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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Inlyta® / Axitinib

PROTOCOL NO.: A4061032

PROTOCOL TITLE: Axitinib (AG-013736) as Second-Line Therapy for Metastatic Renal Cell Cancer: Axis Trial

Study Centers: The study was conducted at 175 centers in 22 countries which enrolled and randomized subjects: 44 centers in the United States, 18 in Japan, 13 in Italy, 10 in the United Kingdom, 9 in France, 8 in Spain, 7 each in Russian Federation and China, 6 each in Germany and Republic of Korea, 5 each in Australia, India, Canada, 4 each in Brazil, Poland and Taiwan, 3 in Slovakia, 2 each in Austria, Greece, and Sweden, and 1 each in Singapore and Ireland.

Study Initiation, Primary Completion, and Final Completion Dates:

Study Initiation Date: 15 September 2008 (first subject first visit).

Primary Completion Date: 31 August 2010 (final data collection date for primary outcome measure).

Final Completion Date: The study is still ongoing, with an estimated last subject last visit date of July 2015.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To compare the progression-free survival (PFS) of subjects with metastatic renal cell carcinoma (mRCC) receiving AG-013736 (hereafter referred to as axitinib) versus (vs) sorafenib following failure of 1 prior systemic first-line regimen containing 1 or more of the following: sunitinib, bevacizumab + interferon-alpha (IFN-α), temsirolimus, or cytokine(s)

Secondary Objectives:

- Compare the overall survival (OS) of subjects in each arm
- Compare the objective response rate (ORR) of subjects in each arm
- Evaluate the safety and tolerability of axitinib

- Estimate the duration of response (DR) of subjects in each arm

- Compare the kidney-specific symptoms and health status of subjects in each arm, as measured by the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) and European Quality of Life (EuroQol) EQ-5D self-report questionnaire (EQ-5D)

METHODS

Study Design: This was a 2-arm, randomized, open-label, multicenter, Phase 3 study of axitinib vs sorafenib in subjects with mRCC following failure of 1 prior systemic first-line regimen containing 1 or more of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s).

Six-hundred fifty subjects were randomized in a 1:1 ratio to receive either axitinib, at a starting dose of 5 mg twice daily (BID), or sorafenib, at a dose of 400 mg BID. The subjects were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 versus 1) and by prior therapy (ie, sunitinib-containing regimens vs bevacizumab-containing regimens vs temsirolimus-containing regimens vs cytokine-containing regimens). On-study tumor assessments were to be performed every 6 weeks for the first 12 weeks, and then every 8 weeks by calendar to determine PFS.

The schedule of study activities is summarized in Table 1.

Table 1. Schedule of Activities

Observation	Screening Day –14 to D 0	D 1 (Predose)	Every 2 Wks × 2, Then Every 4 Wks*	Every 6 Wks × 2, Then Every 8 Wks by Calendar	Post Treatment	
					End of Study Treatment/Withdrawal	Follow-Up D 28 After Last Dose
Informed consent[a]	Day –28 to Day 0					
Medical history[b]	X					
Concomitant treatment[c]	X	X	X		X	X
Physical examination[d]	X	X**	X		X	
Weight, height, temperature, pulse[e]	X	X	X		X	
BP[f]	X	X	X		X	
Home BP monitoring[g]		Throughout the study period				
ECOG performance status	X	X	X (every 4 Wks)		X	
Hematology[h]	X	X**	X (every 4 Wks)		X	
Chemistry[i]	X	X**	X (every 4 Wks)		X	
Thyroid function tests[j]		X**	X[k]			
Urine protein, glucose, and blood[k]	X		X (every 4 Wks)		X	
12-Lead ECG[l]		X[m]	X (D15, C1 only)[m]			
Tumor assessments including CT/MRI and bone scan[m]	X (D –28 to D 0)			X	X	
CT or MRI of brain[n]	X (D –28 to D 0)					
Serum or urine pregnancy test[o]	X (D –3 to 0)					
Study randomization[p]	X (D –7 to 0)					
Population pharmacokinetics (at selected sites)[q]		X (C1, C2, and C3)				
UGT1A1 (and other drug metabolizing enzymes and transporters) genotype test[r]		X***				
Safety assessment (adverse events)[s]		Throughout the study period				
Survival[t]	Until at least 3 years after the randomization of the last subject					
Patient-reported outcomes: FKSI and EQ-5D[u]		X	X (every 4 weeks)		X	X
De-identified blood sample for pharmacogenomics		X *** (Optional)				
De-identified archival tumor sample[v]		X*** (Optional)				

