. It is unlikely that the integrity of the submission is compromised.

5 CLINICAL PHARMACOLOGY

Following the phase 1 studies, a fixed dose of 400 mg PO BID was selected for phase 2 and subsequent development. Twice daily dosing showed better exposure and preclinical data showed more activity with more frequent dosing. Doses ≥ 600 mg BID caused an increase in SAEs, discontinuations for AEs, especially skin toxicities and diarrhea. The increased frequencies of grade 3 and 4 AEs were judged unacceptable by the applicant.

5.1 Pharmacokinetics

Sorafenib is formulated as the tosylate salt. Following oral administration of a 400 mg single

dose to healthy volunteers, the absorption showed a median Tmax of 4 to 8 hours with a mean Cmax of 1.67 to 2.13 mg/L. Following multiple doses, mean C max was 7.7 mg/L. Twice daily dosing did increase the AUC by 57%. Moderate to high interpatient variability in exposure was observed (37 – 75%). Plasma half-life is long, ranging from 24 to 48 hours. Sorafenib is 99.5% protein bound. AUC values at 600 mg BID were 13% higher than the 400 mg BID dose, and the AUC at 800 mg BID was the same as the 600 mg value. Steady state is reached after about 7 days of dosing, and on average the repeated dose C max and AUC are 4 times higher than the single dose levels. Oral bioavailability is about 67%. Approximately 20% of an administered oral radioactive dose is excreted in urine and 76% in feces. AUC and Cmax decreased by 29% and 38%, respectively, when BAY 43-9006 was administered with a high-fat breakfast. Metabolism is via CYP3A4 via demethylation and hydroxylation. There is also glucuronidation through UGT1A9. However, ketoconazole, a potent CYP3A inhibitor, did not substantially change the AUC, C max, or T1/2 of sorafenib. Thus, sorafenib may be safely co-administered with other inhibitors or substrates of CYP3A4. Drugs such as rifampin, St. John's wort, phenytoin, carbamazepine, or phenobarbital, that induce CYP450 3A4 activity may enhance the metabolism of sorafenib and decrease its serum concentrations.

In vitro metabolic inhibition studies indicate that sorafenib inhibits CYP 2B6 (Ki=6.2 μM), 2C8 (Ki =2.4 μM), 2C9 (Ki =7.3 μM), 2C19 (Ki =17 μM), 2D6 (Ki =4.2 μM), and 3A4 (Ki =4.9 μM). In vitro studies with human hepatocytes indicate that sorafenib does not induce CYP 2C9, 2C19, and 3A activity; it slightly induced CYP1A activity.

5.2 Pharmacodynamics

In vitro, sorafenib is an inhibitor of: wild type and mutant B-raf kinase and C-raf kinase in the nM range; c-kit, VEGFR2, PDGFR-β, and flt-3 inhibition occurs at μM doses. The inhibition occurs at the ATP binding site of the (serine-threonine or tyrosine) kinase activity. The Raf kinase pathway has been reported to be "activated" in 50% of a sample of renal cancer biopsies, and the VEGF pathway is implicated in tumor growth in animal models. Thus inhibition of one or both pathways may provide tumor control or shrinkage in RCC. It is unclear whether the potential therapeutic effects of sorafenib may be related to mutant kinases, "overactive" or "overexpressed" enzyme activities. There is no clinically validated assay available for general clinical use for the putative targets of sorafenib.

5.3 Exposure-Response Relationships

Bayer chose a single, fixed-dose level of 400 mg BID based on the phase 1 results for toxicities (in particular, the frequency and severity of hand-foot syndrome and diarrhea). No dose-ranging findings are available. The duration of drug exposure is predicated on the duration of clinically stable or responding disease states.

For further details, please see the review by Dr. Gene Williams.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

As proposed: Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma.

The indication sought does not describe any requirement for prior therapy; this expands on the study protocol design in which the enrolled patients were to have received one and only one prior therapy. This request is supported by the patients (17%) in the phase 3 trial in whom the prior therapy was distinct from the protocol therapy for metastatic disease and was employed in a pre-operative or immediate post-operative adjuvant intent according to the investigator. Results for this subgroup were similar to the overall results.

6.1.1 Methods

A single phase 2 and a single phase 3 study of Nexavar treatment of RCC were submitted and reviewed for the NDA. Phase 1 studies were reviewed in summary form for dose-limiting toxicities and safety. The phase 3 trial is the primary data source for this review. The clinical and statistical reviewers together verified that the two study groups were balanced for eligibility and prognostic factors. Dropouts, early deaths, and narratives were examined for toxicity issues.

6.1.2 General Discussion of Endpoints

For the phase 3 study, overall survival (OS) is the pre-specified primary endpoint. However, OS has not been analyzed as yet as the data is immature. PFS was chosen as a formal additional primary endpoint (with alpha allocation of 0.01, analysis to occur upon reaching 363 events) in agreement with FDA during special protocol assessment to reflect the effect of this specific treatment, to examine the ability of a putative cytostatic agent to delay disease progression, and because progression is typically associated with physical and psychological distress of disease advancement. As noted above, there is no regulatory history of approvals for renal cell carcinoma except for the IL-2 approval in 1992 based on single-arm phase 2 results of occasional CRs of long duration (years).

The relationship between PFS improvement and OS is uncertain in RCC; by analogy to other cancer states, the predictive value of PFS likely will depend on the magnitude and duration of a PFS improvement. In studies of RCC that have examined survival outcomes, response rate has not been found to be predictive of survival benefit, most likely because the rates have been low and of modest duration. In contrast, there is some evidence linking PFS improvement to a survival improvement. For example, in the Medical Research Council and the Pyrhonen studies cited above, improvements of 1-2 months in PFS were associated with survival improvements of 2.5 to 7.5 months. Other studies however, have not supported the association. The relation of PFS to survival should be considered as uncertain. Of note, the European Union Committee for

Human Medicinal Products (CHMP) issued an oncology draft guidance in March 2005 noting that superiority in PFS may be acceptable for a drug approval prior to mature OS findings.

In the Clinical Overview section (M2.5; section 1.4.3, page 17) of the NDA submission, the applicant also discusses the justification for the PFS endpoint.

"The Cochrane Collaboration recently conducted a meta-analysis and systematic review of the advanced renal cell cancer literature. An important conclusion of this review was that there was no correlation observed between remission rate, defined as complete or partial response, and median survival or one-year survival. Two parallel randomized studies of the effect of initial nephrectomy prior to planned interferon-alpha for metastatic renal cancer observed significantly improved survival despite a low and unimproved response rate. (23, 24) Given these data, it is clear that response rate is not a predictor of overall survival and therefore is not a useful surrogate for predicting survival benefit in advanced RCC.(25) A review of the literature in advanced renal cell cancer revealed that a limited number of randomized studies reported PFS and overall survival (OS). Table 1-5 lists studies with positive overall survival and the corresponding reported PFS information. "

Table 4: Randomized Trials in Advanced RCC Reporting Both Overall Survival and Progression-Free Survival

Author(s)	Regimens	No. Pts.	Med. PFS (mo)		Med. OS (mo)	
Atzpodien et al(26)[10]	IFNα/VBL	63	5.0	p=0.0248	16.0	p=0.0227
	IL-2/IFNα/5-FU	132	6.0		25.0	
	IL-2/IFNα/CRA/5-FU	146	7.0		27.0	
Atzpodien et al(27)[11]	IL-2/IFNα/5-FU	41	7	NA	24	p=0.032
	Tamoxifen	37	6		13	
McDermott et al(28)[12]	HD IL-2	95	3.1	p=0.018	17.0	p=0.211
	IL-2/IFNα	91	3.1		13.0	
Mickisch et al(24)[13]	IFNα	43	3.0	p=0.04	7.0	p=0.03
	Nephectomy /IFNα	42	5.0		17.0	
MRCC Study(29)[3]	IFNα	174	4	p=0.009	8.5	p=0.017
	Megace	176	3		6	
Pyrhonen et al(30)[4]	IFNα Plus VBL	79	3.0	p=0.001	15.7	p=0.0049
	VBL	81	2.1		8.2	

RCC = renal cell carcinoma; PFS = progression-free survival; OS = overall survival; IL-2 = interleukin-2; HD = high dose; IFNα = interferon-α; VBL = vinblastine; 5-FU = 5-flurorouracil; mo = month; CRA = cis-retinoic acid.

Applicant's table 1-5, M2.5, section 1.4.3, page 17, submitted 7/6/05

"In contrast to response rate, available positive OS studies indicate that PFS can be considered a reasonable surrogate for overall survival.

In the FDA April 2005 draft guidance for industry on clinical trial endpoints for the approval of cancer drugs and biologics, it is stated that PFS prolongation might be an accepted surrogate endpoint for clinical benefit to support full approval. Important considerations include the magnitude of the effect, the toxicity

profile of the treatment and the clinical benefits and toxicities of available therapies. For the assessment of PFS, randomized blinded studies with a blinded review are recommended."

Reviewer comment: While the applicant offers these study results as supportive of the clinical meaning of a PFS benefit, the evidence is not consistent or compelling. When response rates or time to progression effects are modest, it can be difficult to affect survival endpoints.

For the phase 2 supportive study submitted, the endpoints of interest are the response rate (variously defined by WHO or RECIST or other criteria) and the time to progression of patients during the randomized discontinuation portion who are receiving sorafenib versus those receiving placebo.

6.1.3 Study Design

Study 11213 is a phase III, double-blind, randomized, parallel-group, multicenter study comparing sorafenib plus best supportive care (BSC) to placebo plus BSC in subjects with advanced RCC who received 1 prior regimen of chemotherapy or immunotherapy. Subjects were randomized (1:1) using a blinded computer generated central list, stratified by Motzer category and country to receive sorafenib (400 mg twice daily, total daily dose 800 mg) or placebo in an uninterrupted daily schedule. No subsequent crossover to sorafenib upon progression was provided in the protocol; all patients were to be followed for survival.

Inclusion criteria:
- Signed informed consent
- Men or women and ≥ 18 years of age
- Life expectancy of ≥ 12 weeks
- Documented unresectable and/or metastatic measurable RCC, histologically or cytologically documented (subjects with rare subtypes of RCC, such as pure papillary cell tumor, mixed tumor containing predominantly sarcomatoid cells, Bellini carcinoma, medullary carcinoma, or chromophobe oncocytic tumors, were excluded from study participation)
- No more than 1 prior systemic therapy for advanced disease, during or after which the subject experienced disease progression (prior treatment must have been completed at least 30 days but no more than 8 months prior to randomization); a single chemotherapy agent/regimen, a single immunotherapy agent/regimen, or a single investigational treatment agent/regimen were allowable prior therapies; megestrol acetate or medroxyprogesterone, used as a single agent in first-line treatment, constituted 1 prior systemic therapy (clarified in Amendments 2 and 5)
- At least 1 unidimensional measurable lesion by computed tomography (CT) scan or magnetic resonance imaging (MRI) according to the Response Evaluation Criteria in Solid Tumors (RECIST)
- Risk rated "intermediate" or "low" according to the Motzer score
- Performance status of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale
- Adequate baseline organ function including amylase and lipase each < 1.5 x ULN

Exclusion criteria:
• Completion of prior systemic treatment less than 30 days or more than 8 months before randomization
• Cardiac arrhythmias requiring an anti-arrhythmic (excluding beta-blockers or digoxin), symptomatic coronary artery disease or ischemia (myocardial infarction within the last 6 months), or congestive heart failure > New York Heart Association (NYHA) Class II
• Active clinically serious bacterial or fungal infections (≥ Grade 2 Common Terminology Criteria for Adverse Events [CTCAE], Version 3, provided by the National Cancer Institute
• Known history of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C
• Known history or presence of metastatic brain or meningeal tumors (head CT or MRI at screening to confirm; per Amendments 1 and 2)
• Seizure disorder requiring medications such as anti-epileptics
• History of organ allograft
• Substance abuse or medical, psychological, or social conditions that could have interfered with the subject's participation in the study or with the evaluation of the results
• Risk level "High" according to the Motzer criteria
• Known or suspected allergy to the investigational agent or any agent given in association with this trial
• Any condition that is unstable or that could jeopardize the safety of the subject and his/her compliance in the study
• Pregnant or breastfeeding; a negative pregnancy test (within 7 days before starting study drug) was required for women of childbearing potential; men and women enrolled in this trial were required to use adequate birth control

Reviewer comments: The study design: large, prospective, randomized, stratified, double-blind and placebo-controlled, multicenter and multinational, using an intent-to-treat analysis, represents the strongest form of an "adequate and well-controlled study." The eligibility criteria are appropriate. An independent radiologic review process is assessing the PFS endpoint. The sponsor has excluded patients with high risk Motzer category, those with brain involvement, and those with poor performance status due to the expected early poor outcome for such patients.

6.1.4 Efficacy Findings

DEMOGRAPHICS:
Of 976 evaluated, 164 were not randomized for screening failure (ineligible) and 43 were still in screening at the time of data cutoff for a total of 207 patients. A total of 769 patients were randomized, 385 to placebo and 384 to sorafenib. The largest country enrollment was from France (186 patients), and 146 patients were from U.S. sites. One patient did not receive study drug and thus was not included in the safety population.

Table 5: Demographic baseline characteristics

Characteristic	Placebo		Sorafenib	
	N = 385		N = 384	
	n	(%)	n	(%)
Sex				
Male	287	(74.5)	267	(69.5)
Female	98	(25.5)	116	(30.2)
Missing	0	(0.0)	1	(0.3)
Race				
White	278	(72.2)	276	(71.9)
Black	1	(0.3)	2	(0.5)
Asian	6	(1.6)	1	(0.3)
Hispanic	3	(0.8)	7	(1.8)
Other	0	(0)	1	(0.3)
Missing [a]	97	(25.2)	97	(25.3)
Age (years)				
Mean (range)	58.3	(29-84)	59.0	(19-86)
Median	59		58	
Age group				
< 65	280	(72.7)	255	(66.4)
≥65	103	(26.8)	127	(33.1)
Missing	2	(0.5)	2	(0.5)

sponsor table 11-1, CSR page 59

a: Race was not collected from the 186 subjects enrolled in France due to local regulations. In 8 other subjects, race was not available at the time of analysis.

Table 6: Disease baseline characteristics

Characteristic	Placebo N = 385		Sorafenib N = 384	
	n	(%)	n	(%)
ECOG Performance Status				
0	180	(46.8)	184	(47.9)
1	201	(52.2)	191	(49.7)
2	1	(0.3)	6	(1.6)
Missing	3	(0.8)	3	(0.8)
Motzer risk factors				
Low	194	(50.4)	200	(52.1)
Intermediate	191	(49.6)	184	(47.9)
RCC subtype				
Clear cell	380	(98.7)	377	(98.2)
Papillary subtype	3	(0.8)	1	(0.3)
Other variant	1	(0.3)	1	(0.3)
Missing	1	(0.3)	5	(1.3)
Duration of disease (years)				
Mean (range)	3.3	(0.1-19.9)	2.8	(0.1-19.4)
Median	1.9		1.6	
Duration of metastatic disease (years)				
Mean (range)	1.3	(0-10.2)	1.3	(0.1-11.4)
Median	0.9		0.9	

sponsor's table 11-2, CSR page 60

Reviewer comments: There is excellent balance for baseline demographic and disease characteristics except for the 5% greater proportion of females in the sorafenib arm (These baseline characteristics were audited with the statistical reviewer and with JMP for confirmation.) There is minimal missing data (< 5%). Prognostic factors and risk groups were evenly distributed. Disease progression pre-study was documented in 92%; at study entry, 96% had metastatic disease (stage 4) in both arms. Over 70% of all patients were white. Race was not available for 25% of patients due to French regulations.

Table 7: Prior therapy for RCC before protocol entry

Characteristic	Placebo N = 385		Sorafenib N = 384	
	n	(%)	n	(%)
Type of therapy				
Nephrectomy	362	(94.0)	356	(92.7)
Systemic anticancer therapy	382	(99.2)	381	(99.2)
Radiation therapy	90	(23.4)	108	(28.1)
Type of systemic anticancer therapy				
Interferon	264	(68.6)	260	(67.7)
Interleukin (IL-2)	170	(44.2)	168	(43.8)
Pyrimidine analogues	72	(18.7)	60	(15.6)
Vinca alkaloids	49	(12.7)	44	(11.5)
Progesterone agents	25	(6.5)	25	(6.5)
Investigational drugs	23	(6.0)	12	(3.1)
Intent of systemic anticancer therapy [a]				
Palliative therapy	304	(79.0)	315	(82.0)
Adjuvant therapy	80	(20.7)	65	(16.9)
Neoadjuvant therapy	5	(1.3)	2	(0.5)
Intent not reported	9	(2.3)	11	(2.9)
No palliative therapy [b]	73	(19.0)	60	(15.6)
Intent of cytokine therapy				
IL-2 and/or interferon, any intent	313	(81.3)	319	(83.1)
Palliative IL-2 and/or interferon	247	(64.2)	258	(67.2)
Adjuvant IL-2 and/or interferon	66	(17.1)	58	(15.1)
Neoadjuvant IL-2 and/or interferon	3	(0.8)	2	(0.5)
Intent not reported	8	(2.1)	8	(2.1)

sponsor's table 11-3 CSR page 62
a: Subjects may have had more than 1 type of therapy
b: Subjects had adjuvant and/or neoadjuvant therapy only, and no therapy with palliative intent

Reviewer comments: Almost all patients had an antecedent nephrectomy. Systemic therapy was given to 99% of patients and closely balanced between groups both for type of therapy and intent of the prior therapy.

PROTOCOL DEVIATIONS:
177 subjects (23%) had at least 1 protocol deviation. Overall, 88 subjects with deviations were randomized to sorafenib and 89 were randomized to placebo. The most common deviations were related to inclusion and exclusion criteria (149), especially receipt of more than one prior therapy; the use of local laboratories instead of the designated central laboratory (37); and the continuation of double-blind treatment after disease progression (36). The distribution was very similar for both study arms; an analysis excluding these patients did not alter the efficacy results.

EFFICACY RESULTS:

PROGRESSION-FREE SURVIVAL:
PFS was defined as the time from randomization to progression or death from any cause, which ever occurred earlier, using the ITT population and two-sided logrank test stratified by Motzer prognostic risk category and country. For the analysis of PFS, progression was determined by an independent blinded radiological review of scans performed according to a pre-specified radiological charter [redacted]. Clinical assessments by investigators (blinded to the therapy) were used to determine clinical progression of disease only in those cases where radiologic progression could not be documented. PFS was measured from the date of randomization until the date of radiological or clinical tumor progression, or death, whichever occurred earlier. Data from the independent radiological review of scans were the primary data for determining radiological progression. Clinical progressions based on investigator assessment (as collected in the CRFs) were included in the calculation of PFS unless radiological progression based on independent radiological review was documented on or before the date of the clinical progression.

