CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	21-923
Drug Name:	Nexavar (Sorafenib)
Applicant:	Bayer Pharmaceuticals Corporation
Indication(s):	Unresectable and/or Metastatic Renal Cell Cancer
Date(s):	Submission Date: July 8, 2005
	PDUFA Date: January 8, 2006
	Review Completion Date: November 21, 2005
Review Priority:	Priority
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Keywords:	Superiority, log-rank test

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1 Executive Summary

This is a review of NDA21-923 for the use of sorafenib in patients with advanced renal cell cancer (RCC) who received 1 prior regimen of chemotherapy or immunotherapy.

1.1 Conclusions and Recommendations

In this reviewer's opinion the study results from the submitted single, Phase III, double-blind, international, randomized, parallel-group, multicenter study, support the claim of efficacy of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy with respect to progression free survival (PFS). The sorafenib demonstrated a PFS advantage over the placebo in this clinical study. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

1.2 Brief Overview of Clinical Studies

This NDA submission is to support the use of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy. The submitted Study 11213 was a Phase III, double-blind, international, randomized, parallel-group, multicenter study designed to assess the efficacy and safety of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy. It is the only randomized phase III pivotal study conducted to establish efficacy and safety.

Patients were randomized (1:1) to receive sorafenib (2X200 mg tablets twice daily) or placebo in a double-blind fashion. Subjects were to remain on study drug until disease progression or discontinuation for adverse events or other reasons, and were to be followed until death.

Although PFS was defined as a secondary endpoint in the protocol, one formal analysis of PFS and one formal interim analysis of overall survival were planned in the protocol. The analysis on PFS was planned to occur after approximately 363 progressions were observed. As of January 28, 2005, a total of 342 PFS events (44.5%) occurred and the final and only formal analysis for PFS was performed. The results of the PFS analysis led to the submission of this application.

1.3 Statistical Issues and Findings

In this NDA submission, Study 11213 was the only randomized pivotal phase III study conducted to establish efficacy and safety. The efficacy analysis for the data

collected until the cut-off date of January 28, 2005 included 147 events (38.3%) for PFS in the sorafenib arm and 195 events (50.6%) for PFS in the placebo arm. A total of 342 PFS events (44.5%) occurred at the time of PFS analysis.

Statistical Issues:

Study 11213 included a pre-specified formal final analysis of progression-free survival (PFS). The results of the PFS analysis, which was performed using data available as of 28 Jan 2005, demonstrated a statistically significant prolongation of PFS in patients treated with sorafenib. In April 2005, following review of the data by the Data Monitoring Committee (DMC), the Study Steering committee, European Health Authorities, and the US FDA, a decision was made to unblind treatment allocation in Study 11213 and to offer sorafenib to patients who had been randomized to placebo.

Two-sided α of 0.01 and 0.04 were to be used for the PFS and overall survival analyses, respectively, so that the overall alpha for both the secondary endpoint PFS and the primary endpoint overall survival (OS) combined would be 0.05 or less.

The final and only formal analysis for the PFS endpoint was planned to occur after approximately 363 progressions were observed. As of January 28, 2005, a total of 342 PFS events (44.5%) occurred and the PFS analysis was performed. The results of the PFS analysis led to the submission of this application. The sponsor's study report includes the results of this PFS analysis.

In the protocol, one interim analysis of overall survival was planned when approximately 270 deaths were observed. Due to the unblinding of treatment allocation and possible crossover of placebo patients to sorafenib, on August 18, 2005, the sponsor proposed to perform one interim analysis of overall survival using 220 events with a cutoff date of May 31, 2005 and one interim analysis of overall survival when 270 deaths occur.

The crossover of placebo patients to sorafenib may dilute the effect of sorafenib on OS in favor of placebo. Therefore, the timing of the first interim analysis of OS was chosen to coincide with start of the crossover in May 2005. The second interim analysis will have a data cutoff date of November 30, 2005.

On September 16, 2005, the sponsor submitted results of the first interim OS analysis. The results showed that the statistical significance has not been reached in this interim OS analysis according to the protocol-specified alpha spending of 0.0005, although the results of this interim analysis suggested a decrease in the risk of death in patients with advanced RCC randomized to sorafenib.

Findings:

The independent radiological review data are the primary data sources for the PFS analysis. All randomized patients (ITT population) were included in the PFS analysis. The sorafenib and placebo groups were compared using a 2-sided log-rank test with $\alpha = 0.01$ stratified by country and Motzer prognostic risk category. The efficacy analysis for the data collected until the cut-off date of January 28, 2005 included 147 events (38.3%) for PFS in the sorafenib arm and 195 events (50.6%) for PFS in the placebo arm. A total of 342 PFS events (44.5%) occurred at the time of analysis. The hazard ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm, was 0.44 (p-value<0.000001, Table 1).