Tests and procedures were to be done on schedule, but occasional changes by ±4 days were allowable for holidays, vacations, and other administrative reasons.
* Cycle length was 4 weeks.
** Unnecessary to be repeated before the first dose if screening assessment was performed within 7 days before the first dose.
*** If for some reason the sample was not collected at Cycle 1 Day 1, it may have been collected at any time during study.
AE = adverse event; C = Cycle; CR = complete response; CT = computed tomography; D = Day; ECG = electrocardiogram; EQ-5D = EuroQol EQ-5D self-report questionnaire; FKSI = Functional Assessment of Cancer Therapy Kidney Symptom Index; IEC = Independent Ethics Committee; INR = International Normalized Ratio; IRB = Institutional

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Research Board; PK = pharmacokinetics; MRI = magnetic resonance imaging; PR = partial response; QTc = corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = tri-iodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; UGT1A1 = uridine 5'-diphospho-glucuronosyltransferase 1 family, polypeptide A1; Wks = weeks.

a. Before any procedures performed solely for this study.
b. Including information on prior systemic first-line regimen, which was required to contain 1 or more of the following: sunitinib, bevacizumab + IFN α, temsirolimus, or cytokine(s) as first-line treatment for metastatic renal cell carcinoma; and type of documentation showing disease progression according to RECIST criteria (Version 1.0).
c. Collected from screening to the follow-up period.
d. Examination of major body systems (including neurological examination). Abnormalities from subsequent history and physical examinations were recorded as AEs.
e. Height did not need to be collected after the first measurement.
f. BP was to be measured with the subject in the seated position after the subject had been sitting quietly for 5 minutes.
g. All subjects (in both study arms) were provided a BP monitoring device. Subjects were to measure their BP at least twice daily before taking each dose of medication, and BP was recorded in a subject diary. Subjects were instructed by the study staff to contact their physician immediately for guidance if their systolic BP rose >150 mm Hg, diastolic BP rose >100 mm Hg, or if they developed symptoms perceived to be related to elevated BP (eg, headache, visual disturbance).
h. Hemoglobin, white blood cell count, neutrophil count, lymphocyte count, and platelet count.
i. Blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, bicarbonate or carbon dioxide, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase (or SGPT), aspartate aminotransferase (or SGOT), total protein, albumin, total bilirubin, glucose, phosphate, lipase, and amylase. INR was to be performed to monitor subjects taking concomitant warfarin with sorafenib and when clinically indicated. Bicarbonate and venous carbon dioxide were optional for sites in Japan.
j. Thyroid function tests (free T_3, free T_4, and TSH) were to be performed for all randomized subjects (in both study arms) at Baseline (C1, D1 predose or within 7 days before C1, D1). Subsequently, TSH was done at C1, D15; C2, D1; C3, D1; and C4, D1; and then every 8 weeks starting from C6, D1. Free T_3 and free T_4 was to be performed when clinically indicated. Hypothyroidism was to be treated per standard medical practice to maintain euthyroid state.
k. Protein, glucose, and blood. If protein ≥2+ by semiquantitative method (eg, urine dipstick), protein was to be quantified by 24-hour urine collection. Dose adjustment could have been required (adjustment of the dose once subject was on-study; this did not depend on baseline proteinuria).
l. ECGs: 3 consecutive 12-lead ECGs were to be performed approximately 2 minutes apart to determine the mean QTc interval. The triplicate ECGs were performed at C1, D1 predose (baseline), approximately 1 to 2 hours following a dose of axitinib on C1, D15 at T_{max} (for the first 50 subjects randomized to axitinib only). For all remaining subjects (including the control arm), a single ECG measurement was to be collected at C1, D1 predose. If the mean QTc interval was prolonged (>500 msec), then the ECGs were to be re-read by a cardiologist or other qualified person at the site for confirmation. Additional ECGs could have been performed as clinically indicated.
m. Prestudy objective evidence of disease progression per RECIST was confirmed by the Principal Investigator and documented in the subject's medical record. Baseline (screening) tumor assessments required CT/MRI (no chest x-ray) of the chest, abdomen, and pelvis and a bone scan at the minimum. The baseline CT/MRI and baseline bone scan were to be submitted to the imaging core laboratory for retrospective review. If the interval between any of the baseline tumor assessments and randomization became >28 days, the expired baseline tumor imaging was to be repeated. For all subjects, CT/MRI (covering the same anatomy as the baseline scans, except brain) was required every 6 weeks ×2 then every 8 weeks by calendar. If baseline bone scan showed metastatic lesions, bone imaging was required every 6 weeks ×2 then every 8 weeks by calendar to coincide with the time of the CT/MRI, otherwise, repeat bone scan only if clinically indicated. Response (CR/PR) required confirmation with CT/MRI and a bone scan at least 4 weeks after the response was first noted. Since the progression-free survival, as determined by the independent review committee, was the primary endpoint of this study, these tumor assessments were to be performed by calendar as scheduled until progression of disease by RECIST or death, regardless of whether the subject was receiving study medication or not until permanent discontinuation of study treatment. All radiographic images and bone scans for tumor assessments were to be submitted for the independent review committee.