Table 8: PFS events

Progressions	placebo		sorafenib		Total	
	n	%	n	%	n	%
Radiologic	164	42.6	117	30.5	281	36.5
Clinical	8	2.1	7	1.8	15	2.0
Death	23	6.0	23	6.0	46	6.0
Censored	190	49.4	237	61.7	427	55.5

sponsor's table 14.2/2, CSR page 242

Reviewer comments: A total of 342 progressions/deaths occurred. The number of deaths on each arm was the same. Clinical (investigator determined) progressions were unusual in frequency, were blinded, and did not alter the results based on radiologic findings exclusively. Missing scan data was minimal and balanced on both arms. 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 arms. Deaths comprised 6% of events in each study arm.

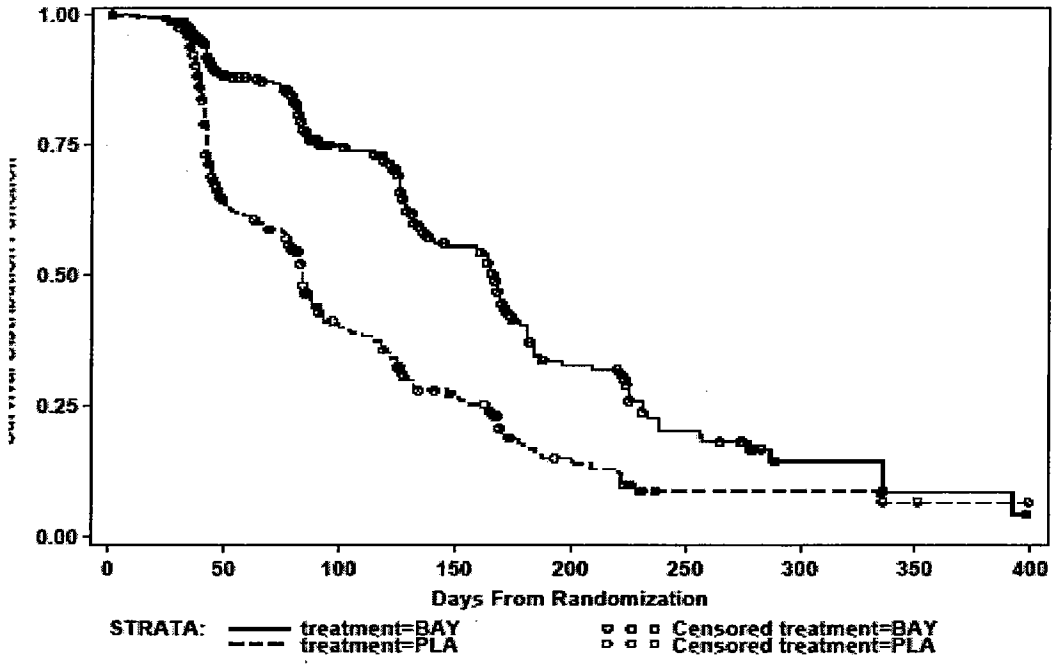
Table 9: PFS results

		Placebo	sorafenib
		N = 385	N = 384
Total failed	(n = 342)	195 (50.6%)	147 (38.3%)
Total censored	(n = 427)	190 (49.4%)	237 (61.7%)
Median PFS (days)		84	167
95% CI for median		(78, 91)	(139, 174)
Logrank p		p < 0.000001	
Hazard ratio (sorafenib/placebo)		0.44	
95% CI for hazard ratio		(0.35, 0.55)	

Reviewer's table, adapted from sponsor's table 11-4, CSR page 64

Reviewer comments: The PFS analysis was conducted as pre-specified based on 342 progressions and the pre-specified alpha of 0.01, two-sided. The median PFS was 84 days in the placebo arm and 167 days in the sorafenib arm. With 342 total events, the logrank p value is <0.000001 and the HR = 0.44. Scheduled tumor assessments were at 6 week intervals for the first 6 months then every 8 weeks. The median time from randomization to first follow-up scan was 41 days for placebo and 42 days for sorafenib groups; for the second scan the median times were 84 days for both arms. Variation in the timing of scheduled assessments occurred in less than 10% of visits and was balanced in the two groups.

Figure 1: Kaplan-Meier curves for PFS, ITT population



sponsor's figure 14.2/1, CSR page 315

TIME TO PROGRESSION:

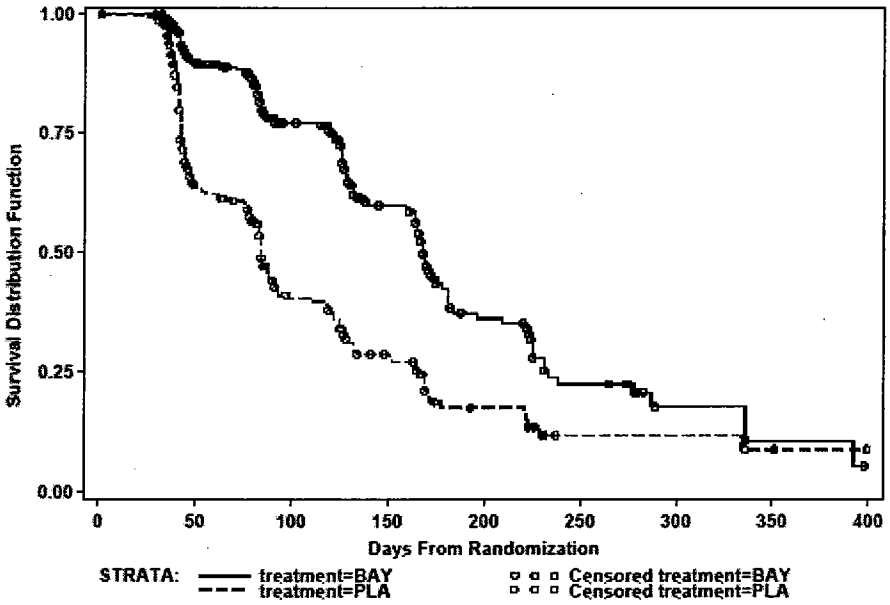
Time to progression (TTP) was defined as the time from randomization to progression or last observation at which the subject was known not to have progressed (censored). The median time to disease progression as per independent radiological review was 84 days for placebo subjects and 168 days for sorafenib subjects ($p < 0.000001$). The estimated hazard ratio (sorafenib over placebo) was 0.40, representing a 60% reduction of risk of progression in subjects treated with compared with placebo.

Table 10: Time to progression for the ITT population

	Sorafenib	**Placebo**
	N = 384	**N = 385**
Total failed	124	172
Total censored	260	213
Time to progression in days Median (95% CI)	168 (164, 181)	84 (81, 91)
Logrank p	p < 0.000001	
Hazard ratio (sorafenib/placebo)	0.40	
95% CI for hazard ratio	(0.31, 0.52)	

Reviewer's table, adapted from applicant's table 11-7, CSR page 68

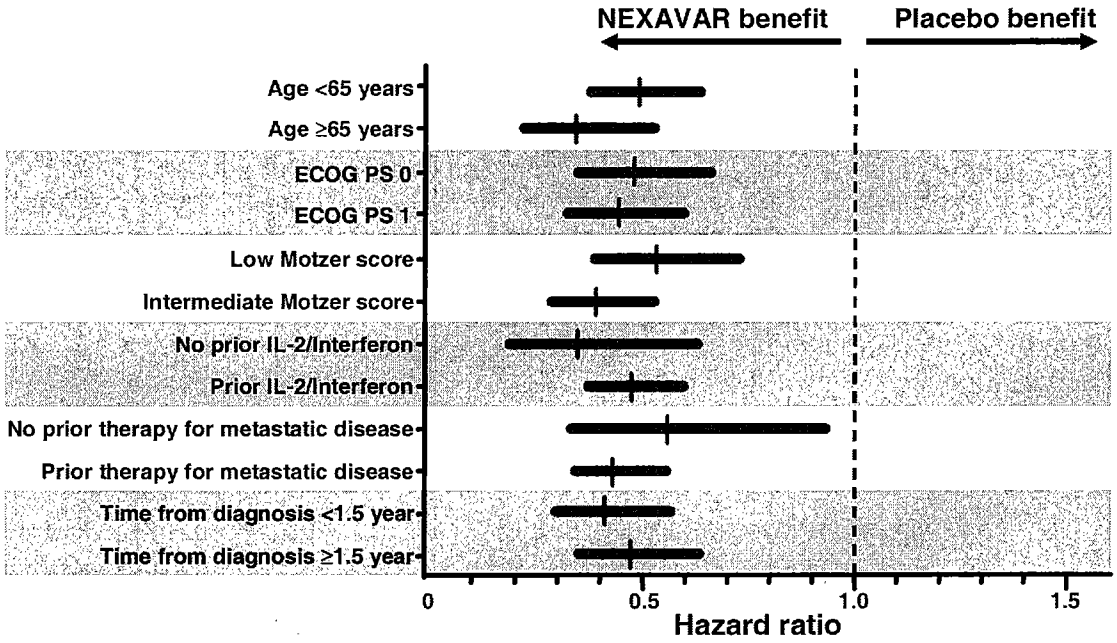
Figure 2: Kaplan-Meier curves for time to progression (TTP), ITT population



sponsor's figure 14.2/2 CSR page 316

Subgroup analyses:
The applicant provided an analysis of PFS based on independent radiological review by demographic, baseline, and prognostic characteristics examined by univariate analysis.

Figure 3: Progression-Free Survival in Patient Subgroups (Hazard Ratio and 95% CI for sorafenib: Placebo



Sponsor's figure 2 from the Nexavar label

The hazard ratio was well below 1 and consistent for all subgroups except for the small group of patients (n=26) who were stage 3 at entry (not shown above). Analyses by sex and age showed a consistent benefit for sorafenib over placebo. Median PFS in the sorafenib group was similar in men and women (166 days and 169 days, respectively versus 84 days for placebo), and the hazard ratio showed a consistent benefit (0.45) for sorafenib in both sexes. Similarly, the benefit of sorafenib was consistent in younger (< 65 years) and older (≥65 years) patients. There were 230 subjects 65 years and older; median PFS in these subjects treated with sorafenib was 181 days, with a hazard ratio of 0.34 (95% CI 0.22, 0.52). In subjects younger than 65 years the HR was 0.49.

For the prognostic subgroups, both by Motzer score (low versus intermediate) and ECOG PS (0 versus 1), sorafenib showed hazard ratios below 0.50 for all categories. Median PFS was longer (171 days) in the low risk patients than in subjects with intermediate score (147 days). In subjects with low Motzer risk score, the hazard ratio of sorafenib over placebo was 0.53 (95% CI: 0.39, 0.73). In subjects with intermediate Motzer score, the hazard ratio was 0.39 (95% CI: 0.29, 0.53).

For subgroups defined by type and intent of prior therapy, the hazard ratio for the 133 subjects who received prior therapy at a separate, earlier time from study entry for metastatic disease therapy (i.e., subjects who had received no therapy other than neoadjuvant or adjuvant regimens) was 0.56 (95% CI: 0.33, 0.93). The benefit of sorafenib was consistent among subjects who had received prior adjuvant or palliative therapy for RCC. In the 632 subjects who had received prior regimens containing interferon and/or IL-2, the median PFS was 164 days for sorafenib treated subjects and 84 days for placebo treated subjects, with a hazard ratio of 0.47 of sorafenib over placebo (95% CI: 0.37, 0.60). In addition, the improvement in PFS with sorafenib was consistent across subgroups categorized by time since diagnosis of RCC and duration of metastatic disease. Also, the hazard ratio was 0.35 for the subgroup of patients who had no prior IL-2 or Interferon (137/769 patients, median 85 days for placebo versus 172 days on sorafenib).

The hazard ratio for PFS for each of the top 3 enrolling countries (France, U.S., and Poland, each with number of subjects randomized greater than 100) was also consistent with the overall result.

Table 11: Hazard Ratio for the top 3 enrolling countries

Country	N	events	censored	HR
France	186	114	72	0.47
United States	146	64	82	0.39
Poland	117	49	68	0.59

Reviewer table

The applicant also provided an exploratory comparison of the effect of prior therapy on the PFS endpoint for several variables as noted in the table below.

# Prior chemo	N	Median PFS/Sorafenib (days)	Median PFS/placebo (days)	HR
IL-2/Interferon	632	164	84	0.47
No IL-2/Interferon	137	172	85	0.35
Prior therapy for metastatic disease	636	169	84	0.43
No prior therapy for metastatic disease	133	132	78	0.56

sponsor's table, submitted to the edr September 20, 2005

Reviewer comments: All of the subgroup findings are robust and consistent with the overall study results. The type or intent of prior therapy did not appear to alter the PFS results.

RESPONSE RATE:
Among the 769 patients randomized, 97 had not yet completed the first 6 weeks on study to be available for response assessment, leaving 672 (337-placebo and 335-sorafenib) for response analysis.

The responses were determined by independent radiology review using RECIST criteria.

Table 12: Response by RECIST criteria for the response population (N =672)

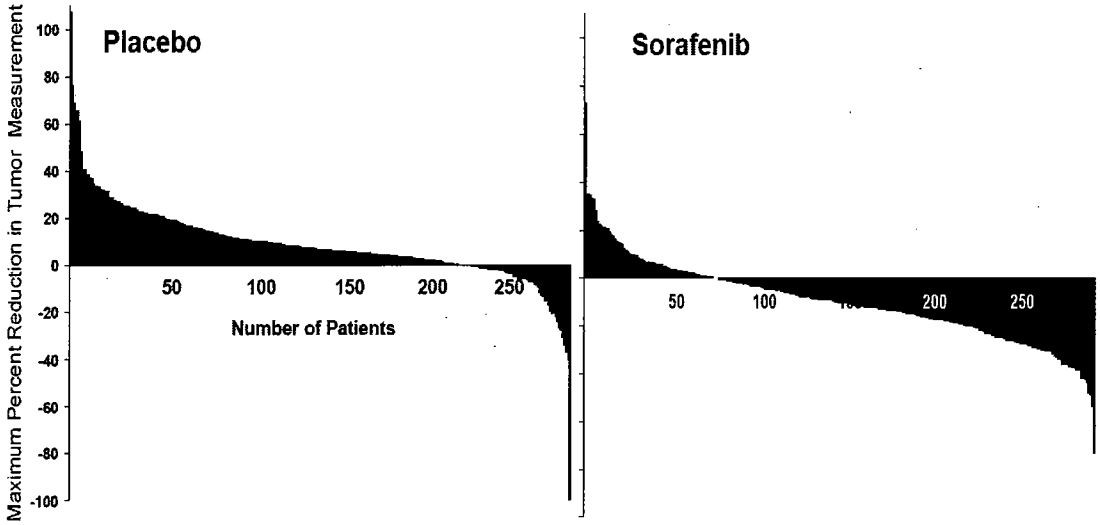
Best Response	Placebo N = 337	Sorafenib N = 335
	n (%)	n (%)
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	0 (0)	7 (2.1)
Stable disease	186 (55.2)	261 (77.9)
Progressive disease (PD)	102 (30.3)	29 (8.7)
Not evaluated	49 (14.5)	38 (11.3)

Sponsor table 11-11, CSR page 77

Based on the site investigator blinded assessments, there were 30 partial responses to sorafenib (9.0%) versus 5 responses (1.5%) in the placebo arm (sponsor table 11-12, not shown).

Another method of assessing response provided by the applicant is shown below. Since RECIST response requires 30% unidimensional shrinkage, the sponsor analyzed all tumor measurement changes (from the independent radiology review) for all patients in the response population. In this display, the greatest magnitude of change from baseline is shown, ordered from largest increase to decrease, for all patients in each group. Visual inspection conveys the fact that many more patients had some tumor shrinkage with sorafenib, although less than the magnitude required for RECIST definition for response.

Figure 4: Maximum percent change in tumor measurements for all measurable disease patients



sponsor figure 11-5, CSR page 80

SURVIVAL:

Following the April 4, 2005 meeting with FDA regarding PFS results, accrual was terminated and sorafenib was offered to all placebo patients. While survival is a primary study endpoint, the survival data is not sufficiently mature (insufficient number of events) for analysis now. A revised statistical plan will now include an interim look at survival at approximately 220 events (deaths) using a cutoff date of May 31, 2005. In revising the survival analysis plan, the applicant considered the timing of the crossover of placebo patients to sorafenib, the potential "dilution" effect of placebo patients crossed over to sorafenib treatment, and the availability of the OS analyses to regulatory agencies.

The decision to allow patients who were randomized to placebo access to sorafenib was made in April 2005 (approximately 130 placebo patients were in the double-blind phase and 180 in the post progression follow-up phase of the study) and an amendment to the protocol provided for this change. Actual crossover to sorafenib began in May 2005 and was completed by July 2005 following IRB and regulatory approvals for this multinational study. In the OS plan, all interim and final analyses of OS are prespecified and alpha spending according to the prespecified spending function is provided to protect the final overall alpha of 0.04 or better. The data cutoff date for the placebo group is June 30, 2005. For this analysis, the maximum possible follow-up time for any placebo patient is approximately one year and six months. The final pre-specified OS is planned at 540 events.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Table 13: Summary of efficacy results

	All Patients	
Efficacy Endpoint	**Sorafenib**	**Placebo**
	n=384	**n=385**
Progression-free survival: Events n (%)	147 (38%)	195 (51%)
Median in days (95% CI)	167 (139, 174)	84 (78,91)
Hazard ratio [a] (95% CI)	0.44 (0.35, 0.55)	
p-value [b]	< 0.000001	
Response Rate [c] n = 672	n= 335	n= 337
CR n (%)	0	0
PR n (%)	7 (2.1%)	0

a: HR is from a Cox regression model with the following covariates: Motzer prognostic risk category and country
b: P-value is from the Logrank test, two-sided, stratified by Motzer prognostic risk category and country
c: Based on the response population
Reviewer's table

Reviewer comments: In this large, single, multi-national, placebo-controlled, well-designed and conducted phase 3 trial, the two groups were well balanced for disease and demographic characteristics. Over 90% of patients had stage 4 (metastatic) disease, and all had one prior therapy. For 17% of patients, the prior therapy was given with an adjuvant or neo-adjuvant intent by the investigator. All patients were good performance status with low or intermediate risk disease prognosis. The placebo control is appropriate since there is no alternative therapy of recognized benefit available for RCC patients. The PFS endpoint is acceptable to encompass the risk of early deaths or discontinuations related to therapy as well as to reflect those patients experiencing disease control of amounts less than partial response.

Sorafenib therapy resulted in a statistically significant prolongation in the time to progression and progression-free survival compared to a control group receiving best supportive care and placebo. All patient subgroups appeared to benefit from sorafenib. PFS was doubled from a median of about 3 months on placebo to 6 months with sorafenib, statistically highly persuasive ($p<0.000001$; HR 0.44). Response, based on RECIST criteria, was documented only in 2.1% of

patients although a majority of patients had some amount of shrinkage, albeit smaller than the 30% amount required for declaring an objective response by RECIST. The objective response proportion is notably small but may be related to the proposed "cytostatic" mechanism of sorafenib. There are a small number of tumor shrinkages in the placebo group as well; this has been observed historically for RCC.