Table 1. Primary Efficacy PFS Analysis in ITT Population

	Sorafenib	**Placebo**
Number of patients (ITT)	384	385
Number of events (%)	147 (38.3%)	195 (50.6%)
Median[1] (days), 95% CI	167, (139,174)	84, (78, 91)
Stratified Logrank test	P<0.000001	
Hazard ratio (95% CI)[2]	0.44 (0.35, 0.55)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm.

2 Introduction

2.1 Overview

The sponsor is seeking approval of using sorafenib in patients with advanced renal cell cancer (RCC) who received 1 prior regimen of chemotherapy or immunotherapy.

Sorafenib is a multikinase inhibitor with effects on tumor proliferation and angiogenesis. Sorafenib inhibits the activity of targets present in the tumor cell, including members of the Raf family of serine/threonine kinases. In addition, sorafenib inhibits 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 -β- (PDGFR-β).

The submitted Phase III, double-blind, international, randomized, parallel-group, multicenter study was designed to assess the efficacy and safety of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy. It is the only randomized phase III pivotal study conducted to establish efficacy and safety. This review will focus on the efficacy results from the Study 11213.

2.1.1 Background

Advanced RCC, defined as metastatic and/or unresectable RCC, is a life-threatening condition with limited therapeutic options. The prognosis of patients with metastatic RCC is poor, with a median survival of 8 to 12 months and a 5-year survival of 2% to 3%. Cytokines, which have been the mainstay of therapy for RCC, are associated with significant toxicities. High dose interleukin-2, which has been approved in the US for therapy of RCC, provides clinical benefit to a relatively small percentage of patients and has limited utility due to its severe toxicity profile. Interferon alpha, which is also as widely used for RCC, is associated with a modest response rate and limited tolerability among many patients. Therapeutic options for patients who fail cytokine therapy are limited, and there are no approved treatments for cytokine-refractory RCC.

The RAS/Raf/MEK/ERK signaling pathway is an important mediator of responses to growth factors. Inhibition of this pathway through inhibition of Raf kinase activity results in anti-proliferative effects. The Raf signaling pathway has also been shown to mediate responses to vascular endothelial growth factor (VEGF), a key angiogenic factor. Sorafenib also targets angiogenesis through direct inhibition of VEGFR-2 and other receptor tyrosine kinases.

There is evidence that angiogenesis is an important pathophysiologic target in RCC. Both hereditary and sporadic RCC are associated with mutations in the von Hippel Lindau (VHL) gene and consequent overexpression of VEGF. In preclinical studies, sorafenib inhibited the growth of a murine model of renal adenocarcinoma (Renca), primarily through inhibition of tumor angiogenesis. Once daily oral dosing of sorafenib produced a dose-dependent tumor growth inhibition against subcutaneous-implanted Renca tumors ranging from 30% at a dose of 7.5 mg/kg to 84% at a dose of 60 mg/kg. Immunohistochemical staining with anti-CD-31 or anti-SMA antibodies confirmed the decrease in tumor vasculature following sorafenib treatment.

Preclinical and Phase I data demonstrated the cytostatic effect of sorafenib on tumors. Sorafenib activity in solid tumors was explored further in a number of Phase I and II trials, including a Phase II randomized discontinuation study (Study 100391), in which subjects with stable disease after a 12-week course of therapy with sorafenib were randomized to receive placebo or remain on sorafenib. Overall, 202 subjects with advanced RCC were enrolled in this trial. Study 100391 reached its primary efficacy endpoint, demonstrating a statistically significant improvement in progression-free rate at 24 weeks in RCC subjects randomized to sorafenib compared to those randomized to placebo. The study demonstrated the activity of sorafenib in RCC, and the data supported the favorable safety profile of sorafenib in subjects with advanced RCC. These data led to the design of Study 11213.

Study 11213 compared sorafenib with placebo in patients with advanced RCC who received 1 prior regimen of chemotherapy or immunotherapy. Patients received either sorafenib or placebo. Enrollment in Study 11213 began on November 24, 2003. Patients were randomized to receive sorafenib (2x200 mg tablets twice daily) or placebo. Randomization (1:1) was stratified by country and prognostic risk category (Intermediate vs. Low).

Although overall survival was the primary endpoint, a single formal analysis of PFS was planned when approximately 363 PFS events occurred, and the sponsor's study report includes the results of this PFS analysis. At the time of the data cutoff for this analysis (28 Jan 2005), 769 subjects were randomized at 117 centers in 19 countries. Of the 769 subjects, 384 were randomized to sorafenib and 385 to placebo.

2.1.2 Statistical Issues

Study 11213 included a pre-specified formal final analysis of progression-free survival (PFS). The results of the PFS analysis, which was performed using data available as of 28 Jan 2005, demonstrated a statistically significant prolongation of PFS in patients treated with sorafenib. In April 2005, following review of the data by the Data Monitoring Committee (DMC), the Study Steering committee,

European Health Authorities, and the US FDA, a decision was made to unblind treatment allocation in Study 11213 and to offer sorafenib to patients who had been randomized to placebo.