Table 1. Schedule of Activities

Observation	Screening Day –14 to D 0	D 1 (Predose)	Every 2 Wks × 2, Then Every 4 Wks*	Every 6 Wks × 2, Then Every 8 Wks by Calendar	Post Treatment	
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n. CT or MRI of brain was required at Baseline and the images were to be sent to the independent review committee for retrospective confirmation. Subjects with any evidence of brain metastasis were excluded from the study. Subsequent CT or MRI of brain was not required, but could have been performed if clinically indicated.
o. Subjects of childbearing potential were required to have a negative pregnancy test within 3 days before treatment and had to be using appropriate birth control or practicing abstinence. Pregnancy tests could have been repeated as per request of IRB/IECs or if required by local regulations.
p. Subject number, randomization, and axitinib bottle number assignments were to be obtained via centralized randomization. Required information: site and subject identifiers, demographic information, and stratification variables (including ECOG performance status [0 vs 1] and prior therapy). Study treatment was to begin within 7 days of randomization.
q. Population PK samples for axitinib were to be obtained from subjects at selected sites on C1, D1; C2, D1; and C3, D1. For subjects who were already past C3, PK samples could have been obtained at any other 1 subsequent clinic visit. On C1, D1, 1 sample was to be obtained 1 to 2 hours after the first axitinib dose in clinic. On other scheduled PK visits, 2 samples were to be collected. One sample was to be obtained just before (ie, 15 minutes) the morning axitinib dose taken in the clinic. If there were scheduling conflicts, then this predose sample could have been obtained up to 2 hours before dosing. The second sample was to be collected 1 to 2 hours after the morning axitinib dose. The exact time of the doses and PK collections was noted.
r. One (2 mL) blood sample was to be collected from subjects in the axitinib arm for genotyping of drug metabolizing enzymes and transporters only, including UGT1A1.
s. AEs were collected from the first day of study treatment throughout the study period until at least 28 days after the last dose of study drug and followed until resolution or stabilization. Serious AEs were monitored and reported from the time the subject provided an informed consent.
t. All subjects were followed for survival at least every 3 months after discontinuing study treatment until at least 3 years after randomization of the last subject.
u. FKSI and EQ-5D (subject-reported outcomes) questionnaires were administered on C1, D1 before dosing and before any other clinical assessments, and then every 4 weeks while on-study, at end of study treatment/withdrawal, and at Follow-Up (28 days after last dose).
v. Refer to Molecular Profiling Supplement. This archived sample (paraffin-embedded blocks, typically formalin fixed) could have been collected anytime during the first 2 months of enrollment.

Number of Subjects (Planned and Analyzed): Six-hundred and fifty subjects were planned to be randomized in a 1:1 ratio to receive either axitinib or sorafenib. A total of 409 subjects with progressive disease (PD) or death were required for a log-rank test with an overall 1-sided significance level of 0.025 to have power of 0.90. A total of 723 subjects were randomized in the study; 361 subjects were randomized to axitinib, of whom 359 subjects received treatment, and 362 subjects were randomized to sorafenib, of whom 355 subjects received treatment.

Diagnosis and Main Criteria for Inclusion: Subjects with histologically or cytologically confirmed renal cell cancer with a component of clear cell subtype, with metastasis, evidence of measurable disease and who had failed 1 prior systemic first-line regimen for metastatic renal cell cancer.

Exclusion Criteria: Subjects with prior treatment for metastatic renal cell cancer with >1 systemic first line therapy or undergone major surgery <4 weeks or radiation <2 weeks of starting study drug.

Study Treatment: Axitinib was supplied as 1 mg and 5 mg film-coated tablets for oral administration in high-density polyethylene bottles. Sorafenib was available commercially as 200 mg tablets. In this study, subjects were randomized at a ratio of 1:1 to receive either axitinib or sorafenib. Study treatment was to continue until disease progression, intolerable adverse drug reactions, or withdrawal of consent. Study treatment was required to begin within 7 days of randomization. The starting dose of axitinib was 5 mg BID taken orally with food. Dose adjustments, including dose increase or dose reduction, were to be based on adverse events (AEs) experienced by the individual subject. Axitinib was to be taken beginning on Day 1 of the study. Doses were to be taken approximately 12 hours apart as continuous dosing. Subjects were instructed to take their doses at approximately the same times each day. Study treatment was to be administered in cycles of 4 weeks in duration. The starting dose of sorafenib was 400 mg (2 × 200 mg tablets) BID taken orally without food (at least 1 hour before or 2 hours after eating). Doses were taken as close to 12 hours apart as possible and at approximately the same times each day.

Efficacy Endpoints:

Primary Endpoint:

- Progression free survival (PFS)

Secondary Endpoints:

- Overall survival (OS)
- Overall response rate (ORR)
- Duration of response (DR)

Safety Evaluations: Adverse events (AEs), clinical laboratory measurements, electrocardiogram (ECG), and vital signs measurements were assessed throughout the study.