The study accrued over 900 patients in 14 months time, of which 769 were eligible for analysis at the time of data cutoff. Patients (who had received one prior therapy) were informed that they would be randomized to receive either an experimental pill or supportive care with a placebo pill. No crossover to sorafenib was provided in the protocol. It is possible that patients who accepted this treatment plan may be different from those who would insist on receiving an active therapeutic option either on both study arms or sequentially.

There is no regulatory precedent in RCC for judging the magnitude and duration of the PFS endpoint as a clinical benefit or as likely to predict one. No other drugs have demonstrated an improvement in PFS or a survival improvement in RCC. However, it is usual for an increase of symptoms and decline in performance status to accompany progressive disease, and the magnitude and duration of the improvement in PFS are statistically compelling and clinically convincing as a meaningful benefit that patients would seek if available to them. Interim overall survival results are anticipated in the next 6 months. Early termination of the study may confound the survival result but is clinically appropriate to expedite the availability of this therapy.

When Bayer announced these interim findings in March 2005, they were invited to present their results to FDA; on the basis of Bayer's analysis, FDA advised the applicant to offer sorafenib to all placebo study participants and to continue the survival analysis per protocol.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The phase 3 placebo-controlled trial is the primary data source. All patients except one (who did not receive any therapy) are included in the safety population. The safety of the study drug was to be evaluated by documentation of all adverse events (graded according to the National Cancer Institute's [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0), changes in laboratory results (hematology, clinical chemistry, urinalysis, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature), and electrocardiograms (ECGs).

Table 14: Summary of safety events

	Sorafenib	Placebo
	N=384	N=384
	n (%)	n (%)
Deaths within 30 days of receiving study medication	23 (6.5%)	18 (4.7%)
Treatment-emergent adverse event	325 (84.6%)	283 (73.7%)
Drug-related adverse event	282 (73.4%)	171 (44.5%)
Serious adverse event	91 (23.7%)	68 (17.7%)
Drug-related serious adverse event	25 (6.5%)	10 (2.6%)
Adverse event leading to permanent discontinuation	24 (6.3%)	28 (7.3%)

Sponsor's table 12-1, CSR module 5.3.5.1, page 85

Reviewer comment: The findings in the placebo group attest to the difficulty of attribution of AEs in advanced cancer patients and provide an important context for assessing the safety of sorafenib by indicating the baseline frequency of AEs unrelated to treatment in a cancer study. The placebo group is appropriate and critical to this study given the lack of other therapy for RCC and uncertain safety of sorafenib. Please see section 7.4.3 also.

7.1.1 Deaths

Deaths within 30 days of study medication were reported for 23 sorafenib patients and 18 placebo patients. Over 70% of deaths for each group were considered due to progressive disease, and the remaining events were solitary events. The other causes of death in sorafenib patients were pulmonary edema, heart failure, valvular heart disease, and infection, which occurred in 1 patient each. The other causes of death in placebo patients were renal failure and cardiac infarction, which occurred in 1 patient each; and circulatory and respiratory insufficiency, which occurred in 2 placebo patients. Cause of death was not available for 1 placebo patient.

7.1.2 Other Serious Adverse Events

Overall, there were 284 serious adverse events reported in 159 patients in Study 11213: 168 in the sorafenib group and 116 in the placebo group. SAEs reported in at least 2% of patients are summarized here.

Table 15: Treatment emergent Serious AEs reported in at least 1% of patients in study 11213

NCI-CTC AE Category/Term	Sorafenib N = 384 n	(%)	Placebo (N = 384) n	(%)
Any Serious Adverse Event	91	(23.7)	68	(17.7)
Blood/bone marrow				
Decreased hemoglobin	4	(1.0)	9	(2.3)
Cardiac general				
Cardiac ischemia/infarction	4	(1.0)	2	(0.5)
Death				
Death not associated with NCI-CTC term,	4	(1.0)	5	(1.3)
disease progression NOS				
Constitutional symptoms				
Fatigue	4	(1.0)	3	(0.8)
Constitutional symptoms – other	8	(2.1)	5	(1.3)
Gastrointestinal				
Constipation	4	(1.0)	0	(0.0)
Musculoskeletal/soft tissue				
Fracture	4	(1.0)	3	(0.8)
Musculoskeletal – other	1	(0.3)	4	(1.0)
Neurology				
Neurology - other	3	(0.8)	4	(1.0)
Pain, tumor pain	6	(1.6)	3	(0.8)
Pain, abdomen NOS	4	(1.0)	1	(0.3)
Pulmonary/upper respiratory				
Pleural effusion	4	(1.0)	3	(0.8)
Pulmonary – other	2	(0.5)	4	(1.0)
Pneumonitis	4	(1.0)	1	(0.3)
Dyspnea	4	(1.0)	4	(1.0)

Sponsor's table 6-11, module 5.3.5.3.1, ISS, page 35

Table 16: Serious Treatment-Emergent Adverse Events Reported in at Least 2% of Patients in Study 11213

Serious Adverse Event CTCAE Category/Term	Sorafenib (N=384) n (%)	Placebo (N=384) n (%)
Blood/Bone Marrow		
Hemoglobin	4 (1.0)	9 (2.3)
Constitutional symptoms		
Constitutional symptoms-other	8 (2.1)	5 (1.3)

Sponsor's table 1-20, module 2.7.4, page 36

Reviewer comment: Of note, there were more SAEs for low hemoglobin in the placebo arm.

7.1.3 Dropouts and Other Significant Adverse Events

By 28 Jan 2005, the data cutoff date for this analysis, 226 (58.9%) placebo subjects and 144 (37.5%) sorafenib subjects for a total of 370 subjects had discontinued double-blind treatment. The most common reason reported by the investigator for discontinuing double blind treatment was disease progression. Of those that discontinued double blind treatment, 14 placebo and 13 sorafenib subjects were reported by the investigator as having discontinued due to adverse events.

Table 17: Discontinuations

	Sorafenib (N=384)		Placebo (N=385)	
	n	(%)	n	(%)
Discontinued double blind treatment	226	(58.9)	226	(58.9)
Reason for discontinuing double blind treatment [a]				
Adverse event	13	(9.0)	14	(6.2)
Progression by radiological assessment	103	(71.5)	174	(77.0)
Progression by clinical judgment	14	(9.7)	22	(9.7)
Non-compliant with study medication	0	(0.0)	1	(0.4)
Consent withdrawn	3	(2.1)	7	(3.1)
Lost to follow-up	1	(0.7)	4	(1.8)
Death	7	(4.9)	3	(1.3)
Missing	3	(2.1)	1	(0.4)

a. Percent based on number discontinuing for each group
Sponsor table 10-2, page 55, CSR 11213

Reviewer comment: The number discontinuing due to AEs is similar in both groups (3.4%); the denominator should be the total number in the group, not the number discontinuing in each group.

Of the 144 sorafenib patients who discontinued double blind treatment, 54 (14.1%) continued on open-label sorafenib treatment after unblinding at the discretion of the investigator. Subsequently, 12 of the 54 patients discontinued open-label treatment, 10 of who discontinued for further disease progression, and 42 continued on open-label sorafenib at data cutoff.

Overall, 158 subjects in the placebo group (41.0%) and 240 in the sorafenib group (62.5%) were still receiving double blind study treatment as of 28 Jan 2005. Also, at that time, 148 (38.4%) placebo subjects and 54 (14.1%) sorafenib subjects were still in post-treatment follow-up.

7.1.3.2 Adverse events associated with dropouts

AEs associated with dropouts were infrequent and were generally balanced on both study arms. One case of pancreatitis occurred on the placebo arm and led to dropout. Three cases occurred on the sorafenib arm; two of the patients resumed therapy subsequently.

7.1.3.3 Other significant adverse events

There are a number of unique AE findings associated with the drug which are evident from the phase 3 study. Reversible skin rashes and hand-foot syndrome are common, probably related to the kinase-inhibiting activity, and dose-limiting. Hypertension occurs in about 10% of patients early in exposure to VEGF-inhibitors (class effect) and requires anti-hypertensive therapy in some patients. Bleeding events (but not thrombo-embolic events) are more common with sorafenib than placebo; these may involve mucosal surfaces preferentially (which could be suggestive of an anti- platelet effect). A sensory peripheral neuropathy, mostly grade 1, appears related to drug exposure. Clinical AEs of special interest are described in detail in section 7.1.12, special safety studies. Lymphopenia, hypophosphatemia, and lipase elevations also are associated with sorafenib treatment as described further below in laboratory findings, section 7.1.7.

7.1.4 Other Search Strategies

A detailed search for the AE, bleeding, looked for hemorrhage or bleeding as part of the MEDDRA Preferred Term (called _M_LLT) or the NCI CTC term (called _ETOXCOD). These results are described below in the special safety studies section 7.1.12.

7.1.5 Common Adverse Events

Please see the subsections below.

7.1.5.1 Eliciting adverse events data in the development program

AEs were defined and reported on case report forms in accordance with the standard oncology reporting system, NCI CTCAE version 3, by investigators who were blinded to the therapy.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

MedDRA usage was uniform and consistent in the coding and reporting.

7.1.5.3 Incidence of common adverse events

Please see tables below which compare the AEs for the placebo control arm with the study drug.

7.1.5.4 Common adverse event tables

Table 18: Treatment emergent AEs in 10% or more patients in study 11213

Adverse Event CTCAE Category/ Term	Sorafenib N=384 n	(%)	Placebo N=384 n	(%)
Any event	325	(84.6)	283	(73.7)
Cardiovascular, General				
Hypertension	41	(10.7)	3	(0.8)
Constitutional symptoms				
Fatigue	101	(26.3)	90	(23.4)
Dermatology/skin				
Rash/ desquamation	129	(33.6)	51	(13.3)
Hand -foot skin reaction	103	(26.8)	18	(4.7)
Alopecia	88	(22.9)	12	(3.1)
Pruritus	65	(16.9)	17	(4.4)
Gastrointestinal symptoms				
Diarrhea	126	(32.8)	38	(9.9)
Nausea	68	(17.7)	57	(14.8)
Anorexia	47	(12.2)	37	(9.6)
Constipation	45	(11.7)	29	(7.6)
Vomiting	43	(11.2)	33	(8.6)
Hemorrhage – all sites *	45	(11.7)	20	(5.2)
Neurology				
Neuropathy-sensory	39	(10.2)	14	(3.6)
Pulmonary				
Cough	35	(9.1)	42	(10.9)

* row added by reviewer
revised sponsor's table 1-14, module 2.7.4, page 30

Table 19: Treatment Emergent Adverse Events Reported in at Least 5% of Patients in Any Treatment Group, phase 3 RCC study (all values are in percent)

Adverse Event	SORAFENIB N=384			Placebo N=384		
NCI-CTCAE v3 Category/Term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Hemoglobin	5	<1	<1	7	3	<1
Hypertension	11	2	<1	<1	<1	0
Fatigue	26	2	<1	23	2	<1
Fever	6	<1	0	6	0	0
Constitutional symptoms-other	8	1	<1	4	1	0
Weight loss	7	<1	0	3	0	0
Rash/desquamation	34	1	0	13	<1	0
Hand -foot skin reaction	27	5	0	5	0	0
Alopecia	23	0	0	3	0	0
Pruritus	17	<1	0	4	0	0
Dermatology-other	9	0	0	4	0	0
Dry skin	8	0	0	3	0	0
Flushing	6	<1	0	2	0	0
Diarrhea	33	2	0	10	1	0
Nausea	18	1	0	15	<1	0
Anorexia	12	1	0	10	1	0
Constipation	12	1	0	8	<1	0
Vomiting	11	<1	0	9	<1	0
Gastrointestinal-other	6	0	<1	4	0	<1
Mucositis, oral cavity	7	<1	0	<1	0	0
Infection-other	5	1	0	4	<1	0
Musculoskeletal-other	3	<1	<1	5	1	0
Neuropathy-sensory	10	<1	0	4	<1	0
Cough	9	<1	0	11	0	0
Dyspnea	9	2	<1	9	2	<1

Sponsor's table, modified, from the proposed label

Reviewer comments: In comparing of the incidence of adverse events in sorafenib versus placebo patients, the events in which rates differed to the largest extent between the two groups were hypertension, diarrhea, mucositis, sensory neuropathy, and dermatologic events. Notably, emergence of hypertension was observed in 1% (3/384) of placebo patients (one of which was grade 3) compared to almost 11% of sorafenib patients. While all skin reactions were more frequent on sorafenib, alopecia and hand-foot reactions were reported among placebo patients also. See section 7.1.12 for further details of these AEs.

Table 20: summary of adverse events, grades 1-4, occurring at higher incidence (≥ 5%) for sorafenib

Adverse Event CTCAE Category/ Term	Sorafenib N=384 n	(%)	Placebo N=384 n	(%)
Any event	325	(84.6)	283	(73.7)
Cardiovascular, General				
Hypertension	41	(10.7)	3	(0.8)
Dermatology/skin				
Rash/ desquamation	129	(33.6)	51	(13.3)
Hand -foot skin reaction	103	(26.8)	18	(4.7)
Alopecia	88	(22.9)	12	(3.1)
Pruritus	65	(16.9)	17	(4.4)
Gastrointestinal symptoms				
Oral mucositis	28	(7.3)	2	(0.5)
Diarrhea	126	(32.8)	38	(9.9)
Nausea	68	(17.7)	57	(14.8)
Anorexia	47	(12.2)	37	(9.6)
Constipation	45	(11.7)	29	(7.6)
Vomiting	43	(11.2)	33	(8.6)
Hemorrhage – all sites	45	(11.7)	20	(5.2)
Neurology				
Neuropathy-sensory	39	(10.2)	14	(3.6)
Pulmonary				
Cough	35	(9.1)	42	(10.9)

Reviewer's table, adapted from sponsor's table 1-16, study 11213, section 2.7.4, page 32

Reviewer comment: This table describes the AEs occurring more commonly (by 5% or more) on the active treatment arm of the study. The AE frequency on the placebo arm provides a critical baseline event rate for RCC patients. Interventions with treatment for AEs are a measure of the clinical importance of an AE; treatment-emergent cardiovascular medications were given to 43% of placebo and 49% of sorafenib patients. Diarrhea was reported in 33% of sorafenib patients compared to 10% of controls; treatment-emergent anti-diarrheal medications were given to 16% of sorafenib patients and 5% of placebo patients. By the end of cycle 4 (24 weeks), there was a mean weight loss of 2.2 kg in the sorafenib treated patients compared to a positive 0.34 kg mean weight change for placebo patients; this may be indirect evidence for adverse GI effects of sorafenib. Oral mucositis by clinical examination was infrequent but was distinctly more common in the sorafenib arm (28 patients, 7.3%) than in the placebo arm (2 patients, 0.5%). Two of the mucositis events in the sorafenib arm were reported as CTCAE Grade 3, defined as confluent ulcerations or pseudomembranes, or bleeding with minor trauma.

further detailed discussion of significant adverse events is provided in section 7.1.12.

Table 21: grade 3 and 4 TEAEs in at least 2% of patients

	Sorafenib				Placebo			
	N=384				N=384			
Adverse Event	**Grade 3**		**Grade 4**		**Grade 3**		**Grade 4**	
CTCAE Category/Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any event	97	(25.3)	19	(4.9)	64	(16.7)	19	(4.9)
Blood/Bone Marrow								
Hemoglobin	2	(0.5)	1	(0.3)	12	(3.1)	2	(0.5)
Cardiovascular, General								
Hypertension	8	(2.1)	1	(0.3)	1	(0.3)	0	(0)
Constitutional symptoms								
Fatigue	9	(2.3)	1	(0.3)	8	(2.1)	2	(0.5)
Dermatology/skin								
Hand -foot skin reaction	20	(5.2)	0	(0)	0	(0)	0	(0)
Pain								
Tumor pain	10	(2.6)	0	(0)	4	(1.0)	1	(0.3)
Pulmonary								
Dyspnea	6	(1.6)	2	(0.5)	7	(1.8)	1	(0.3)

Sponsor's table 1-17, module 2.7.4 page 33

Reviewer comments: For severe AEs (grade 3-4), there were very few grade 4 events and the total number was the same for both arms (4.9%). All 20 grade 3 hand-foot cases (5.2%) were in the sorafenib arm versus 0% placebo. Grade 3-4 hypertension occurred in 2.3% of sorafenib patients versus 0.3% placebo. See section 7.1.12 for further discsuuion.

7.1.5.5 Identifying common and drug-related adverse events

Due to the study design and placebo control, the AE frequencies which exceed those in the placebo arm are likely related to the sorafenib therapy.

7.1.5.6 Additional analyses and explorations

The onset of hypertension was typically early in therapy, during the first 4 weeks. Lymphopenia, hypophosphatemia, and elevated lipase values also occurred early in therapy, during the first 4 cycles and not subsequently. No specific late-onset AEs were encountered.

7.1.6 Less Common Adverse Events

Bleeding is described along with other AEs of special interest in section 7.1.12, special safety studies. Other events are indicated in the tables.

7.1.6 Laboratory Findings

Table 22: Grade 3 or 4 Lab abnormalities observed in ≥ 2% of patients in study 11213

Laboratory Category/Term	Placebo (N = 384)				Sorafenib (N = 384)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	n/Na	(%)	n/Na	(%)	n/Na	(%)	n/Na	(%)
Blood/bone marrow								
Neutrophils	4/336	(1.2)	2/336	(0.6)	9/336	(2.7)	8/336	(2.4)
Hemoglobin	8/336	(2.4)	1/336	(0.3)	3/338	(0.9)	0/338	(0.0)
Lymphopenia	17/336	(5.1)	2/336	(0.6)	27/336	(8.0)	2/336	(0.6)
Coagulation								
INR	21/336	(6.3)	0/336	(0.0)	17/342	(5.0)	0/342	(0.0)
Metabolic/laboratory								
Elevated amylase	8/340	(2.4)	2/340	(0.6)	4/343	(1.2)	0/343	(0.0)
Hyperglycemia	14/340	(4.1)	1/340	(0.3)	9/343	(2.6)	1/343	(0.3)
Hyperkalemia	7/340	(2.1)	2/340	(0.6)	9/343	(2.6)	3/343	(0.9)
Elevated lipase	12/340	(3.5)	6/340	(1.8)	32/343	(9.3)	2/343	(0.6)
Hyponatremia	12/340	(3.5)	0/340	(0.0)	15/343	(4.4)	2/343	(0.6)
Hypophosphatemia	6/340	(1.8)	0/340	(0.0)	37/343	(10.8)	0/343	(0.0)

Sponsor's table 12-12, module 5.3.5.1.1, CSR, page 1-124
Na = number available

In the phase 3 trial, hypophosphatemia was the most common laboratory finding, observed in 139 (40.5%) sorafenib-treated patients as compared with 25 (7.4%) placebo patients. Grade 2 hypophosphatemia (2.0-2.5 mg/dL) occurred in 102 (29.7%) sorafenib patients, and grade 3 hypophosphatemia (1.0-2.0 mg/dL) occurred in 37 (10.8%) sorafenib patients. There were no instances of severe hypophosphatemia, defined as serum phosphate below 1.0 mg/dL. There were no apparent clinical sequelae associated with hypophosphatemia in this study. Hypophosphatemia was not reported as a serious adverse event, nor did the laboratory abnormality lead to discontinuation of study drug. There were no patients with identifiable manifestations of severe phosphorus deficiency such as rhabdomyolysis, cardiomyopathy, respiratory insufficiency, erythrocyte dysfunction, metabolic acidosis, or skeletal demineralization. The incidence of hypophosphatemia did not correlate with the adverse event of diarrhea. (Hypocalcemia occurred in 11.7% of the sorafenib patients and 4.7% of placebo patients.) The etiology of hypophosphatemia associated with sorafenib is not known. The applicant suggests that the choice of management should be based on the risk/benefit assessment for individual patients.