Two-sided α of 0.01 and 0.04 were to be used for the PFS and overall survival analyses, respectively, so that the overall alpha for both the secondary endpoint PFS and the primary endpoint overall survival (OS) combined would be 0.05 or less.

The final and only formal analysis for the PFS endpoint was planned to occur after approximately 363 progressions were observed. As of January 28, 2005, a total of 342 PFS events (44.5%) occurred and the PFS analysis was performed. The results of the PFS analysis led to the submission of this application. The sponsor's study report includes the results of this PFS analysis.

In the protocol, one interim analysis of overall survival was planned when approximately 270 deaths were observed. Due to the unblinding of treatment allocation and possible crossover of placebo patients to sorafenib, on August 18, 2005, the sponsor proposed to perform one interim analysis of overall survival using 220 events with a cutoff date of May 31, 2005 and one interim analysis of overall survival when 270 deaths occur.

The crossover of placebo patients to sorafenib may dilute the effect of sorafenib on OS in favor of placebo. Therefore, the timing of the first interim analysis of OS was chosen to coincide with start of the crossover in May 2005. The second interim analysis will have a data cutoff date of November 30, 2005.

On September 16, 2005, the sponsor submitted results of the first interim OS analysis. The results showed that the statistical significance has not been reached in this interim OS analysis according to the protocol-specified alpha spending of 0.0005, although the results of this interim analysis suggested a decrease in the risk of death in patients with advanced RCC randomized to sorafenib.

2.2 Data Sources

Data and electronic documents used for this review are located on the network with path \\CDSESUB1\N21923\N_000\2005-07-06" in the EDR.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The sponsor has submitted results of analyses from a single, Phase III, double-blind, international, randomized, parallel-group, multicenter study (Study 11213)

designed to assess the efficacy and safety of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy. The main focus of this review will be on the results from the analyses, particularly on the efficacy aspect of this study.

3.1.1.1 Study Design

In Study 11213, patients were randomized (1:1) to receive sorafenib (2X200 mg tablets twice daily) or placebo in a double-blind fashion. Patients were to remain on study drug until disease progression or discontinuation for adverse events or other reasons, and were to be followed up until death.

The DMC reviewed study data for clinically important differences between treatment groups in serious adverse events, toxicities, and deaths. In addition, one formal analysis of PFS and one formal interim analysis of overall survival were planned in the protocol. The analysis on PFS was planned to occur after approximately 363 progressions were observed. This was the final and only formal analysis for the PFS endpoint. The interim analysis of overall survival was planned when approximately 270 deaths were observed. The DMC was also tasked with overseeing the interim analyses and making recommendations regarding study continuation based on the interim results.

The total number of patients to be randomized in the entire study was planned at 884, in order to achieve the desired statistical power overall and at interim analysis points. As of the cutoff date (28 Jan 2005) for the PFS analysis, 769 subjects had been randomized into the study and 342 PFS events occurred.

Reviewer's Comments:

Two-sided α of 0.01 and 0.04 were to be used for the PFS and OS analyses, respectively, so that the overall alpha for both PFS and OS endpoints combined would be 0.05 or less.

3.1.1.2 Study Objectives

Study 11213 was designed to evaluate the efficacy and safety of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy.

3.1.1.3 Efficacy Endpoints

Primary Efficacy Endpoint of Study 11213 was overall survival, which is defined in this study as the time elapsed from randomization to death (from any cause).

Secondary Efficacy Endpoints included:

- To evaluate PFS in subjects treated with sorafenib compared to those treated with placebo. Progression-free survival was defined as the time from randomization to disease progression (radiological or clinical, whichever was earlier) or death (if death occurred before progression). Subjects without tumor progression or death at the time of analysis were censored at their last date of tumor evaluation.

- To evaluate best overall response rate in subjects treated with sorafenib compared to those treated with placebo.

- To assess changes in health-related quality of life (HRQOL) and symptom response in subjects treated with sorafenib compared to those treated with placebo. These data are not part of this report, but will be reported separately.

Reviewer's Comment:

The final and only formal analysis for the secondary endpoint of PFS was planned to occur after approximately 363 progressions were observed. As of January 28, 2005, a total of 342 PFS events (44.5%) occurred and the PFS analysis was performed. The results of the PFS analysis led to the submission of this application. The sponsor's study report includes the results of this PFS analysis.

In the original protocol, one interim analysis of overall survival was planned when approximately 270 deaths are observed. Due to the unblinding of treatment allocation and possible crossover of placebo patients to sorafenib, on August 18, 2005, the sponsor proposed to perform one interim analysis of overall survival using 220 events with a cutoff date of May 31, 2005 and one interim analysis of overall survival when 270 deaths occur.

Results for HRQOL have not been submitted as of the time of review. This review will focus on the PFS and OS efficacy analyses. It will briefly describe best overall response rates.