Statistical Methods: Analysis populations used for the study were as follows:

- The Full Analysis set (FAS) included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. The FAS was the primary population for evaluating all efficacy endpoints, as well as subject characteristics.

- The safety analysis (SA) set consisted of all subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. This SA set was the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefit endpoints may have been evaluated in this population as well.

PFS, based on Independent Review Committee (IRC) assessment, was the primary efficacy endpoint. PFS was summarized for the FAS (ie, all subjects who were randomized) using Kaplan-Meier methods. The median event time for each treatment arm and corresponding 2-sided 95% confidence interval (CI) for the median were provided for PFS. The hazard ratio and its 95% CI were estimated. A stratified (ie, ECOG PS and prior therapy) log-rank test (1-sided, α=0.025) was used to compare PFS between the 2 treatment arms.

An unstratified log-rank test (1-sided, α=0.025) and Cox regression model were also used as secondary analyses for PFS. Cox regression models were used to explore the potential influences of the stratification factors on the primary PFS endpoint. In addition, the potential influences of baseline subject characteristics (eg, age, ethnic origin, sex, geographic region, Memorial Sloan-Kettering Cancer Center [MSKCC] risk group) on the primary PFS endpoint were evaluated. For each treatment arm, the median PFS and a 2-sided 95% CI were provided for each level of the stratification variables.

Baseline tumor assessments required computed tomography (CT)/magnetic resonance imaging (MRI) (no chest x-ray) of the chest, abdomen, and pelvis and a bone scan at the minimum. The baseline CT/MRI and baseline bone scan were sent to the blinded Independent Review Committee (IRC). If the interval between any of the baseline tumor assessments and randomization was >28 days, the expired baseline tumor imaging was repeated. At baseline, tumor lesions were categorized as target or nontarget. All subjects were evaluated for response according to Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0).

CT or MRI of brain was required at baseline and sent to the IRC. Subsequent CT or MRI of the brain could have been performed if clinically indicated, as determined by the treating physician.

For all subjects, CT/MRI (covering the same anatomy as the baseline scans, except brain) was required every 6 weeks for the first 12 weeks, and then every 8 weeks by calendar. If a baseline bone scan showed metastatic lesions, the lesion(s) was confirmed with concomitant x-ray, CT, MRI, and bone scans. Bone imaging was required at the time points matched with the CT/MRI evaluations (every 6 weeks for the first 12 weeks, and then every 8 weeks by

calendar). Otherwise, sequential bone scans were not required unless clinically indicated according to the treating physician's judgment. All scans were sent to the IRC.

Response (complete response [CR]/partial response [PR]) required confirmation with CT/MRI and a bone scan with concomitant imaging (the latter if baseline bone lesions were present) at least 4 weeks after the response was first noted. Since PFS, as determined by the IRC, was the primary endpoint of this study, these tumor assessments were performed as scheduled until progression of disease or death, regardless of whether the subject was receiving study medication or not until permanent withdrawal from study treatment. If a subject was to start a new therapy, these tumor assessments were repeated before the start of the new therapy. All radiographic images and bone scans for tumor assessments were submitted for IRC review.

RESULTS

Subject Disposition and Demography: Of the 361 subjects in the axitinib arm, 361 (100%) subjects were included in the FAS; 359 (99.4%) subjects were included in the SA set; 221 (61.2%) subjects were discontinued from treatment with axitinib; the most common reasons for treatment withdrawal were objective disease progression or relapse (160 [44.3%] subjects) and due to an AE (22 [6.1%] subjects). One hundred and seventeen (32.4%) subjects were discontinued from the study; the most common reasons for study withdrawal were death (103 [28.5%] subjects) and lost to follow-up and objective disease progression or relapse (each with 3 [0.8%] subjects) and 137 (38.0%) subjects were alive, on-study, and progression-free at the time of the final PFS analysis per Investigator.

Of the 362 subjects in the sorafenib arm, 362 (100%) subjects were included in the FAS; 355 (98.1%) subjects were included in the SA set; 256 (70.7%) were discontinued from treatment with sorafenib; the most common reasons for treatment withdrawal were objective disease progression or relapse (180 [49.7%] subjects) and due to an AE (33 [9.1%] subjects). One hundred and nineteen (32.9%) subjects were discontinued from the study; the most common reasons for study withdrawal were death (102 [28.2%] subjects) and objective disease progression or relapse (6 [1.7%] subjects) and 102 (28.2%) subjects were alive, on-study, and progression-free at the time of the final PFS analysis per Investigator. Subject disposition is presented and summarized in Table 2.