The second most common abnormality was elevation of lipase in 39% (134/343) of sorafenib patients and 24.4% (83/340) placebo patients. Of the total, 9.3% of sorafenib patients had a grade 3 elevation (2 to 5X ULN) versus 3.5% placebo patients, and 0.6% (2/343) of sorafenib patients had a grade 4 elevation (> 5X ULN) versus 1.8% (6/340) in the placebo group. Elevated amylase was observed in 86 (25.1%) sorafenib patients and 74 (21.8%) placebo patients. Grade 3 or 4 elevated amylase was observed in 1.2% of sorafenib patients and 3.0% of placebo patients. The

adverse event pancreatitis was reported in 3 sorafenib patients (0.8%). Grade 1 pancreatitis, defined by CTCAE as "asymptomatic enzyme elevation and/or radiological findings," was reported in 1 patient. Grade 4 pancreatitis, defined by CTC as "life-threatening," was reported in 2 patients. One patient (11213-009-001) was a 38-year-old woman who began study drug on 05 Jun 2004 and was found to have acute pancreatitis on [ ], when she presented with pain, accompanied by elevated amylase 298 U/L (normal range: 30 to 110 U/L) and lipase 3288 U/L (normal range: 25 to 208 U/L). She was treated with intravenous hydration and morphine for pain during the event and study drug was discontinued on [ ] The event resolved on [ ]. Amylase and lipase levels were 81 U/L and 509 U/L on [ ]. Study medication was restarted on 09 Jul 2004 at a reduced dose (400 mg po once daily), and the patient continued on sorafenib until disease progression on 15 Oct 2004. The other patient (11213-257-016) was a 54 year-old man who began sorafenib on 19 Oct 2004 and had Grade 4 acute pancreatitis on [ ], when he presented with amylase 151 U/L and lipase 577 U/L. Study drug was discontinued and restarted after the pancreatitis resolved on [ ] There was 1 placebo patient (11213-253- 006) with Grade 2 pancreatitis (symptomatic, requiring medical intervention). Two patients in the phase 2 study were reported to have developed acute pancreatitis on therapy. One occurred one day after the start of therapy; in the other, after discontinuation for 12 days, sorafenib was restarted.

The mechanism of the lipase elevation is uncertain. In repeat-dose toxicology studies in rats and dogs, morphological changes in the exocrine pancreas have been observed as demonstrated by histopathological examinations. Daily treatment for 1, 3, or 6 months with oral doses at or below the MTD did not induce sustained morphological changes in the exocrine pancreas of rats.

Laboratory findings associated with abnormal hepatic function occurred in both treatment arms in Study 11213. Low grade increased transaminases and bilirubin were more common in the sorafenib arm. Increased ALT was observed in 83 (24.2%) sorafenib patients and 65 (19.1%) placebo patients. There was one event of Grade 3 increased ALT in a placebo patient. Increased AST was observed in 71 (20.7%) sorafenib patients and 46 (13.5%) placebo patients. Grade 3 increased AST occurred in one sorafenib patient and 2 placebo patients. Increased bilirubin was observed in 26 (7.6%) sorafenib patients and 21 (6.2%) placebo patients.

Sorafenib did not cause substantial reductions in blood counts or infectious complications. Leukopenia was observed in 73 sorafenib patients (21.6%) and 35 placebo patients (10.4%). The predominant effect appeared to be on lymphocytes; lymphopenia was observed in 62 sorafenib patients (18.5%) and 36 placebo patients (10.7%). There were 29 sorafenib patients (7.5%) and 19 placebo patients (4.9%) with Grade 3 or 4 lymphopenia. While there was more grade 3 lymphopenia in the sorafenib arm (27 versus 17 placebo cases), the incidence of grade 4 lymphopenia was the same in each arm (2 cases each). There was a less striking effect on neutrophil count: 17 sorafenib patients (5.1%) and 6 placebo patients (1.8%) had Grade 3 or 4 neutropenia. The overall rates of neutropenia (all grades) were 16.7% and 7.7% in the sorafenib and placebo groups, respectively. The incidence and types of infections were not different in the two study arms: 49 sorafenib patients (12.8%) and 37 placebo patients (9.6%) had treatment-emergent infection of any grade. Five sorafenib patients (1.3%) and 4 placebo patients (1.0%) had a Grade 3 infection. No grade 4 infections were reported, and no sorafenib patients with grade 3 or 4 leukopenia had an adverse event of infection.

Low hemoglobin occurred in 145 (43.2%) placebo patients and 112 (33.1%) sorafenib patients. Anemia was reported as an adverse event in 26 placebo patients and 18 sorafenib patients; Grade 3 or higher anemia was reported in 14 (3.6%) placebo patients and 3 (0.8%) sorafenib patients. These data suggest that sorafenib is not associated with a decrease in hemoglobin, and that anemia is a manifestation of the underlying RCC.

Alterations in creatinine were not different between placebo and sorafenib-treated groups. There were no grade 3 or 4 elevations; there were 4 patients on sorafenib and 6 patients on placebo who exhibited grade 2 elevations (1.5 – 3.0 times ULN). Approximately 10% in each group showed an increase of one grade as the worst change observed. Renal failure of any grade occurred in 3 patients in each group (see tables 14.3.5/1, 14.3.5/2, and 14.3.1/1).

A signal of hypothyroidism was observed during the nonclinical studies in dogs. Thyroid testing was not required but was performed for clinical indications during the study. Two patients, both receiving sorafenib, were diagnosed to have hypothyroidism during the study and were given on thyroid replacement therapy.

7.1.7.1 Overview of laboratory testing in the development program

The applicant achieved a high degree of compliance with planned lab studies; 87 – 90% of planned laboratory assessments were available for analysis. Lab evaluations are routinely performed frequently in oncology treatment and this expectation may have assisted Bayer. In individual lab result tabulations, commonly less than 10 patients were recorded as lacking a baseline parameter.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Only one study, the phase 3 placebo-controlled trial, is available. This study is the source of all analyses described in this review. See section 7.1.6.

7.1.7.3 Standard analyses and explorations of laboratory data

Only the phase 3 study has been evaluated. In general, the phase 2 study underestimated the important findings of the placebo-controlled trial and identified no different adverse events in type or severity.

7.1.7.3.1 Analyses focused on measures of central tendency

Not presented by the applicant. Changes by CTC grade are more appropriate in oncology reporting.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

See 7.1.6.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

Blood pressure elevations were observed and expected as a class effect. Please see this review under the special safety studies in section 7.1.12.

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure (BP) changes were recognized in phase 1 and 2 and knowledge of the hypertensive effects of other VEGF inhibitors developed during the implementation of the phase 3 study. Dose reductions, discontinuations, and/or institution of anti-hypertensive therapy were specified by the phase 3 protocol.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.12.

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

7.1.8.3.1 Analyses focused on measures of central tendencies

In the placebo group, there was no appreciable change in the mean systolic or diastolic blood pressure at any point during the study.

In sorafenib patients, mean change from baseline was highest at Day 21 of Cycle 1: mean change in systolic blood pressure was +9.1 mmHg (range -53.0 to +69.0 mmHg) and in diastolic blood pressure was +6.9 mmHg (range -27.5 to + 40 mmHg).

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not performed. It is more typical and informative in oncology trials to describe patient groups by proportions experiencing an event graded from 1 to 4 in accord with the NCI CTC criteria.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Not applicable.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

Two studies have been conducted in healthy volunteers where the effect of sorafenib on the QTc interval was evaluated using a single 400 mg dose. Duplicate tracings performed 4 hours post-dose showed no increase in QTc compared to baseline. ECGs were not routinely performed or analyzed in the phase 1, 2, or 3 studies; however, there were no significant mean changes from baseline for the post-baseline QTc where these results were available. No sorafenib patient had a treatment-emergent QTc interval >500 msec or had ventricular tachycardia.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

An in vitro hERG channel assay revealed a tendency for an inhibition of the hERGmediated K-current in the concentration range 1 - 10 μM sorafenib tosylate; however, the differences versus controls were not statistically significant. Measurements of the action potential duration in isolated rabbit Purkinje fibers in vitro indicated a small prolongation of the APD90, which became significant at 10 μM sorafenib tosylate, a concentration which approached the solubility limit. There was no influence on the QT-interval in vivo as demonstrated in the dog safety pharmacology study and in dog repeat-dose toxicity studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The single phase 3 study is reviewed as noted in 7.1.9.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.3.1 Analyses focused on measures of central tendency
Not applicable.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal
Not applicable.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities
Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Not applicable.

7.1.12 Special Safety Studies

While no special safety studies were conducted, specific safety analyses were evaluated in the phase 3 trial by the applicant and this reviewer for several unique adverse events of sorafenib therapy. These include dermatologic events, hand-foot syndrome, hypertension, hemorrhage, wound healing, laboratory alterations, and sensory neuropathy. Hypertension and impaired wound healing are class effects exhibited commonly by the VEGF inhibitors. Hand-foot syndrome occurs with several different chemotherapy agents but not as a drug class-effect. It is uncertain for the other events listed if the findings represent a class effect or are drug-specific. Laboratory abnormalities are described in section 7.1.7.

DERMATOLOGIC:
In the phase 3 study, dermatologic events were the most common adverse events, reported in 244 (63.5%) patients randomized to sorafenib and in 106 (27.6%) patients randomized to placebo. The CTCAE term "Rash/desquamation" was the most common dermatologic event. Rash, which was generally described as a maculopapular erythematous eruption on the scalp, face, and trunk, was reported in 129 (33.6%) sorafenib patients and 51 (13.3%) placebo patients. Almost all were Grades 1 or 2; Grade 3 rash (defined as severe generalized erythroderma or eruption) was reported in 3 (0.8%) sorafenib patients and in 1 (0.3%) placebo patient. No Grade ≥ 4 rash was reported. Most of these events were attributed to study drug; rash was considered to be drug-related in 120 (31.3%) patients in the sorafenib arm and 43 (11.2%) patients in the placebo arm. Rash was not reported as an SAE in either treatment arm. Rash led to the temporary discontinuation of study drug in 5 (1.3%) sorafenib patients and a reduction of dose in 5 (1.3%) sorafenib patients. For those patients developing a rash, 80% of the events occurred during the first cycle. Pruritus was reported independently in 65 (16.9%) sorafenib patients and 17 (4.4%) placebo patients.

HAND-FOOT SYNDROME:
Hand-foot skin reaction is described in the CTCAE v3 definition as "palmar-plantar erythema with numbness (Grade 1), pain (Grade 2), and possible blistering or desquamation interfering with activities of daily living (Grade 3)". Hand-foot skin reaction occurred in 103 (26.8%) sorafenib patients: CTCAE Grade 1 in 49 patients (12.8%); Grade 2 in 34 patients (8.9%), and Grade 3 in 20 patients (5.2%). All but 2 of these events were attributed by the investigator to study drug. Interestingly, hand foot skin reaction was also reported in 18 (4.7%) patients in the placebo arm, and was attributed to study drug in all 18 cases; 16 (4.2%) of these events were assessed as Grade 1, and 2 (0.5%) were Grade 2. Analysis of cycle-specific and cumulative event rates for hand foot skin reaction revealed a similar pattern to that observed for rash. By treatment cycle, considered to be 6 weeks in duration, new-onset hand foot skin reaction was reported in 78

sorafenib patients (20.5%) during Cycle 1, 20 patients (8.0%) in Cycle 2, and in fewer than 2% of patients thereafter. In 2 patients, both in the sorafenib arm, hand-foot syndrome (grade 3) led to permanent drug discontinuation. Hand foot skin reaction was not reported as an SAE in either treatment arm.

Hand foot skin reaction was the most frequent reason for study drug interruption and dose reduction. Study drug was interrupted and restarted in 55 sorafenib patients (14.3%), and 16 placebo patients (4.2%) as a result of hand foot skin reaction. In 18 sorafenib patients (4.7%), the dose of study drug was reduced as a result of hand-foot skin reaction. In 8 of these 18 cases, hand-foot skin reaction resolved or improved; in 3 cases the event was unchanged, and in 1 case it worsened. The outcome of the event for 6 of these patients was not known at the time of data cut-off.

Alopecia was reported in 88 (22.7%) patients in the sorafenib arm and 12 (3.1%) patients in the placebo arm. Most of these events (77 sorafenib patients and 10 placebo patients) were Grade 1 alopecia, defined as thinning or patchy hair loss. Grade 2 (complete) hair loss was reported in 11 (2.9%) sorafenib patients and 2 (0.5%) placebo patients.

HYPERTENSION:
In the phase 3 study, over 90% of patients had had a nephrectomy, which could contribute to baseline hypertension. At screening, 25 patients in the sorafenib arm and 28 patients in the placebo arm had systolic blood pressure ≥160 mmHg, and 4 patients in each arm had systolic blood pressure ≥180 mmHg. In the grading of hypertension in CTCAE version 3.0, hypertension requiring only one medication is included in Grade 2 while a requirement for multiple medications is defined as Grade 3. Blood pressure (BP) elevation, when it occurred, was generally apparent at the first follow-up visit, 21 days after initiation of study medication. In sorafenib patients, mean change from baseline was highest at Day 21 of Cycle 1: mean change in systolic blood pressure was +9.13 mmHg (range -53.0 to +69.0 mmHg) and mean change in diastolic blood pressure was +6.9 mmHg (range -27.5 to +40 mmHg). At Day 21 of Cycle 1, 48 sorafenib patients (15.4%) and 11 placebo patients (3.5%) had systolic blood pressure ≥160 mmHg; 14 sorafenib patients (4.2%) and 3 placebo patients (0.9%) had systolic blood pressure ≥180 mmHg. In total, for sorafenib, 29 patients (7.5%) at baseline had systolic blood pressure (elevations) of 160 mmHg or greater; at day 22 on therapy, 62 sorafenib patients had the same BP findings, representing 16% of patients, versus 14 placebo patients (3.6%) with this BP range on day 22. In the placebo group, there was no appreciable change in the mean systolic or diastolic blood pressure at any point during the study.

Notably, hypertension was reported as a treatment-emergent adverse event in 41 sorafenib patients (10.7%) and 3 placebo patients (0.8%). There were 54 sorafenib patients (14.1%) and 10 placebo patients (2.6%) who initiated a concomitant medication for hypertension on study. Grade 1 hypertension, defined by CTCAE as an asymptomatic and transient increase by of blood pressure >20 mmHg diastolic or to >150/100 mmHg if previously normal, occurred in 9 (2.3%) sorafenib patients. Grade 2 hypertension, defined as recurrent or persistent (>24 hours) hypertension, or a symptomatic increase by >20 mmHg or to >150/100 mmHg if previously normal, with monotherapy possibly indicated, was reported in 23 (6.0%) sorafenib patients. Grade 3 hypertension, defined by CTCAE as hypertension necessitating more than one drug or

more intensive therapy than previously, was reported in 8 sorafenib patients (2.1%); and Grade 4 hypertension (life threatening, such as hypertensive crisis) was reported in 1 sorafenib patient (11213-290-001), a 63 year old female with history of hypertension and coronary artery disease. The patient had a baseline blood pressure of 170/90 mmHg. Forty-nine days after starting sorafenib, she had a blood pressure of 220/100 mmHg which required hospitalization for treatment. She was treated with nifedipine and the hypertension resolved 1 week later. There was 1 case of Grade 3 hypertension in a patient in the placebo arm. Hypertension led to permanent discontinuation of study drug in 1 sorafenib patient, and was reported as a serious adverse event in 3 sorafenib patients. In 4 patients, sorafenib dosing was interrupted (for 7-20 days), and in 3 of these patients the dose of study drug was also reduced. The hypertension resolved in 1 of these patients, was improved in 1, unchanged in 1 and the outcome was unknown in 1 patient.

Reviewer comments: At baseline, 7.5% of both study arms had systolic BP values of 160 mm Hg or greater. At the end of cycle 1 (6 weeks on study), 16% of sorafenib patients and 3.6% of placebo patients had similar BP elevations. Hypertension therapy was not pre-specified and varied considerably. In examining concomitant medications as an indication of baseline cardiovascular status, 37% in both arms were taking cardiovascular medications. Initiation of cardiovascular medications while on-study occurred in 43% of placebo patients and 49% of sorafenib patients. This category, cardiovascular medications, includes primarily diuretics, beta blockers, rennin-angiotensin agents, calcium channel blockers, and anti-hypertensives, and most closely describes drugs which might have been selected for blood pressure therapy. The actual therapeutic intent could not be determined since such medications have a variety of uses. For the overall sorafenib group, the identification and treatment of blood pressure elevations for patients on sorafenib appears to be modest. Patients with RCC may be more likely to have and to develop increasing blood pressure related to the neoplastic kidney impairment and the common intervention of surgical nephrectomy.
Findings of hypertension during the RCC study and studies of other VEGF inhibitors led CTEP to request FDA suggestions on a guide for BP management.
The following guide was developed by the oncology division and CTEP, based on the current CTCAE grading of elevated blood pressure to provide consistency with current reporting.
Table 23: Suggested guide for hypertension management for sorafenib and other VEGF inhibitors

Grade of Event (CTCAE v.3)	**Management/ Next Dose**
grade 1	Consider increased BP monitoring
grade 2 asymptomatic and diastolic BP < 110 mm Hg	Begin anti-hypertensive therapy and continue agent
grade 2 symptomatic/ persistent OR diastolic BP ≥ 110 mm Hg OR grade 3	1. Agent should be held* until symptoms resolve and diastolic BP ≤ 100 mm Hg; also treat patient with anti-hypertensives and when agent is restarted, reduce by 1 dose level.** 2. If diastolic BP not controlled (≤ 100) on therapy, reduce another dose level ***
grade 4	Discontinue protocol therapy

* Patients requiring a delay of > 2 weeks should go off protocol therapy.
** May be able to resume full dose later.
*** Patients requiring > 2 dose reductions should go off protocol therapy.