3.1.1.4 Sample Size Considerations

Sample size was based on the primary endpoint of overall survival. A clinically meaningful improvement was defined as a 33.3% increase in overall survival. Assuming a 2-sided α of 0.04, a total of 540 events were required to achieve 90% power if one interim and one final analysis were performed during this study. Overall survival data are considered mature and the final analysis performed when 540 events are observed, if the stopping rule has not been met at the interim analysis. The expected study duration was estimated at 29 months assuming subjects enroll at a rate of 50 subjects per month, an exponentially distributed event time, a 12 month median time for the control group and a 17

month long enrollment for a total of 856 subjects in the 2 treatment groups combined (428 subjects in each arm). Assuming a 3% rate for subjects lost to follow-up, approximately 884 subjects were to be randomized.

The Data Safety Monitoring Board (DSMB) reviews safety as per a separate DSMB charter approximately every 6 months. The committee included an odd number of members including but not limited to an independent statistician and oncologist. Data were reviewed for clinically important differences between treatment groups in serious adverse events, toxicities and deaths. In addition, one formal PFS analysis and one formal interim OS analysis were planned in the protocol. The PFS analysis was planned when approximately 363 progressions were observed, and a two-sided alpha of 0.01 was used for the final and only formal PFS analysis. The interim analysis of overall survival was planned when approximately 270 deaths were observed. For this overall survival interim analysis, per protocol specification, the Lan-Demets alpha spending function would determine the criteria for early stopping for efficacy so that the overall false positive rate, alpha, is less than or equal to 0.04 (two-sided). The alpha spending function is the O'Brien-Fleming type boundary. Information is based on number of events. Stopping boundaries are calculated for the interim analysis based on the actual number of events (deaths) observed up to the time of the interim analysis.

Reviewer's Comments:

As of January 28, 2005, a total of 342 PFS events (44.5%) occurred and the PFS analysis was performed. This PFS analysis included 769 subjects who were randomized into the study.

3.1.1.5 Efficacy Analysis Methods

All randomized patients (ITT population) was to be included in the PFS and OS analyses. The independent radiological review data were to be the primary data sources for the PFS analysis. The sorafenib and placebo groups were compared using a 2-sided log-rank test with $\alpha = 0.01$ stratified by country and Motzer prognostic risk category. Patients with "intermediate" risk have 1 or 2 risk factors; subjects with "low" risk have no risk factors. The relevant risk factors are: ECOG performance status ≥ 2, high LDH $> 1.5 \times$ ULN, low serum hemoglobin (< lower limit of normal), high corrected serum calcium (> 10 mg/dL), and absence of prior nephrectomy. Kaplan–Meier survival curves will also be produced

Reviewer's Comments:

Although PFS was defined as a secondary endpoint in the protocol, it was treated as a co-primary endpoint in this report because of alpha location of 0.01 to the

PFS analysis. Again, the significant PFS results led to the submission of this NDA.

3.1.1.6 Sponsor's Results and Statistical Reviewer's Findings/ Comments

At the time of the data cutoff for this analysis (28 Jan 2005), 769 subjects were randomized at 117 centers in 19 countries. Among randomized subjects, 186 (24%) were enrolled from France, 146 (19%) from the US, 117 (15%) from Poland, 57 (7%) from Germany, 56 (7%) from the United Kingdom, and 41 (5%) from Russia. All other countries contributed less than 5% of subjects each.

3.1.1.6.1 Baseline Characteristics

The baseline Characteristics of the overall population are presented in Table 2.

Reviewer's Comments:

In the overall patient population the baseline characteristics appear to be balanced between the two treatment arms.

Table 2. Baseline Characteristics of the Patients in the Study 11213

Characteristic	Sorafenib (N=384)	Placebo (N=385)	ALL (N=769)
Age — yr			
Mean (SD)	59.0 (10.0)	58.3 (9.4)	58.6 (9.7)
Median (Range)	58 (19–86)	59 (29–84)	58 (19-86)
Age grouped — no. (%)			
<65	255 (66.4)	280 (72.7)	535 (69.6)
+65	127 (33.1)	103 (26.8)	230 (29.9)
Missing	2 (0.5)	2 (0.5)	4 (0.5)
Sex — no. (%)			
Male	267 (69.5)	287 (74.5)	554 (72.0)
Female	116 (30.2)	98 (25.5)	214 (27.8)
Missing	1 (0.3)		1 (0.2)
Race — no. (%)			
Caucasian	276 (71.9)	278 (72.2)	554 (72.0)
Black	2 (0.5)	1 (0.3)	3 (0.4)
Oriental/Asian	1 (0.3)	6 (1.6)	7 (0.9)
Hispanic	7 (1.8)	3 (0.8)	10 (1.3)
Others	1 (0.3)	0	1 (0.1)
Missing	97 (25.3)	97 (25.2)	194 (25.3)
ECOG performance-status — no. (%)			
0	184 (47.9)	180 (46.8)	364 (47.3)
1	191 (49.7)	201 (52.2)	392 (51.0)
2	6 (1.6)	1 (0.3)	7 (0.9)
Missing	3 (0.8)	3 (0.8)	6 (0.8)
Motzer risk factors — no. (%)			
Low	200 (52.1)	194 (50.4)	394 (51.2)
Intermediate	184 (47.9)	191 (49.6)	375 (48.8)
RCC Subtype — no. (%)			
Clear cell	377 (98.2)	380 (98.7)	757 (98.4)
Papillary subtype	1 (0.3)	3 (0.8)	4 (0.5)
Other variant	1 (0.3)	1 (0.3)	2 (0.3)
Missing	5 (1.3)	1 (0.3)	6 (0.8)
Duration of disease — yr			
Mean (SD)	2.8 (2.9)	3.3 (3.7)	3.1 (3.3)
Median (Range)	1.6 (0.1–19.4)	1.9 (0.1–19.9)	1.8 (0.1-19.9)
Duration of metastatic disease — yr			
Mean (SD)	1.3 (1.2)	1.3 (1.3)	1.3 (1.3)
Median (Range)	0.9 (0.1–11.4)	0.9 (0.02–10.2)	0.9 (0.02-11.4)