Table 2. Overall Summary of Subject Disposition by Treatment

Subject Disposition by Treatment Parameter	Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Full analysis set[a]	361 (100.0)	362 (100.0)
Safety analysis set[b]	359 (99.4)	355 (98.1)
Maximum cycle started[c]		
1	15 (4.2)	29 (8.0)
2	48 (13.3)	57 (15.7)
3	26 (7.2)	32 (8.8)
4	18 (5.0)	19 (5.2)
5	21 (5.8)	29 (8.0)
6	23 (6.4)	27 (7.5)
7	40 (11.1)	31 (8.6)
8	16 (4.4)	21 (5.8)
9	21 (5.8)	23 (6.4)
10	22 (6.1)	14 (3.9)
11	15 (4.2)	13 (3.6)
12	17 (4.7)	14 (3.9)
13	9 (2.5)	4 (1.1)
14	15 (4.2)	13 (3.6)
≥15	53 (14.7)	29 (8.0)
Primary reason for discontinuation from study treatment		
Adverse event	22 (6.1)	33 (9.1)
Subject died	12 (3.3)	13 (3.6)
Protocol violation	4 (1.1)	2 (0.6)
Lost to follow-up	1 (0.3)	3 (0.8)
Other	3 (0.8)	9 (2.5)
Objective progression or relapse	160 (44.3)	180 (49.7)
Global deterioration of health status	9 (2.5)	9 (2.5)

Subject refused continued treatment for reason other than adverse event	10 (2.8)	7 (1.9)
Primary reason for discontinuation from study		
Adverse event	1 (0.3)	0
Subject died	103 (28.5)	102 (28.2)
Protocol violation	2 (0.6)	0
Lost to follow-up	3 (0.8)	4 (1.1)
Other	2 (0.6)	3 (0.8)
Objective progression or relapse	3 (0.8)	6 (1.7)
Global deterioration of health status	1 (0.3)	0
Subject refused continued treatment for reason other than adverse event	2 (0.6)	4 (1.1)

% = (n/N) × 100.
Data cutoff date: 31 August 2010.
N = number of subjects, n = number of subjects meeting specified criteria.
a. The full analysis set included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.
b. The safety analysis set consisted of all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.
c. A subject was considered to have started a cycle if the subject took at least 1 dose of axitinib or sorafenib.

The demographic and baseline characteristics were similar between the treatment arms, as shown in Table 3. The majority of subjects in each treatment arm were <65 years of age (238 [65.9%] subjects in the axitinib arm; 238 [65.7%] subjects in the sorafenib arm), male (265 [73.4%] subjects in the axitinib arm; 258 [71.3%] subjects in the sorafenib arm), and white (278 [77.0%] subjects in the axitinib arm; 269 [74.3%] subjects in the sorafenib arm). Approximately half of the subjects in each treatment arm had an ECOG PS score of 0 (195 [54.0%] subjects in the axitinib arm; 200 [55.2%] subjects in the sorafenib arm) and were in the intermediateMSKCC risk group (199 [55.1%] subjects in the axitinib arm; 210 (58.0%] subjects in the sorafenib arm).

Table 3. Demographic and Baseline Characteristics by Treatment; Full Analysis Set

Variable		Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Age, years	Mean (SD)	59.7 (10.5)	60.0 (10.1)
	Median	61.0	61.0
	Minimum, maximum	20, 82	22, 80
	N	361	362
Age (years)	<65	238 (65.9)	238 (65.7)
	≥65	123 (34.1)	124 (34.3)
Sex	Male	265 (73.4)	258 (71.3)
	Female	96 (26.6)	104 (28.7)
Race	White	278 (77.0)	269 (74.3)
	Black	1 (0.3)	4 (1.1)
	Asian	77 (21.3)	81 (22.4)
	Other	5 (1.4)	8 (2.2)
Weight (kg)	Mean (SD)	76.6 (18.4)	77.9 (19.2)
	Median	74.8	73.9
	Minimum, maximum	36.9, 154.0	37.5, 182.8
	N	361	360
Height (cm)	Mean (SD)	170.5 (9.8)	169.8 (9.1)
	Median	171.0	170.0

Table 3. Demographic and Baseline Characteristics by Treatment; Full Analysis Set

Variable		Axitinib N=361 n (%)	Sorafenib N=362 n (%)
	Minimum, maximum	140.0, 195.0	144.2, 198.0
	N	360	359
ECOG performance status[a]	0	195 (54.0)	200 (55.2)
	1	162 (44.9)	160 (44.2)
	>1	1 (0.3)	0
Geographic region	North America	88 (24.4)	98 (27.1)
	Europe	187 (51.8)	170 (47.0)
	Asia	73 (20.2)	79 (21.8)
	Other	13 (3.6)	15 (4.1)
MSKCC risk group[b]	Favorable	158 (43.8)	148 (40.9)
	Intermediate	199 (55.1)	210 (58.0)
	Poor	4 (1.1)	4 (1.1)