Reviewer's table

Current CTCAE definitions used by CTEP:

Grade 1: asymptomatic, transient (< 24 hours) increase by > 20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated

Grade 2: recurrent or persistent (> 24 hours) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated

Grade 3: requiring more than one drug or more intensive therapy than previously

Grade 4: life threatening (e.g. hypertensive crisis)

HEMORRHAGE AND THROMBO-EMBOLIC EVENTS:

Bevacizumab, which targets VEGF and for which there is a larger clinical experience, has been associated with a twofold increase in serious arterial thromboembolic events in some colon cancer patients, and a 5% overall risk of serious thromboembolic events has been reported.[14] For sorafenib, the applicant examined treatment-emergent thrombotic events under several CTCAE categories, including cardiovascular, neurology, and vascular. Thrombosis/ embolism was not reported in any patient in the sorafenib arm, but was reported in 3 (0.8%) patients taking placebo. Phlebitis was reported in 2 patients taking sorafenib and in no patients taking placebo. Vascular-other event was reported in 1 patient in the sorafenib arm, and peripheral arterial ischemia was reported in 1 patient in the sorafenib arm. Thrombosis of a vascular access catheter was reported in 1 patient taking placebo and 2 patients taking sorafenib in this study. Approximately 6% of patients in each treatment arm entered the study with a history of "ischemic coronary disease" or "coronary artery disease" (as categorized by high level MedDRA term). Cardiac ischemia/infarction was reported as an adverse event in 6 patients (1.6%) in the sorafenib arm and 2 patients (0.5%) in the placebo arm. One of these events, in a placebo patient, resulted in death. In sorafenib patients, 4 of the cardiac ischemia events were reported as serious adverse events, although only 1 was reported as related to study drug. One cardiac ischemia event in each treatment arm led to permanent discontinuation of study drug. CNS ischemia was reported in 3 patients in the placebo arm and in no patients taking sorafenib.

Anti-angiogenic agents may also be associated with an increased risk of hemorrhage. Bevacizumab therapy is associated with serious and some fatal cases of hemoptysis in patients with non-small cell lung cancer, presumably related to tumor and blood vessel necrosis or disruption. See section 7.2.7 for further class effects analysis.

Regarding lab coagulation studies, an abnormal PT-INR was observed during therapy in 83/342 sorafenib patients (24.3%) and 72/336 placebo patients (21.4%), and PTT values above the upper limit of normal were observed in 40/252 sorafenib patients (15.9%) and 25/231 placebo patients (10.8%) However, the incidence of Grade 3 INR (defined as INR >2x ULN) was similar in both arms: 17 (5.0%) in sorafenib patients and 21 (6.3%) in placebo patients. Vitamin K antagonists such as warfarin were reported as concomitant medications in 25 placebo subjects and 17 sorafenib subjects. There were 2 reversible bleeding AEs among these sorafenib patients and one in this placebo group.

Reviewer comment: No clear pattern of alteration in warfarin metabolism was evident to this reviewer.

Thrombocytopenia very unusual and was unlikely to account for hemorrhage.

Table 24: Platelet count reductions on therapy

CTC grade	value	Sorafenib	Placebo
		n (%)	n (%)
grade 1	< LLN - 75 X 10^9/L	22 (6.5%)	12 (3.6%)
grade 2	< 50-75 X 10^9/L	3 (0.9%)	0
grade 3	< 25-49 X 10^9/L	2 (0.6%)	0

Reviewer's table

The applicant identified a total of 65 AEs under the CTC category Hemorrhage/Bleeding, 45 (11.7%) in sorafenib patients and 20 (5.2%) in placebo patients. A majority of these events (32 in the sorafenib arm and 16 in the placebo arm) were CTCAE Grade 1, defined as mild bleeding with intervention not indicated. The most common bleeding events in sorafenib patients were hemorrhage-other, which occurred in 18 (4.7%) patients (16 were Grade 1), and hematoma which occurred in 10 (2.5%) patients (all Grade 1). There were 6 (1.6%) Grade 3 events and no Grade 4 events in the sorafenib group; there were no Grade 3 events and 1 Grade 4 event reported in the placebo group. Twelve (3.1%) hemorrhagic events in sorafenib patients and 4 (1.0%) in placebo patients were reported as serious adverse events. There was one fatal hemorrhagic event in each arm: pleural hemorrhage in a placebo patient and bronchopulmonary hemorrhage in a sorafenib patient. Most of the serious adverse reports occurred in sites of metastatic disease or previous radiation therapy. There was no apparent site-specific pattern of bleeding according to the applicant. In sorafenib patients, serious adverse events in the hemorrhage category included pulmonary, respiratory tract, or bronchopulmonary hemorrhage in a total of 4 patients, hemorrhage-other in 3 patients, CNS hemorrhage in 1 patient, and bleeding from the nose, duodenum, rectum, anus, and genitourinary tract in 1 patient each. Hemorrhagic events led to permanent discontinuation of study drug in 3 sorafenib patients (CNS hemorrhage, respiratory tract hemorrhage, and hemorrhage-other), and 1 placebo patient (pulmonary hemorrhage).

Reviewer comments: This reviewer searched for hemorrhage, spelled various ways, or bleeding as part of the MEDDRA Preferred Term (called _M_LLT) or the NCI CTC term (called _ETOXCOD) in the define variables listings. A total of 82 events in 73 patients were identified. There were 22 placebo patients and 51 sorafenib patients. In the placebo patients, the bleeding sites/descriptions commonly reported included the nose, mouth, hemoptysis, hematuria, and gastrointestinal (GI). One subungual hemorrhage (nail bed bleeding) was reported in a placebo patient from France. Among the sorafenib patients, subungual hemorrhage (also called splinter hemorrhages) were described in 11 French patients and 1 Australian as isolated sites of hemorrhage. Two other French patients had subungual hemorrhages described along with an additional lower GI bleeding site. Removing the subungual hemorrhage patients, there remain 21 placebo and 39 sorafenib patients, similar to the applicant's analysis. Notably, while no organ system was predominant in the bleeding events, many could be considered as related to mucosal

surfaces. There were 6 (1.6%) Grade 3 hemorrhage events and no Grade 4 events in the sorafenib group; there were no Grade 3 events and 1 Grade 4 event reported in the placebo group. Platelet function studies such as [ ] testing was not performed in the phase 2 or 3 studies but should be examined since the pattern of mucosal bleeding may result from impaired platelet function. Also, these mucosal surfaces experience continuous turnover and require sustaining blood flow; VEGF inhibition may compromise this capability in some way.

WOUND HEALING:
In the phase 3 study, a separate CRF page was used to capture details regarding all interventional procedures occurring during the study. There were 38 patients (9.9%) in the placebo group and 40 patients (10.4%) in the sorafenib group who underwent some procedure during the study. The most common procedure was biopsy, which was performed in 9 placebo patients and 7 sorafenib patients. Other diagnostic procedures included endoscopy, bronchoscopy, and fine needle aspiration. Minimally-invasive therapeutic procedures included thoracentesis, paracentesis, nephrostomy insertion, and stent insertion. Open surgical procedures included laparotomy (1 placebo patient and 2 sorafenib patients), spine surgery (1 placebo patient), nephrectomy (3 placebo patients), amputation (1 placebo patient),and lung resection (1 placebo patient). Unknown or unspecified procedures, or "procedures-other" were reported in 9 placebo patients and 18 sorafenib patients. Among the sorafenib patients, "other" procedures included lower lip biopsy, hernia repair, oral surgery, small bowel resection, laminectomy, bone pinning, clavicle repair, and hip fixation. There were no cases of post-operative wound dehiscence or other wound complications. No formal studies of the effect of sorafenib on wound healing have been conducted.

Based on the above, the applicant recommends (see label) temporary interruption of sorafenib therapy in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of re-initiation of sorafenib therapy following surgical intervention. Therefore, the decision to resume sorafenib therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Reviewer comment: The applicant does not specify the timing of discontinuation or resumption of sorafenib therapy in surgical situations. There is no evidence on which to base a recommendation.

NEUROPATHY:
Motor and sensory neuropathies were reported during the phase 3 study. Motor neuropathy was uncommon. There were 7 patients (1.8%) in the sorafenib arm and 1 (0.3%) in the placebo arm with motor neuropathy. The placebo patient and 5 of the sorafenib patients had grade 1 motor neuropathy, defined as asymptomatic weakness identified by examination. Two sorafenib patients had Grade 2 motor neuropathy, defined as symptomatic weakness interfering with function.

Treatment-emergent sensory neuropathy was reported in 39 sorafenib subjects (10.2%) and 14 placebo subjects (3.6%). Grade 1 events, defined by CTCAE Version 3.0 as asymptomatic loss

of deep tendon reflexes or paresthesia not interfering with function, were reported in 32 (8.3%) sorafenib subjects and 10 (2.6%) placebo subjects. Grade 2 sensory neuropathy, defined as sensory alteration or paresthesia interfering with function but not interfering with activities of daily living, occurred in 5 (1.3%) sorafenib subjects and 3 (0.8%) placebo subjects. There were 2 subjects in the sorafenib group and 1 subject in the placebo group with Grade 3 sensory neuropathy. Neuropathy did not lead to permanent discontinuation of study drug in any subjects. In 1 subject, sensory neuropathy (Grade 1) led to reduction in dose of sorafenib. The neuropathy resolved after 1 week.

The events of sensory neuropathy occurred early in the course of sorafenib therapy. In sorafenib patients, 24 events were reported in Cycle 1, 5 events were reported in Cycle 2, 4 events each were reported in Cycles 3 and 4, and no events were reported thereafter. These data suggest that sorafenib is not associated with cumulative neurologic toxicity. The sensory neuropathy may possibly be related to a dermatologic or vascular effect of sorafenib such as hand foot syndrome. This was supported by anecdotal reports from investigators who noted that sensory neuropathy occurred after hand foot skin reaction had resolved in a number of patients. Analysis of the correlation of sensory neuropathy of any grade with hand foot skin reaction revealed that hand-foot skin reaction was reported in approximately half of the patients with sensory neuropathy (18 patients, 48.6%). It is conceivable that hand foot skin reaction was reported as sensory neuropathy in some patients rather than as a dermatologic event. In addition, it is possible that neuropathy is a sequela of inflammation due to hand foot skin reaction.

Reviewer comment: Neuropathy associated with other chemotherapy agents such as the vincas, taxanes, and bortezomib, which appears to result from direct damage to neurons, usually occurs upon continued exposure, is progressive until the drug is stopped, then slowly resolves. The mechanism of sorafenib-related sensory neuropathy is uncertain.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no withdrawal or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

There is no human reproduction and pregnancy data.

7.1.15 Assessment of Effect on Growth

There is no assessment of effects on growth or pediatric experience.

7.1.16 Overdose Experience

There is no overdose experience known to the applicant.

7.1.17 Postmarketing Experience

There is no postmarketing experience as the drug has not yet been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

At the time of this NDA submission, there were 1219 patients from completed, single agent studies who received sorafenib, including the 384 patients in the single phase 3 study. All patients in the phase 3 and 2 studies received the fixed dose of 400 mg BID. In the phase 3 study, the mean duration of therapy is 136 days (SD 13 days) and the range is 5-399 days to the time of data cutoff.

Table 25: Duration of exposure in single agent studies

	Any Exposure	≥6 Months	≥12 Months
Phase I	197	33	13
Phase II	638	135	23
Phase III	384	85	6
Total	1219	253	42

Sponsor's table 1-23, module 2.7.4, page 41

7.2.1.2 Demographics

Please see section 6.1.4 for this information.

7.2.1.3 Extent of exposure (dose/duration)

In the phase 3 study, the mean treatment duration was 13.4 weeks for placebo versus 19.4 weeks for sorafenib. Median treatment duration was 9.2 weeks for placebo and 18.0 weeks for sorafenib. The median daily dose taken in the sorafenib group was 791 mg/day. In the placebo group, the median number of pills taken per day was 3.9. Dosing with study drug was reduced or interrupted for toxicity in 26 subjects (7%) in the placebo group and 76 (20%) in the sorafenib group.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.2.1 Other studies

Phase 1 and phase 2 clinical study reports were included in the application. These were reviewed in summary form.

7.2.2.2 Postmarketing experience

There is no postmarketing experience.

7.2.2.3 Literature

The applicant's literature review is thorough and timely. The information in the phase 3 clinical study report is the most detailed and informative critical assessment of the safety of sorafenib yet available.

7.2.3 Adequacy of Overall Clinical Experience

The single fixed-dose schedule selected did achieve inhibition of the relevant targets in pre-clinical models and was appropriately chosen for a balance of toxicity and efficacy. The phase 2 and phase 3 studies achieved similar exposure times which are primarily limited by the duration of anti-cancer treatment benefit. Most patients tolerated the full, intended dose without interruption or reduction. Overall, the AEs were modest and manageable. New and unique adverse events were elicited and likely represent fairly the expected toxicities of the drug. The total number of patients with drug exposure of 6 months or more is adequate for an oncology drug assessment. Possible long-term toxicities are not assessable in an exposure of this type. The protocol exclusions are plausible and would likely have confounded the assessment of the drug's benefit. This phase 3 study is one of the largest conducted in advanced RCC.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see the pharmacology review section.

7.2.5 Adequacy of Routine Clinical Testing

The frequency and content of the routine clinical testing is adequate to assess the drug.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see sections 5 and 8.2.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The placebo-controlled phase 3 trial provides high quality evidence to discriminate adverse effects which are disease related and drug related. Notably, a number of AEs in the placebo arm were attributed to study drug including neuropathy, hand-foot syndrome, and hemorrhage. The applicant was aware of VEGF inhibitor class toxicities; monitoring and reporting of these is satisfactory. Close monitoring of blood pressure during the initiation of sorafenib may be helpful in calling attention to and prompting therapy of associated elevations in blood pressure.

Other class effects observed with other agents in the VEGF inhibitor category include arterial thrombotic events and impaired wound healing. In this phase 3 study, it was unusual for patients to have invasive procedures performed ("open" or "other" surgical procedures occurred in 16 placebo patients and 20 sorafenib patients). While there were no cases of post-operative wound dehiscence or other wound complications reported, the possibility of some impairment in wound healing is not excluded by this study. Cardiac ischemia/infarction was reported as an adverse event in 6 subjects (1.6%) in the sorafenib group and 2 subjects (0.5%) in the placebo group. One of these events, in a placebo subject, resulted in death. One cardiac ischemia event in each treatment group led to permanent discontinuation of study drug. In 4 sorafenib subjects, cardiac ischemia events were reported as serious adverse events. These serious adverse events, which all resolved, were reported in men with cardiac risk factors. Central nervous system ischemia was reported in 3 subjects in the placebo group and in no subjects taking sorafenib.

Reviewer comments: The patient population is similar in age to the bevacizumab population in which higher event rates for wound dehiscence, hemorrhage, and thrombotic events occurred; however, the total number of patients and duration of exposure is less for sorafenib at this time.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data are excellent. Missing assessments were very uncommon. The dates of the first and second on study assessments (6 and 12 weeks on study, when tumor measurements were most important) were almost identical (within 1 day). Audited case report forms and narratives were complete and succinct. Inquiries to the applicant were answered promptly and satisfactorily.

7.2.9 Additional Submissions, Including Safety Update

The 120 day safety update was submitted in early October, 2005, as planned. The report provides additional data from the phase 3 study using a data cutoff date of May 31, 2005. As of 31 May 2005, 903 patients were randomized. One patient in Study 11213 was randomized to placebo but withdrew consent before receiving any study medication; therefore 902 patients were valid for safety analysis: 451 patients received sorafenib, and 451 patients received placebo. As of 31 May 2005, treatment durations were longer than in the earlier report. The median treatment duration

was 23.3 weeks for the sorafenib group and 12.0 weeks for the placebo group. Similarly, the mean treatment duration was 25.4 weeks for sorafenib and 15.5 weeks for placebo.

A comparison of the rates of adverse events between the 28 Jan 2005 database and the 31 May 2005 database reveals that the rate of treatment-emergent adverse events increased by approximately 10% in both treatment groups, while the proportionate ratios were very similar. One adverse event in which the difference between sorafenib and placebo appears more pronounced is fatigue, which was reported in 165 (36.6%) sorafenib patients and 125 (27.7%) placebo patients as of 31 May 2005; the rates had been 26.3% versus 23.4% for sorafenib and placebo, respectively, in the original analysis. (According to the applicant, when adjusted for patient-weeks of therapy, the rates of fatigue are similar in both groups.)

As of 31 May 2005, Grade 3 treatment-emergent adverse events were reported in 139 (30.8%) sorafenib patients and 97 (21.5%) placebo patients, while Grade 4 events were reported in 32 (7.1%) sorafenib patients and 27 (6.0%) placebo patients. The five most common drug-related adverse events, reported in >20% of patients, were diarrhea, rash, fatigue, hand-foot skin reaction, and alopecia. Serious adverse events (SAEs) were reported in 153 (33.9%) sorafenib patients and 110 (24.4%) placebo patients.