3.1.1.6.2 Primary Efficacy Analyses

Progression-free Survival Analysis

Primary efficacy analysis in this submission is PFS analysis for the ITT population as assessed by independent radiological review. Three hundred fourty-two PFS events were independently confirmed. A stratified log-rank test was performed to compare PFS between the Sorafenbin arm and the placebo arm in the ITT population. The stratification factor were country and Motzer prognostic

risk category. Although PFS was defined as a secondary endpoint in the protocol, it was treated as a co-primary endpoint in this report because of alpha allocation of 0.01 to the PFS analysis.

The efficacy analysis for the data collected until the cut-off date of January 28, 2005 included 147 events (38.3%) for PFS in the sorafenib arm and 195 events (50.6%) for PFS in the placebo arm. A total of 342 PFS events (44.5%) occurred at the time of analysis. Medians of PFS in the sorafenib arm and the placebo arm were 167 days and 84 days respectively. The hazard ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm, was 0.44 (p-value<0.000001).

The results from the stratified log-rank test are presented in the Table 3 (same as reported by the sponsor). The Kaplan-Meier curves for the ITT population are illustrated in Figure 1.

Table 3. Primary Efficacy PFS Analysis in ITT Population

	Sorafenib	**Placebo**
Number of patients (ITT)	384	385
Number of events (%)	147 (38.3%)	195 (50.6%)
Median[1] (days), 95% CI	167, (139,174)	84, (78, 91)
Stratified Logrank test	P<0.000001	
Hazard ratio (95% CI)[2]	0.44 (0.35, 0.55)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm.

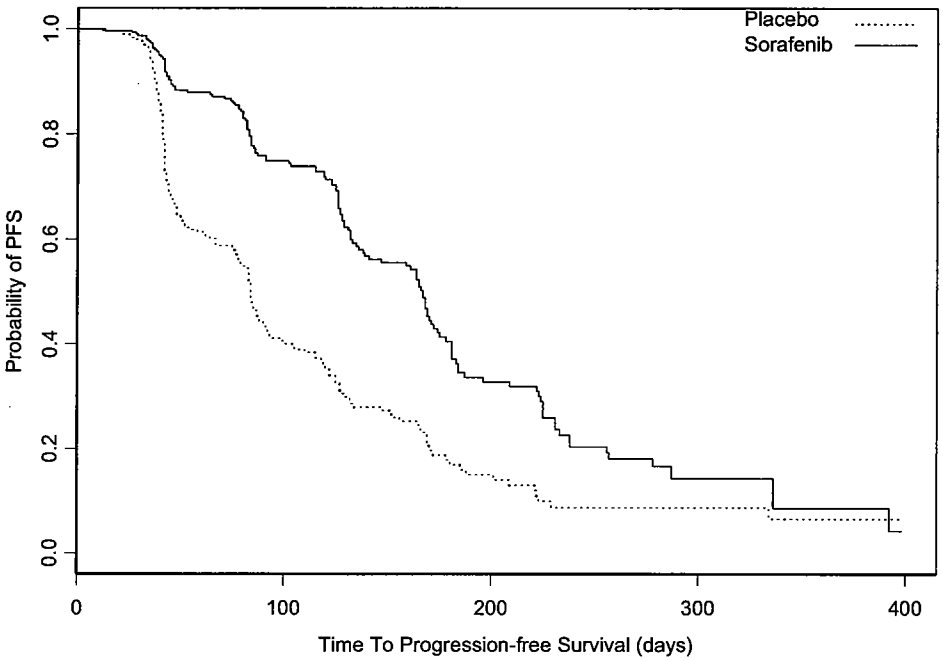

Figure 1: Kaplan-Meier Curves for PFS in the ITT Population

Reviewer's Comments:

The protocol pre-specified that two-sided α of 0.01 was used for the PFS. The analysis on PFS was planned to occur after approximately 363 progressions were observed. As of the cutoff date (28 Jan 2005) for the PFS analysis, 769 subjects had been randomized into the study and 342 PFS events occurred. The results from the PFS analysis demonstrate superiority of the sorafenib arm over the placebo arm with respect to PFS. The p-value from the unstratified log-rank test was less than 0.0001 and the unadjusted hazard ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm, was 0.456 (95%CI: 0.367, 0.567).