Data cutoff date: 31 August 2010.
Countries included in each geographic region are as follows: Asia: China, India, Japan, Korea, Singapore, and Taiwan; European Union: Austria, Germany, France, United Kingdom, Greece, Ireland, Italy, Poland, Russia, Slovakia, Spain, and Sweden; North America: Canada and United States; and Other: Australia and Brazil.
ECOG = Eastern Cooperative Oncology Group, MSKCC = Memorial Sloan-Kettering Cancer Center, N = number of subjects, n = number of subjects meeting specified criteria, SD = standard deviation.

a. ECOG Performance Status was taken from case report forms and was the last measure obtained before dosing.
b. MSKCC risk groups were derived using the following 4 risk factors: high lactate dehydrogenase (>1.5 × upper limit of normal), low serum hemoglobin (less than the lower limit of normal), high corrected serum calcium (>10 mg/dL), and absence of prior nephrectomy.

Efficacy Results: Table 4 presents a summary of PFS by treatment (stratified analysis) based on IRC assessment for the FAS.

Table 4. Summary of Progression-Free Survival by Treatment and Stratification Factor, Stratified Analysis, IRC Assessment; Full Analysis Set

Progression-Free Survival Parameter	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Overall stratified analysis (N)	**361**	**362**
Subject observed to have progressed or died due to any cause while on-study[a]	192 (53.2)	210 (58.0)
Type of event		
Objective progression	180 (93.8)	200 (95.2)
Increase in existing lesion (target or nontarget)	83 (46.1)	97 (48.5)
New lesion	51 (28.3)	47 (23.5)
Increase and a new lesion	32 (17.8)	45 (22.5)
Other	14 (7.8)	11 (5.5)
Death without objective progression	12 (6.3)	10 (4.8)
Subject did not progress or die due to any cause while on-study[a]	169 (46.8)	152 (42.0)
Reason for censorship[b]		
No baseline or on-study assessments	14 (8.3)	28 (18.4)
Alive, on-study, and progression-free at the time of the analysis	148 (87.6)	115 (75.7)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on-study	4 (2.4)	4 (2.6)

Table 4. Summary of Progression-Free Survival by Treatment and Stratification Factor, Stratified Analysis, IRC Assessment; Full Analysis Set

Progression-Free Survival Parameter	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
PD or death occurred after ≥2 consecutive, missed assessments	1 (<1.0)	3 (2.0)
PD occurred after given new anti-tumor treatment	2 (1.2)	0
Withdrew consent for follow-up	0	0
Lost to follow-up	0	2 (1.3)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	2.7 (1.7, 2.9)	2.5 (1.6, 2.8)
50%	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)
75%	15.2 (12.1, NE)	8.8 (7.2, 12.0)
Axitinib vs sorafenib		
Hazard ratio[d]	0.665	
95% CI of hazard ratio	0.544-0.812	
p-value[e]	<0.0001	
Stratification Category: Prior Sunitinib-Containing Regimen (N)	**194**	**195**
Subject observed to have progressed or died due to any cause while on-study[a]	117 (60.3)	120 (61.5)
Type of event		
Objective progression	109 (93.2)	114 (95.0)
Increase in existing lesion (target or nontarget)	46 (42.2)	55 (48.2)
New lesion	35 (32.1)	27 (23.7)
Increase and a new lesion	20 (18.3)	25 (21.9)
Other	8 (7.3)	7 (6.1)
Death without objective progression	8 (6.8)	6 (5.0)
Subject did not progress or die due to any cause while on-study[a]	77 (39.7)	75 (38.5)
Reason for censorship[b]		
No baseline or on-study assessments	8 (10.4)	16 (21.3)
Alive, on-study, and progression-free at the time of the analysis	67 (87.0)	56 (74.7)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on-study	0	2 (2.7)
PD or death occurred after ≥2 consecutive, missed assessments	1 (1.3)	1 (1.3)
PD occurred after given new anti-tumor treatment	1 (1.3)	0
Withdrew consent for follow-up	0	0
Lost to follow-up	0	0
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI) [c]		
25%	1.7 (1.5, 2.8)	1.5 (1.5, 2.0)
50%	4.8 (4.5, 6.4)	3.4 (2.8, 4.7)
75%	12.0 (8.3, 17.7)	6.7 (5.2, 15.7)
Axitinib vs sorafenib		
Hazard ratio[d]	0.741	
95% CI of hazard ratio	0.573-0.958	
p-Value[e]	0.0107	
Stratification Category: Prior Cytokine-Containing Regimen (N)	**126**	**125**
Subject observed to have progressed or died due to any cause while on-study[a]	50 (39.7)	69 (55.2)
Type of event		
Objective progression	47 (94.0)	65 (94.2)
Increase in existing lesion (target or nontarget)	28 (59.6)	33 (50.8)
New lesion	9 (19.1)	15 (23.1)