Table 26: Treatment-Emergent Serious Adverse Events Reported in at Least 1% of Patients in Any Treatment Group

	As of 28 Jan 2005 Sorafenib		Placebo		As of 31 May 2005 Sorafenib		Placebo	
	N = 384		N = 384		N=451		N=451	
NCI-CTCAE Term	n	%	n	%	n	%	n	%
Any Serious Adverse Event	91	(23.7)	68	(17.7)	153	(33.9)	110	(24.4)
Blood/bone marrow								
Decreased hemoglobin	4	(1.0)	9	(2.3)	8	(1.8)	11	(2.4)
Cardiac:								
Cardiac ischemia/infarction	4	(1.0)	2	(0.5)	11	(2.4)	2	(0.4)
Cardiopulmonary arrest	1	(0.3)	1	(0.3)	5	(1.1)	1	(0.2)
Hypertension	3	(0.8)	0	(0.0)	5	(1.1)	0	(0.0)
Death								
Death not associated with NCI-CTCAE term; Disease progression NOS	4	(1.0)	5	(1.3)	11	(2.4)	10	(2.2)
Constitutional symptoms								
Fatigue	4	(1.0)	3	(0.8)	7	(1.6)	4	(0.9)
Constitutional symptoms – other	8	(2.1)	5	(1.3)	10	(2.2)	7	(1.6)
Gastrointestinal								
Vomiting	1	(0.3)	3	(0.8)	2	(0.4)	5	(1.1)
Constipation	4	(1.0)	0	(0.0)	4	(0.9)	2	(0.4)
Metabolic/laboratory								
Hypercalcemia	0	(0.0)	1	(0.3)	3	(0.7)	6	(1.3)
Musculoskeletal/soft tissue								
Fracture	4	(1.0)	3	(0.8)	7	(1.6)	5	(1.1)
Musculoskeletal – other	1	(0.3)	4	(1.0)	2	(0.4)	4	(0.9)
Neurology								
Neurology - other	3	(0.8)	4	(1.0)	4	(0.9)	6	(1.3)
Pain								
Pain, tumor pain	6	(1.6)	3	(0.8)	7	(1.6)	4	(0.9)
Pain, abdomen NOS	4	(1.0)	1	(0.3)	4	(0.9)	1	(0.2)
Pulmonary/upper respiratory								
Dyspnea	4	(1.0)	4	(1.0)	11	(2.4)	8	(1.8)
Pleural effusion	4	(1.0)	3	(0.8)	8	(1.8)	4	(0.9)
Pneumonitis	4	(1.0)	1	(0.3)	6	(1.3)	1	(0.2)
Pulmonary – other	2	(0.5)	4	(1.0)	5	(1.1)	4	(0.9)
Renal/genitourinary								

Renal Failure	2	(0.5)	3	(0.8)	8	(1.8)	2	(0.4)
Renal-other	3	(0.8)	0	(0.0)	4	(0.9)	2	(0.4)
Vascular								
Thrombosis/embolism	0	(0.0)	2	(0.5)	4	(0.9)	5	(1.1)

sponsor's table 4-8, four month safety update

Adverse events leading to drug discontinuation occurred in 46 sorafenib patients and 37 placebo patients. No unusual pattern of discontinuation was present. As of 31 May 2005, 97 sorafenib patients had at least one dose interruption due to adverse events. The most common reasons for temporary discontinuation of sorafenib were hand foot skin reaction (22 patients) and diarrhea (15 patients). Most of these patients had a reduction of dose upon resumption of sorafenib. In total, dose reductions due to adverse events were reported in 58 sorafenib patients. The most common events leading to dose reductions were hand foot skin reaction (24 patients) and diarrhea (10 patients). Hypertension led to dose interruption in 8 patients and dose reduction in 5 patients treated with sorafenib. Laboratory changes were similar to those reported in the NDA.

Hemorrhage/Bleeding: bleeding events were reported in 69 (15.3%) sorafenib patients and 37 (8.2%) placebo patients. The large majority were grade 1 and 2. The most common AE term was hematoma, all Grade 1, which was reported in 19 (4.2%) sorafenib patients and 5 (1.1%) placebo patients. The second most common bleeding event was categorized in CTCAE as "Hemorrhage-other." The 19 cases of "Hemorrhage-other" in the sorafenib group included 9 cases of Grade 1 subungual hemorrhage (all reported in France), 3 cases of hemoptysis (one of which was Grade 2 and two of which were Grade 1), 2 cases of gastrointestinal bleeding (one of which was Grade 1 and one was Grade 2), 1 case each of gum bleeding, hemorrhoidal bleeding, hematuria, and epistaxis, and 1 case of Grade 5 esophageal bleeding associated with progress patients. In addition, there were two other patients in single agent sorafenib studies with SAEs in the Hemorrhage category: a case of recurrent hemoptysis, ultimately fatal, in a patient with squamous cell NSCLC and a case of Grade 4 hematemesis, which resolved, in a patient with hepatocellular carcinoma.

Wound healing: Gastrointestinal perforation and wound dehiscence have been reported in patients treated with the anti-angiogenic agent bevacizumab. The data do not suggest an impairment of wound healing in patients who have undergone surgery while taking sorafenib. In total, there were 70 patients in the sorafenib group and 72 patients in the placebo group who underwent a surgical procedure while on study. Most of the procedures were relatively minor, including biopsies, thoracentesis, paracentesis, endoscopy, and central intravenous catheter placement. The incidence of more invasive surgeries such as cholecystectomy, laparotomy, and orthopedic surgery was well balanced between the two treatment groups.

For the purposes of this update, the applicant performed a search of the sorafenib safety database for events of wound healing impairment, impaired healing, and wound infection was performed. Seven cases of wound healing complications were identified: Six in patients treated with sorafenib and 1 in a placebo patient. Three of these events were reported in patients who were being treated in Study 100375, in which patients received sorafenib in combination with carboplatin and paclitaxel, although one of these patients was being treated with single agent

sorafenib at the time of the event. Two of these cases (100375-002-048 and 100391-001-107) were previously noted in the NDA submission; however, all 7 cases had multiple co-existing conditions capable of contributing to the wound healing delay such as concomitant chemotherapy, infection, tumor in the wound, or prior radiation to the wound site. The role of sorafenib in these cases is not likely rrelevant.

Thromboembolism: In order to examine the rates of thromboembolic disease in Study 11213, the sponsor searched adverse event terms in the CTCAE categories "Vascular," "Neurology," and Cardiac-general" for terms including "infarction," "ischemia," "thrombosis," and "infarction." The rates of venous thrombosis, cerebrovascular thrombosis, and peripheral arterial thromboembolic events in Study 11213 were similar to those observed in the earlier summary. As of the earlier data cutoff, 28 Jan 2005, there were 6 treatment-emergent adverse events of cardiac ischemia/infarction in the sorafenib group and 2 cases in the placebo group. At the time of this update, a total of 13 cardiac events have now been observed on the sorafenib arm versus 2 on the placebo arm. The numbers of patients with cardiac events are higher in the sorafenib arm at each time point.

Table 27: Thromboembolic and Ischemic Treatment Emergent Adverse Events in phase 3 Study as of 31 May 2005 (Population: Patients Randomized)

	Sorafenib N=451				Placebo N=452			
	Any		Fatal (Grade 5)		Any		Fatal (Grade 5)	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac ischemia/infarction	13	(2.9)	3	(0.7)	2	(0.4)	1	(0.2)
CNS ischemia	1	(0.2)	0	(0.0)	4	(0.9)	0	(0.0)
Thrombosis/embolism	6	(1.3)	0	(0.0)	6	(1.3)	0	(0.0)
Thrombosis/vascular access	3	(0.7)	0	(0.0)	1	(0.2)	0	(0.0)
Vascular-other	3	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Phlebitis	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral arterial ischemia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

sponsor's table 6-4, three month safety update

Table 28: Cardiac history and events on Sorafenib study arm in phase 3 study 11213

patient number	age / gender	prior C-V history	Event on study /day	Outcome
024-026	69/ M	CAD, chol, arrhythmia	chest pain / 105	resolved
028-005	59/ M	HTN, DM,	acute MI / 266	death
128-004	52/ M	HTN	acute MI / 222	resolved
203-010	72/ M	Edema, on furosemide	cardiac arrest / 96	death
258-008	55/ M	HTN, DM	acute MI / 282	death
276-004	55/ M	none	acute MI / 144	resolved
290-003	66/ M	CAD, HTN	cardiopulmonary failure / 403	death
458-005	62/ M	CAD, HTN	cardiac ischemia/85	resolved
478-006	50/ M	CAD, HTN, arrhythmia	acute MI / 146	death
023-006	59/ M	HTN, DM	chest pain / 209	resolved
026-204	71/ M	CAD, HTN, arrhythmia	acute MI / 209	resolved
151-001	69/ M	DM, CHF	acute MI / 142	resolved
429-007	57/ M	CAD	acute MI / 99	resolved
290-014	64/ M	CAD, HTN	acute MI / 20	resolved
404-001	66/ M	HTN	acute MI / 156	death

abbreviations: C-V = cardiovascular; CAD = coronary artery disease; chol = elevated cholesterol; HTN = hypertension; DM = diabetes mellitus; MI = myocardial infarction; CHF = congestive heart failure;
Reviewer's table, adapted from sponsor table 6-5, three month safety update

Reviewer comment: Continued monitoring for cardiovascular safety events is necessary. Most of these patients had pre-existing cardiovascular disease, and survival was longer on the sorafenib study arm (which may allow a time bias), but the acute MI events are concerning. Closer monitoring and management of blood pressure elevations may be helpful.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the phase 3 study, 384 RCC patients received sorafenib and comprise the principal safety population for analysis. The phase 1 experience was comprised of 197 patients of various tumor types which led to the selection of the subsequent fixed dose schedule. The phase 2 randomized discontinuation study enrolled 202 RCC patients. In the phase 3 study, the mean duration of therapy is 136 days (SD 13 days) and the range is 5-399 days to the time of data cutoff. Among all studies, 253 patients received sorafenib for at least 6 months and 42 patients received more than 12 months therapy. In the phase 3 study, the mean treatment duration was 13.4 weeks for placebo versus 19.4 weeks for sorafenib. Median treatment duration was 9.2 weeks for placebo and 18.0 weeks for sorafenib. The median daily dose taken in the sorafenib group was 791 mg/day based on pill counts and compliance estimates. In the placebo group, the median number

of pills taken per day was 3.9. Dosing with study drug was reduced or interrupted for toxicity in 26 subjects (7%) in the placebo group and 76 (20%) in the sorafenib group.

AEs tended to appear in the early weeks of therapy; there were no toxicities which appeared to be cumulative or progressive over time. AEs were defined and reported on case report forms in accordance with the standard oncology reporting system, NCI CTCAE version 3, by the site investigators who were blinded to the therapy.
The principal AEs of concern include:

- Dermatologic: reversible skin rashes, most often described as a maculopapular erythematous eruption on the scalp, face, and trunk (34%), and hand-foot syndrome in 27% are common on sorafenib therapy, probably are related to the kinase-inhibiting activity, and are dose-limiting
- Hypertension: At baseline, 7.5% of both study arms had systolic BP values of 160 mm Hg or greater; medication therapy for increased blood pressure was instituted during therapy in 14% of sorafenib patients compared to 3% of placebo patients
- Diarrhea: although a common AE (33% with sorafenib versus 10% with placebo), management was usually successful without dose reduction
- Neuropathy: sensory neuropathic changes were reported for 10% of sorafenib patients versus 3.6% on placebo
- Alopecia, pruritis, and oral mucositis also were observed more frequently on the sorafenib treatment arm

Grade 3 and 4 AEs were unusual; only one occurred at 5% or greater, hand-foot syndrome

Notable laboratory findings include asymptomatic hypophosphatemia in 40% of sorafenib patients versus 7% in the placebo arm, elevation of serum lipase in 39% of sorafenib patients versus 24% in the placebo arm, and lymphopenia in 8% of sorafenib patients versus 5% of placebo patients. Grade 4 pancreatitis, defined by CTC as "life-threatening," was reported in 2 sorafenib patients although both patients subsequently resumed sorafenib, one a full dose. Sorafenib did not cause important reductions in blood counts or infectious complications when compared to placebo.

The elevated lipase findings are unusual and unexplained. Amylase elevations occurred approximately equally on both study arms. Pancreatic involvement by tumor (assessed primarily by CT scans) was not the explanation where this considered for several patients. In a patient with abdominal pain, making a diagnosis of pancreatitis could be confounded by these "spurious" elevations, and laboratory findings of elevated lipase and/or amylase should at least be considered as possibly occurring independently of a clinical process such as pancreatitis. One of three patients diagnosed as having pancreatitis in the phase 3 study, who was described as asymptomatic, likely had only the laboratory findings; this occurred relatively early in the study, before the frequency of these abnormal lipase findings were appreciated.

Please see the summary table in section 7.4.3 regarding causality.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable. The phase 3 study design (single study) provides a much higher level of confidence in the findings that the phase 2 study.

7.4.1.1 Pooled data vs. individual study data

Only the phase 3 single study provides the opportunity for comparison with a placebo control to discriminate the drug toxicities from the disease toxicities. A pooled analysis of the phase 1 toxicities noted a clear increase in severe (Grade 3 and 4) drug-related adverse events at the higher dose levels (600 mg bid; 45%; 800 mg bid 61.5%) as compared to lower dose levels (100 mg bid: 23.8%; 400 mg bid: 29.2%). Drug-related diarrhea, stomatitis, fatigue, palmar-plantar erythrodysesthesia, alopecia, pruritis and skin reaction all showed a dose-relationship. Doses up to 400 mg bid were better tolerated than 600 mg bid. The dose of 800 mg bid was poorly tolerated. There was an increase in serious adverse events with increase in dose, with the incidence rate being 19.0% at 100 mg bid, 14.6% at 400 mg bid, 22.5% at 600 mg bid and 30.8% at 800 mg bid.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

Drug plasma levels were not performed in the phase 2 or 3 studies for correlation with AEs. The placebo-controlled experience in phase 3 as described elsewhere is the strongest evidence for the relationship of AEs to the drug treatment. All of the toxicities of special interest – hypertension, hand-foot syndrome, and lab abnormalities (lipase, phosphate, and lymphopenia) occurred early in the therapy (cycles 1-3). While some differences in frequency of AEs occurred in different age groups (see 8.3, special populations), there was no clear predictive or mechanistic pattern evident.

7.4.2.1 Explorations for dose dependency for adverse findings

Dose reductions due to adverse events occurred in 9 (2.3%) placebo patients and 40 (10.4%) sorafenib patients. For sorafenib patients, the most common events that led to dose reductions were hand-foot skin reaction (18 subjects, 4.7%), diarrhea (5 subjects, 1.3%), and rash/desquamation (5 subjects, 1.3%). In some patients, dose reductions were attributed to more than 1 event (e.g., hand foot skin reaction and rash). No other adverse events led to dose reduction in more than 4 patients in either treatment arm.

Dose interruption for adverse events was reported in 16 placebo patients (4.2%) and 55 sorafenib patients (14.3%). The most common events resulting in dose interruption in the sorafenib group

were hand-foot skin reaction (17 patients, 4.4%), diarrhea (8 patients, 2.1%), hypertension (5 patients, 1.3%), and rash/desquamation (5 patients, 1.3%). No other adverse events led to dose interruption in more than 4 patients in either treatment arm. Diarrhea was the most common reason for dose interruption in the placebo arm (4 subjects, 1.0%).

7.4.2.2 Explorations for time dependency for adverse findings

The applicant performed analyses of time dependence for the toxicities of special interest. All of these toxicities of special interest – hypertension, hand-foot syndrome, sensory neuropathy, and lab abnormalities (lipase, phosphate, and lymphopenia) occurred early in the therapy (cycles 1-3) and were not progressive or cumulative.

7.4.2.3 Explorations for drug-demographic interactions

Not performed.

7.4.2.4 Explorations for drug-disease interactions

Not performed.

7.4.2.5 Explorations for drug-drug interactions

Not applicable.

7.4.3 Causality Determination

The placebo controlled trial is the strongest design from which to infer causality. The following table highlights the important differences observed between the two study arms:

Table 29: Clinically relevant safety differences observed between sorafenib and placebo study arms

Event	Sorafenib	Placebo
	n (%)	n (%)
Permanent discontinuation due to AE	24 (6)	28 (7)
Dose interruption due to AE	55 (14)	16 (4)
Dose reduction due to AE	40 (10)	9 (2)
Grade 3-4 AEs	116 (30)	83 (22)
Hypertension AE	41 (11)	3 (1)
Hypertension grades 3-4 AE	9 (2.4)	1 (0.3)
Hand-foot skin reaction AE	103 (27)	18 (5)
Hand-foot skin reaction grades 3-4 AE	20 (5)	0 (0)
Hemorrhage AE	51 (13)	22 (5.7)
Hemorrhage grades 3-4 AE	6 (2)	1 (<1)
Hypophosphatemia grades 3-4 AE	37 (11)	6 (1.8)
Lipase elevations grade 3-4 AE	34 (10)	20 (5)
Sensory neuropathy	39 (10)	14 (3.6)
Sensory neuropathy grades 2 or 3	7 (2)	4 (1)

Reviewer's table

The frequency and severity of these events are modest when compared with typical cytotoxic chemotherapy.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Phase 1 studies identified unacceptable toxicity with 600 mg BID and a well-tolerated dose of 400 mg BID. This single, fixed dose was chosen for all subsequent studies, thus dose response explorations are not available. In phase 3, all patients started therapy with sorafenib, 200 mg tablets, taking 2 tablets each morning and evening (800 mg daily) or identical matching placebo. Dose adjustments were specified for toxicity: first reduction to 400 mg daily (one tablet every 12 hours), second reduction to 400 mg every other day, third level was to discontinue therapy. A reduced dose could be re-escalated following reduction of toxicity to grade 1 or less. Dose reductions for AEs were relatively uncommon (10% of patients) and not associated with particular demographic or disease characteristics; temporary dose interruptions for AEs occurred in 14% of patients. Permanent discontinuation was reported in 6% of patients. In patients who do not experience AEs on the standard dose, it would be of interest to attempt dose escalation. Sorafenib should not be taken with a high-fat meal.

8.2 Drug-Drug Interactions

The following medications were not permitted on the phase 2 or 3 studies:
- Rifampin, ketoconazole, itraconazole and ritonavir
- St. John's Wort

• Other investigational therapy or other approved anticancer therapy (such as immunotherapy, chemotherapy, etc) except bisphosphonates
• Bone marrow transplant or stem cell rescue
• Bevacizumab or any drugs (licensed or investigational) that target VEGF or VEGF receptors
• Anticancer chemotherapy, immunotherapy, or hormonal therapy
• Biological response modifiers, such as granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF), within 3 weeks prior to study entry or during the study; G-CSF and other hematopoietic growth factors were only permitted for the management of acute toxicity such as febrile neutropenia; they were not permitted in lieu of a required dose reduction
• Megestrol acetate or medroxyprogesterone

In vitro studies performed by the applicant:
1. In vitro studies of enzyme inhibition: Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, andCYP3A4 as indicated by Ki values of 17 μM, 22 μM, and 29 μM, respectively, and of CYP2B6, CYP2C8 and CYP2C9 with Ki values of 6, 1 - 2, and 7 - 8 μM, respectively. Sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways (Ki values: 1 – 2 μM). Sorafenib may increase the blood level of drugs that are substrates of these enzymes.
In vitro studies of CYP enzyme induction: 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.

Clinical studies:
Effect of CYP3A4 inhibitors on sorafenib: Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers, did not alter the mean AUC of a single 50 mg dose of sorafenib. Therefore, clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely.
Effect of CYP3A4 inducers on sorafenib: There is no clinical information on the effect of drugs that cause induction of CYP3A4 on the pharmacokinetics of sorafenib.
Warfarin (CYP2C9 substrate): Warfarin is primarily metabolized by the CYP2C9 pathway. In vitro, this pathway is inhibited by sorafenib. The effect of sorafenib on warfarin metabolism was evaluated by assessing normalized prothrombin time (PT-INR) in Study 11213. PT-INR was evaluated in patients on warfarin treated either with sorafenib or placebo. There was no appreciable difference in the change in PTINR from baseline in sorafenib patients compared to placebo patients. This suggests that sorafenib may not be an in vivo inhibitor of CYP2C9.