In April 2005, following review of these data by the Data Monitoring Committee (DMC), the Study Steering committee, European Health Authorities, and the US FDA, a decision was made to unblind treatment allocation in Study 11213 and to offer sorafenib to patients who had been randomized to placebo.

Overall Survival Analysis

According to the original protocol, one interim analysis of overall survival was planned when approximately 270 deaths were observed. After the results of PFS led to the submission of this application, on August 18, 2005, the sponsor proposed to perform one interim analysis of overall survival using 220 events with a cutoff date of May 31, 2005 and one interim analysis of overall survival when 270 deaths occur. A log-rank test stratified by country and Motzer category are used to compare patients randomized to sorafenib with those randomized to placebo. The O'Brien-Fleming type alpha spending function is used to ensure that the overall false positive rate, alpha, is 0.04 or less (two-sided). For the interim analyses, information fraction is the total number of deaths in both groups (regardless of crossover) on or before the data cutoff date divided by 540 (the protocol-specified total number of events for the study). Patients still alive at the time of OS analysis are censored at their last date of follow-up.

On September 16, 2005, the sponsor submitted results of the first interim OS analysis. As of 31 May 2005, a total of 903 patients with advanced RCC were randomized to receive sorafenib or placebo. This OS analysis included 451 patients who were randomized to sorafenib and 452 patients who were randomized to placebo.

This OS analysis included 220 deaths: 97 deaths in the sorafenib group and 123 deaths in the placebo group. They comprised 41% of the protocol specified 540 survival events. According to the pre-specified O'Brien-Fleming alpha spending function, the alpha value for this OS interim analysis is 0.0005 (twosided).

The OS results are presented in the Table 4 (same as reported by the sponsor). The Kaplan-Meier curves for the ITT population are illustrated in Figure 2.

Table 4. Overall Survival Analysis in ITT Population

	Sorafenib	**Placebo**
Number of patients (ITT)	451	452
Number of events (%)	97 (21.5%)	123 (27.2%)
Median[1] (days), 95% CI	-	446, (392, -)
Stratified Logrank test	P=0.018	
Hazard ratio (95% CI)[2]	0.72 (0.55, 0.95)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for death in the sorafenib arm, as compared with the placebo arm.

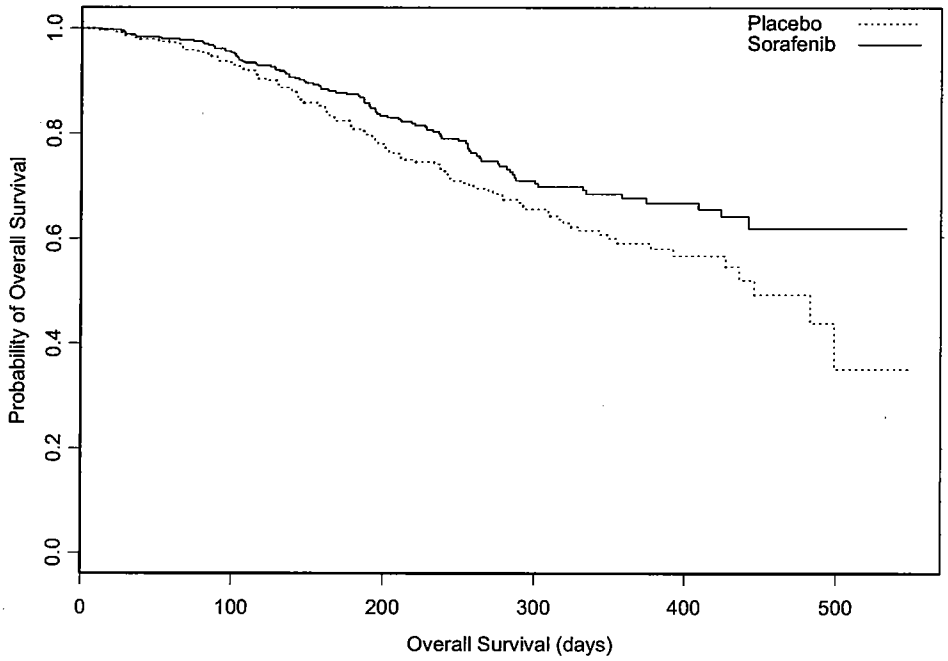

Figure 2: Kaplan-Meier Curves for OS in the ITT Population

Reviewer's Comments:

The crossover of placebo patients to sorafenib may dilute the effect of sorafenib on OS in favor of placebo. Therefore, the timing of the first interim analysis of OS was chosen to coincide with start of the crossover in May 2005. The second interim analysis will have a data cutoff date of November 30, 2005.