Table 4. Summary of Progression-Free Survival by Treatment and Stratification Factor, Stratified Analysis, IRC Assessment; Full Analysis Set

Progression-Free Survival Parameter	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Increase and a new lesion	8 (17.0)	13 (20.0)
Other	2 (4.3)	4 (6.2)
Death without objective progression	3 (6.0)	4 (5.8)
Subject did not progress or die due to any cause while on-study[a]	76 (60.3)	56 (44.8)
Reason for censorship[b]		
No baseline or on-study assessments	4 (5.3)	9 (16.1)
Alive, on-study, and progression-free at the time of the analysis	67 (88.2)	43 (76.8)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on-study	4 (5.3)	0
PD or death occurred after ≥2 consecutive, missed assessments	0	2 (3.6)
PD occurred after given new anti-tumor treatment	1 (1.3)	0
Withdrew consent for follow-up	0	0
Lost to follow-up	0	2 (3.6)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	6.4 (3.3, 8.6)	2.8 (2.7, 4.6)
50%	12.1 (10.1, 13.9)	6.5 (6.3, 8.3)
75%	- (13.9, -)	10.1 (8.3, 12.8)
Axitinib vs sorafenib		
Hazard ratio[d]	0.464	
95% CI of hazard ratio	0.318-0.676	
p-value[e]	<0.0001	

% = (n/N) × 100

The efficacy tables contain those subjects with prior sunitinib and cytokine regimens. Presentation of PFS for subgroups based on prior bevacizumab and temsirolimus regimens were not included based on the low number of subjects with these prior regimens (59 and 24 subjects, respectively), and which resulted in wide confidence intervals.

Data cutoff date: 31 August 2010.

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IRC = Independent Review Committee; N = number of subjects; n = number of subjects meeting prespecified criteria; NE = not evaluable; PD = progressive disease; PFS = progression-free survival.

a. On study included treatment plus 28-day follow-up period.
b. The denominator for reason for censorship was based on the number of subjects who did not progress or die due to any cause while on-study.
c. Based on the Brookmeyer and Crowley method.
d. Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test.
e. For overall stratified analysis, p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status and prior treatment. For the population with prior sunitinib-containing regimen or cytokine-containing regimen, the p-value was from a 1-sided log-rank test stratified by ECOG performance status.

The data cutoff date for the final OS analysis was 01 November 2011. A summary of OS by treatment (stratified analysis) for the FAS is presented in Table 5.

Table 5. Summary of Overall Survival by Treatment, And Stratification Factor, Stratified Analysis (Full Analysis Set)

Overall Survival Parameter	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Overall stratified analysis (N)	**361**	**362**
Dead	211 (58.4)	214 (59.1)
Cause of death [n (%)]		
Disease under study	179 (84.8)	175 (81.8)
Study treatment toxicity	0	2 (<1.0)
Unknown	16 (7.6)	25 (11.7)
Other	16 (7.6)	12 (5.6)
Alive[a]	150 (41.6)	148 (40.9)
Reason for censorship [n (%)]		
Alive	136 (90.7)	134 (90.5)
Subject no longer willing to participate	3 (2.0)	7 (4.7)
Lost to follow-up	11 (7.3)	7 (4.7)
Survival probability at Month 12 (95% CI)[b]	67.1 (62.0, 71.7)	68.2 (63.1, 72.7)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	8.9 (7.2, 10.6)	9.3 (7.9, 10.8)
50%	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)
75%	34.6 (31.6, NE)	34.5 (31.9, 35.0)
Axitinib versus sorafenib		
Hazard ratio[d]	0.969	
95% CI of hazard ratio	0.800-1.174	
p-Value[e]	0.3744	
Stratification Category: Prior Sunitinib-Containing Regimen (N)	**194**	**195**
Dead	131 (67.5)	131 (67.2)
Cause of death		
Disease under study	115 (87.8)	111 (84.7)
Study treatment toxicity	0	1 (<1.0)
Unknown	6 (4.6)	12 (9.2)
Other	10 (7.6)	7 (5.3)
Alive[a]	63 (32.5)	64 (32.8)
Reason for censorship [n (%)]		
Alive	56 (88.9)	59 (92.2)
Subject no longer willing to participate	3 (4.8)	3 (4.7)
Lost to follow-up	4 (6.3)	2 (3.1)
Survival Probability at Month 12 (95% CI)[b]	59.8 (52.5, 66.3)	61.8 (54.5, 68.2)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)c		
25%	7.0 (6.4, 9.1)	7.5 (6.0, 10.0)
50%	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)
75%	32.4 (24.4, NE)	35.0 (24.0, 35.0)
Axitinib versus sorafenib		
Hazard ratio[d]	0.997	
95% CI of hazard ratio	0.782-1.270	
p-Value[e]	0.4902	