8.3 Special Populations

Both the phase 2 and phase 3 studies used a single, fixed-dose of 800 mg daily for all patients. The applicant assessed efficacy and safety by race, gender, and age in the phase 3 study. No notable differences were found. Patients with severe organ impairments were not enrolled, nor were pregnant or lactating patients enrolled. No specific demographic characteristics were identified that predicted differences in outcome. The phase 3 study is one of the largest studies in advanced RCC reported. A larger database may allow additional inferences.

Sorafenib is cleared primarily by the liver. The applicant reported that, in patients with mild (Child-Pugh A, n = 14) or moderate (Child-Pugh B, n = 8) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment.

In four Phase 1 clinical trials, the applicant evaluated sorafenib in patients with normal renal function (n = 71) and in patients with mild renal impairment (CrCl > 50 – 80 mL/min, n = 24) or moderate renal impairment (CrCl 30 – 50 mL/min, n = 4). No relationship was observed between steady state sorafenib AUC and renal function at doses of 400 mg twice daily. The pharmacokinetics of sorafenib have not been studied in patients with severe renal impairment (CrCl < 30 ml/min) or patients undergoing dialysis. (In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine.) Notably in the phase 3 trial, at the time of study entry, renal function was reduced in almost all patients (> 90% of patients) by virtue of prior nephrectomy performed for RCC.

8.4 Pediatrics

RCC is very uncommon in children. A pediatric waiver was not required because the drug has received orphan drug status.

8.5 Advisory Committee Meeting

Presentation to ODAC is not contemplated at this time. However, consultation was obtained from ODAC member Dr. Maha Hussain who reviewed a summary of the review findings. Dr. Hussain advised that the PFS improvement appears substantial enough to warrant regular approval and that the AEs in particular of hypertension, bleeding, hypophosphatemia, diarrhea, and increased lipase in addition to the possibility of thyroid dysfunction should be noted.

Consultation with a patient representative has been requested but not received at this time.

8.6 Literature Review

The applicant provided a thorough literature review of the diagnosis, staging, and therapy options for RCC and safety findings for sorafenib. The reviewer's independent literature review concurred with the applicant's description of the disease and its therapy. References are cited in the relevant introductory sections.

8.7 Postmarketing Risk Management Plan

See section 9.3.

8.8 Other Relevant Materials

DDMAC has been consulted and will report separately.

9 OVERALL ASSESSMENT

9.1 Conclusions

Advanced renal cell carcinoma (RCC) is a serious and life-threatening malignancy for which there is no therapy of general benefit to patients. While interleukin-2 has received FDA approval for this condition and interferon has been used off-label, these agents have considerable toxicity and have not shown convincing evidence for a survival benefit in controlled studies. No traditional chemotherapy agents have shown clinical benefit in a controlled study.

In this context, Bayer has submitted a single, large, double-blind, randomized, well-controlled phase 3 study in which sorafenib therapy is compared to a control group receiving placebo with best supportive care for patients with advanced RCC. Sorafenib is a new molecular entity that appears to target and inhibit certain cellular proliferative pathways. Patients were not selected on the basis of test results for these biomarkers. Efficacy is based on statistically compelling and clinically convincing evidence of improvement in progression-free survival (PFS) for RCC patients treated with sorafenib (after one prior therapy). The median PFS was improved from 84 days in the control group to 167 days for sorafenib; hazard ratio = 0.44; $p < 0.000001$. Safety is demonstrated in the context of this efficacy benefit by the low frequency and/or low severity of adverse effects, dose reductions, and withdrawals for drug-related toxicity. The magnitude and severity of adverse events observed with sorafenib are modest and credible when compared to the placebo arm of the study. Following the applicant's report of the PFS improvement, in consultation with the FDA and other agencies, the study was prematurely terminated and all placebo patients were offered the opportunity to receive sorafenib. The applicant was encouraged to prepare an NDA submission and an expanded access protocol.

While the magnitude of PFS improvement in this study is substantial, the clinical benefit conveyed by this PFS improvement is not well defined. PFS improvements have been a basis for the regular approval of hormonal therapy for advanced breast cancer as well as for accelerated approval in other disease states. In oncology, PFS is often evaluated in conjunction with response rate for confirmatory evidence of drug effect.

The objective response rate in the study is low (2.1%), as assessed by the usual oncology (RECIST) criterion (30% reduction in the sum of tumor diameters), although lesser degrees of tumor shrinkage did occur for the majority of patients as assessed by the applicant. Tumor shrinkage may not be an appropriate indicator of its effect since sorafenib is considered to act as a cytostatic agent to reduce tumor proliferation.

Overall survival, a primary study endpoint, is premature at this time to analyze but may be available in the next 3-6 months. The survival results may be able to confirm that a clear clinical benefit is conveyed by the PFS benefit of sorafenib.

9.2 Recommendation on Regulatory Action

I recommend approval of sorafenib under subpart H of 21 CFR 314, accelerated approval, for the applicant's proposed indication, the treatment of patients with advanced renal cell carcinoma (RCC), on the basis of substantial evidence of effectiveness and safety derived from a single, large, adequate and well-controlled, double-blind study comparing sorafenib with placebo for this patient population. A supportive phase 2 study is also included. Advanced renal cell carcinoma (including unresectable and metastatic disease) is a serious and life-threatening disease for which there is no standard therapy of general benefit to patients. Effectiveness is demonstrated by statistically compelling and clinically convincing evidence of prolongation in progression-free survival (PFS) for sorafenib treated patients after receiving one prior therapy as well as for a patient group who had not received previous treatment directed toward metastatic disease (the prior therapy occurred pre- or post-operatively). Safety is demonstrated in the context of this therapy by the low frequency and/or low severity of adverse effects, dose reductions, and withdrawals for drug-related toxicity. While PFS has been shown to convey clinical benefit in other disease states, this relationship has not been established for advanced RCC. Notably, the response rate is low – 2.1% – when measured using traditional RECIST criteria.

Bayer should continue to follow all patients for the survival outcome results. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted based on the completion of the survival analysis as pre-specified and provided there is no finding of an adverse survival effect of sorafenib.

The applicant examined one fixed dose schedule, 400 mg twice daily by mouth, and found it to be well tolerated by the majority of patients. Hand-foot skin reaction, blood pressure elevation, and sensory neuropathy may require interruption of therapy. Temporary dose interruptions occurred in 14% of sorafenib patients, and dose reductions were employed in 10% of sorafenib patients for AEs. The label adequately conveys the clinical information and directions for use.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Blood pressure should be monitored weekly during the first 4 to 6 weeks of treatment with sorafenib to allow detection and management of the 10% of patients who may experience hypertension on sorafenib therapy. This monitoring is described in the label. No unique risk management actions are necessary at present.

9.3.2 Required Phase 4 Commitments

Bayer should continue to follow all patients for the survival outcome results. However, given the early study termination and cross-over of patients to sorafenib, regular approval should be granted based on the completion of the survival analysis provided there is no finding of an adverse survival effect of sorafenib. The study also should continue to follow all patients to provide further experience regarding duration of exposure for sorafenib safety and tolerance.

The applicant should propose and implement a plan to monitor wound healing in a larger population of patients receiving invasive procedures on sorafenib given the bevacizumab experience and limited number of observations to date.

See section 1.2.2

9.3.3 Other Phase 4 Requests

See section 1.2.3.

9.4 Labeling Review

A detailed labeling review has been conducted.

9.5 Comments to Applicant

The applicant should propose and implement a plan to monitor wound healing in a larger population of patients receiving invasive procedures/surgery while on sorafenib given the bevacizumab experience and limited number of surgeries performed on patients receiving sorafenib to date.

The applicant should propose and implement (with FDA concurrence on the details) a plan: (1) to monitor arterial thrombosis and hemorrhage in a larger population of patients.

The applicant should perform a study of platelet function ([redacted] assay) in patients before and during sorafenib therapy to ascertain if platelet function is impaired by sorafenib.

The applicant should inform physicians specifically of the unusual findings associated with sorafenib therapy, in particular the expected elevations in lipase, reductions in phosphate, and the elevations in blood pressure which may occur.

The applicant should study further the mechanism of hypophosphatemia. If renal tubular re-absorptive function is altered by sorafenib, other substances in plasma may have altered renal handling as well.

The applicant should conduct a prospective study to assess changes in thyroid function in a cohort of sorafenib-treated patients over time. Thyroid changes and hypothyroidism were

observed in some nonclinical studies of sorafenib and are associated with tyrosine kinase inhibitory activity. Although only 2 sorafenib-treated patients were diagnosed with clinical hypothyroidism in the phase 3 study, this was not prospectively assessed in the study.

See section 1.2.3 also.

Appears This Way
On Original

10 Appendices

10.1 Review of Individual Study Reports

PHASE 3 STUDY:
The principal study for this submission is study 11213, "A Phase 3 randomized study of BAY 43-9006 in patients with unresectable and/or metastatic renal cell cancer" performed at 117 international sites including the U.S., Canada, Europe, Australia, and South America. Enrollment was from November 24, 2003 to January 28, 2005, the data cutoff date, determined by the statistical plan and projected date of disease progression in approximately 363 subjects.

This is a Phase III, double-blind, randomized, parallel-group, multicenter study comparing sorafenib plus best supportive care (BSC) to placebo plus BSC in subjects with advanced RCC who had received 1 prior regimen of chemotherapy or immunotherapy. Subjects were randomized (1:1) in a blinded computer generated central list, stratified by Motzer category and country, to receive sorafenib (400 mg twice daily, total daily dose 800 mg) or matching placebo in an uninterrupted daily schedule. For data recording purposes, the treatment period was divided into 6-week cycles for the first 24 weeks of treatment; cycles beyond 24 weeks were to be 8 weeks in duration. On progression, the blind was broken to determine the patient's protocol therapy. No subsequent cross-over to sorafenib upon progression was provided in the protocol; patients entered post-study follow-up for survival.

The primary objective is the comparison of overall survival between patients treated with sorafenib and placebo.

The secondary objectives are to compare the progression-free survival, best response rate, and changes in HRQOL and symptoms between the two groups.

Nine hundred seventy-six subjects with advanced RCC were enrolled in this study; 769 were randomized and were valid for the efficacy analyses (intent-to-treat [ITT] population) and 768 were treated with at least 1 dose of study drug and were valid for the safety analysis. Randomization was prospectively stratified according to country and Motzer prognostic criteria (low or intermediate risk). Of the 769 randomized subjects, 554 were men and 214 were women (sex for 1 subject was missing); 554 were White, and the median age was 58 years (age range: 19 to 86 years). Of the 769 subjects, 384 were randomized to sorafenib and 385 to placebo. Outpatients with documented unresectable and/or metastatic RCC, histologically or cytologically documented were permitted to enroll in the study. Eligible subjects were to have had exactly 1 prior systemic therapy for advanced disease on which the subject progressed, at least 1 unidimensional measurable lesion, intermediate or low Motzer risk score, life expectancy of at least 12 weeks, an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1, adequate hepatic function, and a prothrombin time (PT) or partial thromboplastin time (PTT) of <1.5 x upper limit of normal (ULN).

Treatment continued until the occurrence of unacceptable toxicity (thought to be related to the study drug), disease progression, withdrawal of consent, or death. Subjects from the sorafenib

treatment group could continue treatment beyond the endpoint of radiological progression at the investigator's discretion.

Radiological scans were reviewed by an independent panel of radiologists. The independent radiologists performed the review using a prospectively defined radiological charter, without knowledge of the investigators' assessments of scans. The independent radiological review data (plus data on clinical progressions and deaths without progression) were the primary data sources for the PFS analysis.

Safety: A data safety and monitoring committee reviewed periodic reports on the study. The population for safety analysis was comprised of all subjects who had received at least 1 dose of study medication. The safety of study drug was to be evaluated by documentation of all adverse events (graded according to the National Cancer Institute's [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0), changes in laboratory results (hematology, clinical chemistry, urinalysis, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature), and electrocardiograms (ECGs).

Statistical methods:
One formal analysis of PFS and one formal interim analysis and one final analysis of overall survival were planned. The analysis of PFS was to be performed when approximately 363 PFS events were observed, and was considered the final and only formal analysis for the secondary endpoint of PFS.

Primary endpoint:
All randomized subjects (ITT population) will be included in the analysis of the primary endpoint, overall survival. Subjects still alive at the time of analysis will be censored at their last date of follow-up. Overall survival in the sorafenib and placebo groups will be compared using a 2-sided log rank test with $\alpha = 0.04$ and stratified by country and Motzer prognostic risk category. A clinically meaningful improvement is being defined as a 33.3% increase in overall survival. Assuming a 2-sided alpha of 0.04, a total of 540 events are required to achieve 90% power if one interim and one final analysis are performed during this study. Overall survival data will be considered mature and the final analysis performed when 540 events have been observed. Overall survival data has not been presented in this report. The interim survival analysis is planned at 270 events.

Secondary endpoint:
The planned, single, final analysis of PFS was planned at an interim time point after 363 events (progressions or deaths); the sorafenib and placebo groups were to be compared using a 2-sided log-rank test with alpha= 0.01, stratified by country and risk category. Descriptive statistics for best overall response rate and PFS by treatment group were to be summarized within each category of the following variables: race, sex, age (<65 or ≥65 years), and Motzer risk category (intermediate or low).

Estimates of the objective tumor response rates (confirmed PR and CR according to RECIST) and their respective 95% confidence intervals were computed for each treatment group. The confirmation scan for tumor responses assessed as CR or PR was to be conducted on Day 1 of

the next cycle, as long as it was at least 4 weeks after the first scan. The objective response rates were to be compared between treatment groups using the Cochran–Mantel–Haenszel test adjusting for prognostic group (intermediate or low) and country.

Efficacy results:
This report presents the only and final analysis of progression-free survival (PFS) data. At the time of this analysis, the study remained ongoing with a primary endpoint of overall survival (OS). As of the date of this report, the study has been unblinded and is ongoing for OS.

Disease and prognostic characteristics were balanced between the study arms. Analysis of efficacy data revealed that sorafenib significantly prolonged PFS compared to placebo. Based on independent radiological assessment of scans, median PFS was 84 days in subjects randomized to placebo and 167 days in subjects randomized to sorafenib. The estimated hazard ratio for progression (sorafenib over placebo) was 0.44 ($p<0.000001$).

In addition, analyses of TTP assessed by independent radiological review and PFS assessed by investigators also revealed a statistically significant and clinically meaningful improvement in favor of sorafenib.

The effect of sorafenib on PFS was consistent among men and women, and in subjects older and younger than 65 years. Moreover, subgroup analyses across clinical characteristics including duration of disease, performance status, Motzer score, and prior cytokine therapy revealed consistent prolongation of PFS in sorafenib-treated subjects. The results were also consistent among patients who had not received any prior therapy for metastatic RCC.

Summary of safety:
This study was placebo-controlled; toxicities associated with sorafenib and events associated with underlying advanced RCC (occurring in the placebo arm) could be distinguished. Sorafenib was well tolerated, and most adverse events were Grades 1 or 2. Overall, 91% of subjects in the placebo group and 84% in the sorafenib group received more than 90% of the planned dose of study drug. Grade 3 or 4 adverse event terms that were reported at a $\geq 2\%$ higher incidence in sorafenib subjects than in placebo subjects were hand-foot skin reaction and hypertension. Subjects treated with sorafenib were found to have an increase in blood pressure, which generally occurred early in the treatment course (during the first cycle).

Although constipation, anorexia, nausea, fatigue, and anemia were relatively common adverse events, comparison with placebo revealed that these events were attributable to advanced RCC rather than to sorafenib since they were equally frequent on both arms. Adverse events under the NCI CTCAE Version 3.0 category Hemorrhage/Bleeding were reported in 11.7% of subjects in the sorafenib group and 5.2% of subjects in the placebo group. Dermatologic events represented the most common adverse event attributed to sorafenib. Although these events frequently led to temporary discontinuation or dose reduction of study drug, there were only 2 cases in which dermatologic events led to permanent discontinuation of study drug. Hair thinning or patchy hair loss was reported in 20% of sorafenib subjects, although complete alopecia was uncommon. Dermatologic toxicities were usually reversible.

Sensory neuropathy was more common in sorafenib treated subjects than in placebo subjects. Preclinical toxicology data suggest that the mechanism of the neuropathy is not related to direct toxicity to nerves. Grade 3 or 4 laboratory events occurring at ≥ 2% higher rate in sorafenib subjects than in placebo subjects were lymphopenia, neutropenia, hypophosphatemia, and increased lipase. Hypophosphatemia was also common but was not associated with clinical findings and was amenable to therapy. An increase in lipase and amylase was observed in sorafenib subjects, and clinical pancreatitis was reported in 2 subjects in the sorafenib group.

Addendum: Further enrollment to the study ceased on February 15, 2005. At that time 903 patients had been randomized.

PHASE 2 STUDY: (Randomized discontinuation design, RDD, mrr 00157)
Study 100391 began as a phase 2 study with broad eligibility seeking evidence of anti-tumor activity for patients without other therapeutic options. The study was open between September 2002 and July 2004. The initial objectives were:

- To determine the proportion of randomized patients who remain progression-free at 12 weeks post-randomization (24 weeks from study entry)
- Secondary endpoints included progression-free survival (PFS) after randomization, overall PFS from Day 1 of study treatment, tumor response rate, and safety

When responses were noted in patients with RCC, the study was amended to enroll RCC patients specifically. All patients received sorafenib, 400 mg orally (PO) bid, during a 12-week Run-in Period. At the end of this 12-week Run-in Period, antitumor responses were assessed by the investigators based upon tumor evaluation performed according to modified WHO Tumor Response Criteria (25% change):

- Subjects whose target lesion measurements increased ≥ 25% during the Run-in Period were considered to have progressive disease (PD) and were to be discontinued from the study.
- Subjects with new lesions and/or an increase in non-target lesions were also considered progressors. Subjects whose target lesions showed shrinkage of ≥ 25% during the Run-in Period were considered to be "responders" and continued sorafenib in an open label phase.
- Subjects whose target lesion measurements remained within ± 25% of the baseline pretreatment measurements were considered to have stable disease and were to be randomized 1:1 in a blinded fashion to continued sorafenib versus placebo during the 12-week Randomization Period.
- The percentage of subjects who were progression-free in the sorafenib versus placebo arms was assessed at Week 24 of the study.
- Later, time to progression during the randomized period was added as an endpoint and an independent radiologic review for response and progression was added.

Subjects who progressed during the Randomization Period were given the opportunity to cross over to sorafenib at the treating physician's discretion. If they had been randomized to sorafenib,

study medication was discontinued unless the subject had been taking sorafenib at a reduced dose; in this case the subject was permitted to increase the dose of sorafenib and continue on open label therapy.
Amendment 5 allowed for randomized subjects who had completed 12 weeks of blinded therapy (Week 24) to have their treatment assignment unblinded. Unblinded subjects who had been randomized to sorafenib could continue open label sorafenib while those who had been randomized to placebo could be crossed over to sorafenib.