The results showed that the statistical significance has not been reached in this interim OS analysis according to the protocol-specified alpha spending of 0.0005, although the results of this interim analysis suggested a decrease in the risk of death in patients with advanced RCC randomized to sorafenib. The p-value from the unstratified log-rank test was 0.0136 and the unadjusted hazard ratio for death in the sorafenib arm, as compared with the placebo arm, was 0.717 (95%CI: 0.549, 0.935).

3.1.1.6.3 Secondary Efficacy Analyses

The protocol specified secondary endpoints included best overall response rate and quality of life. This section will focus on description of best overall response. At the time of data cutoff for this analysis (28 Jan 2005), 769 subjects were

randomized and therefore defined as valid for ITT: 384 in the sorafenib group and 385 in the placebo group. As per the protocol, the first post-baseline tumor evaluation was to be performed at the end of Cycle 1 (6 weeks post-randomization). There were 97 subjects (49 in the sorafenib group and 48 in the placebo group) who had been randomized within 6 weeks of the data cutoff (28 Jan 2005) and consequently did not have the opportunity to undergo a post-baseline tumor evaluation. These 97 subjects were prospectively defined (prior to unblinding) as not valid for response rate assessment, and were not included in the analysis of best response. Therefore, the population defined as valid for response assessment is 672 subjects: 335 in the sorafenib group and 337 in the placebo group.

Table 5 presents a summary of the best overall tumor response as determined by independent radiological review according to RECIST criteria. Overall, 7 (2.1%) sorafenib subjects and 0 (0.0%) placebo subjects had a confirmed PR, and 261 (77.9%) sorafenib subjects and 186 (55.2%) placebo subjects had Stable Disease. For the 7 sorafenib subjects with independently reviewed with confirmed PR, the time to response ranged from 42 to 129 days with a median of 84 days.

Table 5. Overall Best Confirmed Tumor Response by Independent Radiological Review (Using RECIST Criteria) (Population: Subjects Valid for Response Assessment)

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

3.1.6.4. Exploratory Analyses

In order to evaluate if timing of post-baseline radiological scan influenced the primary outcome the following exploratory analyses were conducted.

Time from randomization to post-baseline radiological scan was calculated. Means and standard deviations of radiological scan times are presented in Table 6.

Table 6. Mean and SD (in weeks) of Time To Raiological Scan From Randomization

Time from randomization to Radiological Scan	# of Patients		Mean (SD)	
	Sorafenib	Placebo	Sorafenib	Placebo
Week 6	294	282	6.0 (0.9)	5.9 (0.7)
Week 12	194	125	12.2 (1.2)	12.2 (1.0)
Week 18	131	61	18.2 (1.3)	18.1 (1.2)
Week 24	80	33	24.3 (1.1)	24.2 (1.0)
Week 32	36	14	31.8 (2.3)	31.9 (3.5)
Week 40	14	4	40.0 (0.8)	38.1 (2.0)
Week 48	5	4	48.0 (0.1)	46.1 (3.5)
Week 56	2	2	56.4 (0.6)	53.6 (4.8)

Log-rank test was used to test if cumulative percentages (survival curves) were equal. Results from the tests are presented in Table 7.

Table 7. Median (in Weeks) of Time to Radiological Scan and Log-rank Test

Time from randomization to Radiological Scan	Sorafenib	Placebo	Log-rank Test
Week 6	6.0	5.9	0.0306
Week 12	12.0	12.0	0.9073
Week 18	18.0	18.0	0.6841
Week 24	24.0	24.0	0.7331
Week 32	32.0	32.0	0.9709
Week 40	40.0	39.9	0.2106
Week 48	48.0	47.9	0.0765
Week 56	56.4	53.6	0.6949

The log-rank test showed that there was no difference between two distributions of time to assessment, except time to Week 6 assessment. The median difference at time to Week 6 assessment was only 0.1 week. A large number of patients at Week 6 allowed us to detect such a small difference with respect to distributions. With PFS medians of 167 days in the sorafenib arm and 84 days in the placebo arm, this small difference in time to Week 6 assessment is unlikely to influence the final outcome of the study.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

For each subgroup population, a separate unadjusted log-rank test was performed. Because race was not collected from 186 patients (25%) enrolled in France due to local regulations and the 72% of patients were Caucasian, no race subgroup analysis will be performed in this review. Therefore, this section will focus on PFS analyses by gender (male vs. female, Table 8) and age (< 65 years vs. ≥ 65 years, Table 9).

Table 8. PFS Analyses by Gender in ITT Population

	Sorafenib	Placebo
Gender		
Male		
Number of patients (ITT)	267	287
Number of events (%)	105 (39.3%)	150 (52.3%)
Median (days), 95% CI[1]	166 (138, 175)	84 (78, 93)
Hazard ratio [95% CI][2]	0.45 (0.35, 0.58)	
Unadjusted log-rank test	P-value[3]<0.0001	
Female		
Number of patients (ITT)	116	98
Number of events (%)	42 (36.2%)	45 (45.9%)
Median (days), 95% CI[1]	169 (131, 184)	83 (45, 92)
Hazard ratio (95% CI)[2]	0.45 (0.29, 0.69)	
Unadjusted log-rank test	P-value[3]=0.0002	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm; [3]: not adjusted for multiple analyses.

Table 9. PFS Analyses by Age in ITT Population

	Sorafenib	Placebo
Age		
<65		
Number of patients (ITT)	255	280
Number of events (%)	103 (40.4%)	142 (50.7%)
Median (days), 95% CI[1]	165 (132, 169)	84 (77,91)
Hazard ratio (95% CI)[2]	0.49 (0.38, 0.63)	
Uadjusted log-rank test	P-value[3]<0.0001	
>=65		
Number of patients (ITT)	127	103
Number of events (%)	44 (34.6%)	53 (51.5%)
Median (days), 95% CI[1]	181 (139, 225)	83 (67, 115)
Hazard ratio (95% CI)[2]	0.34 (0.22, 0.52)	
Uadjusted log-rank test	P-value[3]<0.0001	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm; [3]: not adjusted for multiple analyses.

Reviewer's Comments:

The treatment effect appears to be similar in female patients and male patients. The treatment effect also appears to be similar in younger (<65 years) and older (>=65 years) patients.

5 Summary and Conclusions

This NDA submission is to support the use of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy. The submitted Study 11213 was a Phase III, double-blind, international, randomized, parallel-group, multicenter study designed to assess the efficacy and safety of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy. It is the only randomized phase III pivotal study conducted to establish efficacy and safety.

The efficacy PFS analysis for the data collected until the cut-off date of January 28, 2005 included 147 events (38.3%) for PFS in the sorafenib arm and 195 events (50.6%) for PFS in the placebo arm. A total of 342 PFS events (44.5%) occurred at the time of the PFS analysis.

5.1 Statistical Issues and Collective Evidence

In this NDA submission, Study 11213 was the only randomized pivotal phase III study conducted to establish efficacy and safety. The efficacy analysis for the data collected until the cut-off date of January 28, 2005 included 147 events (38.3%)

for PFS in the sorafenib arm and 195 events (50.6%) for PFS in the placebo arm. A total of 342 PFS events (44.5%) occurred at the time of PFS analysis.

Statistical Issues:

Study 11213 included a pre-specified formal final analysis of progression-free survival (PFS). The results of the PFS analysis, which was performed using data available as of 28 Jan 2005, demonstrated a statistically significant prolongation of PFS in patients treated with sorafenib. In April 2005, following review of the data by the Data Monitoring Committee (DMC), the Study Steering committee, European Health Authorities, and the US FDA, a decision was made to unblind treatment allocation in Study 11213 and to offer sorafenib to patients who had been randomized to placebo.

Two-sided α of 0.01 and 0.04 were to be used for the PFS and overall survival analyses, respectively, so that the overall alpha for both the secondary endpoint PFS and the primary endpoint overall survival (OS) combined would be 0.05 or less.

The final and only formal analysis for the PFS endpoint was planned to occur after approximately 363 progressions were observed. As of January 28, 2005, a total of 342 PFS events (44.5%) occurred and the PFS analysis was performed. The results of the PFS analysis led to the submission of this application. The sponsor's study report includes the results of this PFS analysis.

In the protocol, one interim analysis of overall survival was planned when approximately 270 deaths were observed. Due to the unblinding of treatment allocation and possible crossover of placebo patients to sorafenib, on August 18, 2005, the sponsor proposed to perform one interim analysis of overall survival using 220 events with a cutoff date of May 31, 2005 and one interim analysis of overall survival when 270 deaths occur.

The crossover of placebo patients to sorafenib may dilute the effect of sorafenib on OS in favor of placebo. Therefore, the timing of the first interim analysis of OS was chosen to coincide with start of the crossover in May 2005. The second interim analysis will have a data cutoff date of November 30, 2005.

On September 16, 2005, the sponsor submitted results of the first interim OS analysis. The results showed that the statistical significance has not been reached in this interim OS analysis according to the protocol-specified alpha spending of 0.0005, although the results of this interim analysis suggested a decrease in the risk of death in patients with advanced RCC randomized to sorafenib.

5.2 Conclusions and Recommendations

In this reviewer's opinion the study results from the submitted single, Phase III, double-blind, international, randomized, parallel-group, multicenter study, support the claim of efficacy of sorafenib in patients with RCC who received 1 prior regimen of chemotherapy or immunotherapy with respect to progression free survival (PFS). The sorafenib demonstrated a PFS advantage over the placebo in this clinical study. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

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