Of the 202 subjects with metastatic RCC who were treated, 149 were men and 53 were women; 182 were Caucasian and the median age was 58 years (age range: 23 to 82 years). Of these, 65 subjects were randomized; 32 subjects to sorafenib and 33 to placebo. Eligibility also included measurable disease, ECOG PS 0-1, and adequate baseline organ function.

The efficacy criteria were response and progression, evaluated by the investigator using the modified WHO Tumor Response Criteria using the ITT population. For subjects with RCC an independent assessment of response was also conducted. Tumor response was evaluated at the end of 12 weeks of treatment in the Run-in Period, at the end of Week 6 and Week 12 of the Randomization Period, and every 6 weeks in the Open Label (applicable to subjects who were not randomized) and Extended Open Label Periods (applicable to subjects who were randomized).
The safety of study drug therapy was to be evaluated by careful documentation of all adverse events, vital signs and laboratory testing of renal, hepatic and hematologic function. Subjects were to be evaluated for adverse events every 3 weeks during the Run-in and Randomization Periods, and every 4 weeks during the Open Label (applicable to subjects who were not randomized) and Extended Open Label Periods (applicable to subjects who were randomized). The incidence, severity (grade according to the National Cancer Institute Common Toxicity Criteria [NCI CTC] Version 2.0) and relationship to study drug of adverse events were recorded. Following completion of treatment, a toxicity assessment was to be made 30 days after study drug was discontinued.

RESULTS:
A total of 202 RCC patients entered the initial, run-in period. 15 discontinued during this interval and 187 were assessed at week 12. At week 12, 43 went off study, 79 continued the drug, and 65 were randomized. Of the 79, 73 were judged by the investigators to have a PR or minor response. A later independent radiologic review judged 16% as responders using the non-standard (25% decrease) WHO criteria. Of the 65 randomized, 32 received sorafenib and 33 received matching placebo pills. As of July 2004, 15 patients remained on the blinded therapy; 13 patients remained on the sorafenib arm and 2 patients on placebo. The mean duration of blinded therapy with sorafenib (84 days) was longer than placebo (54 days)

For the RCC patients, the progression-free rate at the end of the 12-week randomization period (24 weeks on study) was significantly higher for the sorafenib group than for the control (placebo) group. Overall, per investigator assessment, 16 of 32 subjects (50%) with RCC randomized to sorafenib and 6 of 33 subjects (18%) with RCC randomized to control (placebo) were progression-free at 12 weeks after randomization (CMH P value = 0.0077). In addition, the

median progression-free survival (PFS) was also statistically significantly longer for subjects randomized to sorafenib (163 days) than for subjects randomized to placebo (41 days, logrank P value = 0.0001). The hazard ratio of sorafenib to placebo for PFS was 0.29. Furthermore, the median time to disease progression (TTP) was statistically significantly longer for subjects randomized to sorafenib (163 days) than for subjects randomized to placebo (42 days, P value = 0.0002). The hazard ratio of sorafenib to placebo for time to disease progression was 0.29.

Table 30: Sponsor's efficacy results for the Randomized phase of the RDD study for RCC (N=65)

	Placebo (N = 33)	**Sorafenib (N = 32)**
Number progression-free at 24 weeks	6 (18%)	16 (50%)
Progression-free Survival (days)		
n (number with followup data)	32	31
Number failed	26 (81.3%)	17 (54.8)
Number censored	6 (18.8%)	14(45.2%)
Median Days (95% confidence interval)	41(37, 75)	163 (84, 191)
Hazard ratio (sorafenib/placebo)	0.29	
P value (logrank)	0.0001	

Reviewer's table

Response rate was investigator-determined after the initial 12 weeks on therapy for all patients. Using 25% shrinkage WHO criteria, 11% (22/202) were judged as responders. An independent radiologic review was implemented during the study. A total of 152 patients were evaluable by [ ] Using the non-standard (25%) WHO criteria, the PR rate was 4%; by RECIST criteria, the PR rate was 2.5% (95% C.I. 0.8, 5.7%).

Reviewer comment: The estimated mean dose of sorafenib administered was 712 ± 158 mg over a mean number of days of 214 ± 74 days representing a mean dose intensity of 89%. However, drug accountability records were incomplete.

In the RCC group of 202 patients, there were 28 deaths within 30 days of sorafenib. None of the deaths was attributed to the drug. In 25 patients, death was attributed to progressive disease and in 3 it was related to pulmonary illnesses. AEs were the cause for treatment discontinuation in 16 patients. Dyspnea or shortness of breath led to study drug discontinuation in 3 subjects. Other adverse events leading to study drug discontinuation occurred in only 1 subject each. These events were fatigue, thoracic compression fracture, gastritis, anemia, anorexia, dehydration, rash, fever, hand-foot skin reaction, mucositis, pneumonia, hemothorax, diarrhea, edema of legs, sepsis, hyponatremia, urine retention, and hyperthyroidism

All 202 patients had at least one AE. Grade 3 or 4 AEs occurred in 133 (66%) of patients. There were 186 SAEs reported for 78 patients (39%); dyspnea, related to cancer, occurred in 21 patients (10%), pain in 5%, and infection without neutropenia in 5%

Table 31: AEs for at least 10% of patients in the RDD study safety population (N = 202)

	Any Grade	Grade 3	Grade 4
Any event	202(100%)	108 (53%)	25 (12%)
Allergy/immunology	21(10%)	0 (0%)	0 (0%)
Blood/bone marrow	63(31%)	13 (6%)	3 (1%)
Hemoglobin	54(27%)	11 (5%)	3 (1%)
Cardiovascular (general)	114(56%)	69 (34%)	2 (1%)
Edema	30(15%)	0 (0%)	0 (0%)
Hypertension	86(43%)	62 (31%)	0 (0%)
Dermatology/skin	187(93%)	34 (17%)	0 (0%)
Alopecia	107(53%)	0 (0%)	0 (0%)
Dry skin	47(23%)	0 (0%)	0 (0%)
Flushing	32(16%)	0 (0%)	0 (0%)
Hand-foot skin reaction	125(62%)	27 (13%)	0 (0%)
Dermatology/skin-other	87(43%)	0 (0%)	0 (0%)
Rash/desquamation	134(66%)	5 (2%)	0 (0%)
Constitutional symptoms	181(90%)	17 (8%)	1 (<1%)
Fever (in the absence of neutropenia)	24(12%)	1 (<1%)	0 (0%)
Fatigue (lethargy, malaise, asthenia)	147(73%)	12 (6%)	1 (<1%)
Weight loss	66(33%)	5 (2%)	0 (0%)
Constitutional symptoms-other	45(22%)	2 (1%)	0 (0%)
Gastrointestinal	192(95%)	26 (13%)	2 (1%)
Anorexia	95(47%)	6 (3%)	0 (0%)
Constipation	65(32%)	0 (0%)	0 (0%)
Diarrhea	117(58%)	8 (4%)	0 (0%)
Nausea	61(30%)	2 (1%)	0 (0%)
Gastrointestinal-other	58(29%)	6 (3%)	1 (<1%)
Stomatitis/pharyngitis	70(35%)	0 (0%)	0 (0%)
Vomiting	48(24%)	2 (1%)	0 (0%)
Renal/genitourinary	50(25%)	1 (<1%)	0 (0%)
Creatinine	29(14%)	1 (<1%)	0 (0%)
Hemorrhage	45(22%)	8 (4%)	0 (0%)
Hepatic	59(29%)	10 (5%)	0 (0%)
SGPT (ALT)	22(11%)	3 (2%)	0 (0%)
SGOT (AST)	23(11%)	3 (2%)	0 (0%)
Infection/febrile neutropenia	75(37%)	10 (5%)	0 (0%)
Infection without neutropenia	73(36%)	10 (5%)	0 (0%)
Musculoskeletal	29(14%)	3 (2%)	0 (0%)
Metabolic/laboratory	84(42%)	25 (12%)	10 (5%)
Hyperglycemia	34(17%)	5 (2%)	1 (<1%)
Hyperuricemia	26(13%)	0 (0%)	6 (3%)
Hypophosphatemia	31(15%)	14 (7%)	0 (0%)
Neurology	97(48%)	8 (4%)	4 (2%)
Neuropathy-sensory	40(20%)	0 (0%)	0 (0%)
Pain	158(78%)	22 (11%)	3 (1%)
Abdominal pain or cramping	39(19%)	4 (2%)	0 (0%)
Headache	38(19%)	2 (1%)	0 (0%)
Arthralgia (joint pain)	25(12%)	2 (1%)	0 (0%)
Myalgia (muscle pain)	22(11%)	0 (0%)	0 (0%)
Pulmonary	127 (63%)	17 (8%)	4 (2%)

Sponsor's table 12-4, study 100391, mrr 00158, page 126

Grade 3 AEs were reported in 108 subjects (54%) and Grade 4 events were reported in 25 subjects (12%). The most common Grade 3 events were hypertension (62 subjects, 31%) and hand-foot skin reaction (27 subjects, 13%). While 12% of patients reported grade 4 AEs, individual event categories were all less than 5%

For all AEs, dermatologic events were the most common adverse events, reported in 187 subjects (92.6%). Rash, generally described as a maculopapular erythematous eruption on the scalp, face, and trunk, was reported in 134 subjects (66.3%). The vast majority of these were Grades 1 or 2; Grade 3 rash was reported in only 5 subjects (2.5%). The other common dermatologic event was hand-foot skin reaction, described as palmar plantar erythema with numbness and erythema (Grade 1), pain (Grade 2), and possible blistering or desquamation interfering with activities of daily living (Grade 3). Hand-foot skin reaction occurred in 125 subjects (61.9%); 67 subjects (33.2%) were Grade 1, 31 subjects (15.3%) were Grade 2, and 27 subjects (13.4%) were Grade 3. Hand-foot-skin reaction, with or without concomitant rash, was the most frequent reason for study drug interruption or dose reduction. In 20 subjects (10%), dose of study drug was reduced as a result of hand-foot skin reaction. Study drug was discontinued and restarted in 33 subjects (16.7%) as a result of hand-foot skin reaction, and in 10 subjects (4.5%) as a result of rash or erythema without hand-foot skin reaction. Interruption and dose reduction of study drug generally led to resolution of hand-foot skin reaction and rash.

Hypertension, which occurred in 86 subjects (42.6%), was reported more often in subjects with RCC than it had been in previous sorafenib studies in other solid tumor populations. Grades 1 and 2 hypertension occurred in 9 subjects (4.5%) and 15 subjects (7.4%), respectively. Grade 3 hypertension, defined as hypertension necessitating medication or an increase in medication, occurred in 62 subjects (30.7%); there was no Grade 4 hypertension. Hypertension was attributed to study drug in most cases (71 subjects, 35.1%). The prevalence of hypertension during the Randomization Period was 11 of 33 subjects (33.3%) in the placebo arm and 13 of 32 subjects (40.6%) in the sorafenib arm. The prevalence of Grade 3 hypertension was similar in the 2 arms (8 [24.2%] in placebo, 10 [31.3%] in sorafenib; the incidence of hypertension increased slightly in subjects who were randomized to placebo and crossed over to sorafenib (5 of 26 subjects, 19.2%. The interval specific event rate of Grade 3 hypertension in non-randomized subjects was highest at Day 42 (Week 6); there were 19 events in 135 at-risk subjects (14.1%). There were only 7 new events in the 116 subjects at risk from Days 43 to 84 (6 to 12 weeks),

Hemorrhagic events were reported as serious adverse events in 4 subjects; these included Grade 3 upper gastrointestinal bleeding, Grade 3 hemorrhagic gastritis, Grade 1 hemoptysis, Grade 3 tracheostomy site hemorrhage, and Grade 5 intermittent chest wall bleeding (associated with PD and resulting in death). None of these serious adverse events were reported as related to study drug. The most common hemorrhagic event was hemorrhage-other, which was reported in 14 subjects (6.9%); 12 of these were Grade 1 and the other 2 were reported as serious adverse events as described above. Grade 1 hemoptysis occurred in 13 subjects (6.4%); in 1 subject, Grade 1 hemoptysis was considered serious (the event resolved). Other hemorrhagic events included epistaxis in 11 subjects (5.5%), rectal bleeding in 6 subjects (3.0%), hematuria in 5

subjects (2.5%), melena in 4 subjects (2.0%), hematemesis in 2 subjects (1.0%), and vaginal bleeding in 1 subject (0.5%). The majority of these events was Grade 1 and 2 and reported as unrelated to study drug.

Table 32: Laboratory toxicities by worst NCI CTC version 2 grade during the RCC study (N = 202)

	Grade 1	Grade 2	Grade 3	Grade 4
	N/N (%)	N/N (%)	N/N (%)	n/N (%)
Blood/bone marrow				
Neutrophils/granulocytes (ANC/AGC)	1/197 (0.5%)	1/197 (0.5%)	0/197 (0.0%)	2/197 (1.0%)
Hemoglobin	87/200 (43.5%)	33/200 (16.5%)	11/200 (5.5%)	3/200 (1.5%)
Lymphopenia	9/194 (4.6%)	52/194 (26.8%)	36/194 (18.6%)	0/194 (0.0%)
Platelets	29/200 (14.5%)	1/200 (0.5%)	0/200 (0.0%)	0/200 (0.0%)
Leukocytes (total WBC)	16/200 (8.0%)	3/200 (1.5%)	2/200 (1.0%)	0/200 (0.0%)
Coagulation				
Fibrinogen	0/ 1 (0.0%)	0/ 1 (0.0%)	0/ 1 (0.0%)	0/ 1 (0.0%)
Prothrombin time	18/101 (17.8%)	1/101 (1.0%)	13/101 (12.9%)	0/101 (0.0%)
Partial thromboplastin time	22/ 97 (22.7%)	4/ 97 (4.1%)	3/ 97 (3.1%)	0/ 97 (0.0%)
Renal/genitourinary				
Creatinine	62/200 (31.0%)	16/200 (8.0%)	0/200 (0.0%)	0/200 (0.0%)
Hepatic				
Hypoalbuminemia	34/198 (17.2%)	46/198 (23.2%)	8/198 (4.0%)	0/198 (0.0%)
Alkaline phosphatase	71/200 (35.5%)	8/200 (4.0%)	8/200 (4.0%)	0/200 (0.0%)
SGPT (ALT)	47/200 (23.5%)	6/200 (3.0%)	4/200 (2.0%)	0/200 (0.0%)
SGOT (AST)	47/198 (23.7%)	7/198 (3.5%)	5/198 (2.5%)	0/198 (0.0%)
Bilirubin	26/200 (13.0%)	5/200 (2.5%)	1/200 (0.5%)	0/200 (0.0%)
GGT	8/ 40 (20.0%)	6/ 40 (15.0%)	7/ 40 (17.5%)	0/ 40 (0.0%)
Metabolic/laboratory				
Amylase	7/ 37 (18.9%)	2/ 37 (5.4%)	0/ 37 (0.0%)	0/ 37 (0.0%)
Lipase	3/ 10 (30.0%)	2/ 10 (20.0%)	1/ 10 (10.0%)	1/ 10 (10.0%)
Hypercalcemia	11/200 (5.5%)	1/200 (0.5%)	3/200 (1.5%)	1/200 (0.5%)
Hypercholesterolemia	0/ 2 (0.0%)	1/ 2 (50.0%)	0/ 2 (0.0%)	0/ 2 (0.0%)
Hyperkalemia	28/200 (14.0%)	15/200 (7.5%)	2/200 (1.0%)	0/200 (0.0%)
Hypermagnesemia	1/ 12 (8.3%)	0/ 12 (0.0%)	1/ 12 (8.3%)	0/ 12 (0.0%)
Hypernatremia	23/200 (11.5%)	2/200 (1.0%)	0/200 (0.0%)	0/200 (0.0%)
Hypertriglyceridemia	0/ 2 (0.0%)	0/ 2 (0.0%)	0/ 2 (0.0%)	0/ 2 (0.0%)
Hypocalcemia	46/200 (23.0%)	22/200 (11.0%)	5/200 (2.5%)	3/200 (1.5%)
Hypoglycemia	24/180 (13.3%)	6/180 (3.3%)	0/180 (0.0%)	1/180 (0.6%)
Hypokalemia	26/200 (13.0%)	0/200 (0.0%)	1/200 (0.5%)	0/200 (0.0%)
Hypomagnesemia	2/ 12 (16.7%)	0/ 12 (0.0%)	0/ 12 (0.0%)	1/ 12 (8.3%)
Hyponatremia	45/200 (22.5%)	0/200 (0.0%)	15/200 (7.5%)	4/200 (2.0%)
Hypophosphatemia	0/188 (0.0%)	68/188 (36.2%)	33/188 (17.6%)	0/188 (0.0%)

Sponsor's table 12-9, study 100391, mrr 00158, page 141

Reviewer comments: The most common treatment-emergent metabolic laboratory abnormality was hypophosphatemia, observed in 101/188 subjects (53.7%), of whom 33 subjects (17.6%) had Grade 3 (< 2 mg/dL). In randomized subjects, hypophosphatemia was more common in the sorafenib arm (23/31, 74.2%) than in the placebo arm (10/33, 30.3%). Leukopenia and thrombocytopenia were rare, although lymphopenia was observed in 50% of patients and was

grade 3 in 19%. The mechanism of the lymphopenia is unknown. Amylase and lipase elevations also occurred; clinical pancreatitis was reported in 2 patients in the phase 2 study.

Cardiovascular: Systolic and diastolic blood pressures are summarized separately for each cycle, as are changes from baseline. There was a trend towards a 10 to 15 mmHg increase in systolic blood pressure and 5 to 10 mmHg increase in diastolic blood pressure beginning at the Cycle 2 visit (approximately 4 weeks after starting sorafenib). Blood pressures were similar among study groups and the mean blood pressure was relatively constant across subsequent cycles after Cycle two. Electrocardiogram changes were observed in 117 of 201 subjects. The most common ECG finding was bradycardia (21 subjects, 10.4%), followed by tachycardia (18 subjects, 8.9%).

Reviewer comments: The phase 2 results for efficacy and toxicity are remarkably consistent with the randomized placebo-controlled phase 3 results. The RDD design was intended to enrich the population of patients that might be capable of "responding" or benefiting from sorafenib and in this respect, did produce a group of patients (65 of the original 202) in whom the question of a continuing drug benefit could be explored. Within this randomized group of 65, those continuing on Sorafenib showed a prolongation of time to progression compared to the placebo group and more patients remained on sorafenib at week 24, 12 weeks after the randomization point. While statistically significantly different, the magnitudes of difference appear clinically modest. As is usually the case, attribution of AEs in a single arm study is difficult; while there was a group of 33 patients who were removed from active therapy at week 12, the study was too small and too brief to ascertain safety differences between the groups in the 12 week window.

Phase 1 studies: Reviewed in summary form, were not additionally helpful for safety assessment.

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