Table 5. Summary of Overall Survival by Treatment, And Stratification Factor, Stratified Analysis (Full Analysis Set)

Overall Survival Parameter	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Stratification Category: Prior Cytokine-Containing Regimen (N)	**126**	**125**
Dead	51 (40.5)	57 (45.6)
Cause of death [n (%)]		
Disease under study	37 (72.5)	42 (73.7)
Study treatment toxicity	0	1 (1.8)
Unknown	9 (17.6)	10 (17.5)
Other	5 (9.8)	4 (7.0)
Alive[a]	75 (59.5)	68 (54.4)
Reason for censorship [n (%)]		
Alive	69 (92.0)	61 (89.7)
Subject no longer willing to participate	0	3 (4.4)
Lost to follow-up	6 (8.0)	4 (5.9)
Survival probability at Month 12 (95% CI)[b]	82.3 (74.4, 87.9)	80.5 (72.4, 86.5)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	15.9 ([13.1, 22.5)	13.8 (11.7, 18.0)
50%	29.4 (24.5, NE)	27.8 (23.1, 34.5)
75%	NE (31.6, NE)	34.5 (31.9, 34.5)
Axitinib versus sorafenib		
Hazard ratio[d]	0.813	
95% CI of hazard ratio	0.555-1.191	
p-Value[e]	0.1435	
Stratification Category: Prior Bevacizumab-Containing Regimen (N)	**29**	**30**
Dead	22 (75.9)	15 (50.0)
Cause of death		
Disease under study	20 (90.9)	13 (86.7)
Study treatment toxicity	0	0
Unknown	1 (4.5)	2 (13.3)
Other	1 (4.5)	0
Alive[a]	7 (24.1)	15 (50.0)
Reason for censorship [n (%)]		
Alive	7 (100)	13 (86.7)
Subject no longer willing to participate	0	1 (6.7)
Lost to follow-up	0	1 (6.7)
Survival probability at Month 12 (95% CI)[b]	55.2 (36.1, 70.7)	72.2 (52.6, 84.9)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	7.2 (4.1, 11.0)	10.7 (6.0, 17.9)
50%	14.7 (9.2, 20.0)	19.8 (13.1, NE)
75%	22.0 (15.8, NE)	NE (20.2, NE)
Axitinib versus sorafenib		
Hazard ratio[d]	1.825	
95% CI of hazard ratio	0.942-3.535	
p-Value[e]	0.9648	

Table 5. Summary of Overall Survival by Treatment, And Stratification Factor, Stratified Analysis (Full Analysis Set)

Overall Survival Parameter	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Stratification Category: Prior Temsirolimus-Containing Regimen (n)	**12**	**12**
Dead	7 (58.3)	11 (91.7)
Cause of death		
Disease under study	7 (100)	9 (81.8)
Study treatment toxicity	0	0
Unknown	0	1 (9.1)
Other	0	1 (9.1)
Alive[a]	5 (41.7)	1 (8.3)
Reason for censorship [n (%)]		
Alive	4 (80.0)	1 (100)
Subject no longer willing to participate	0	0
Lost to follow-up	1 (20.0)	0
Survival probability at Month 12 (95% CI)[b]	55.6 (25.6, 77.6)	33.3 (11.7, 56.9)
Kaplan-meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	3.8 (2.9, 16.4)	4.8 (2.4, 9.1)
50%	14.0 (3.8, NE)	8.5 (5.7, 13.5)
75%	NE (14.0, NE)	14.1 (8.0, 17.4)
Axitinib versus sorafenib		
Hazard ratio[d]	0.459	
95% CI of hazard ratio	0.165-1.278	
p-Value[e]	0.0638	

Data cutoff date: 01 November 2011.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; n = number of subjects with prespecified criteria; N = total number of subjects; NE = not evaluable.

a. Subjects who are not known to be dead at the time the database was closed for analysis are censored on the date they were last known to be alive.
b. Calculated from the log[-log(12-month survival probability)] using a normal approximation and back transformation
c. Based on the Brookmeyer and Crowley Method.
d. Assuming proportional hazards model, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test.
e. For overall stratified analysis, p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status and prior treatment. For the population with prior treatment, the p-value was from a 1-sided log-rank test stratified by ECOG performance status.

Objective Response Rate: The data cutoff date for the blinded IRC assessment and overall stratified analysis was 31 August 2010. A summary of the best overall response by treatment (stratified analysis) is presented in Table 8.

Table 6. Summary of Best Overall Response by Treatment and Stratification Factor; Stratified Analysis; IRC Assessment; Full Analysis Set

Best Overall Response Parameter	Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Overall stratified analysis (n)	**361**	**362**
Subjects with baseline assessment	360 (99.7)	359 (99.2)
Subjects with measureable disease at Baseline	350 (97.0)	349 (96.4)
Best overall response		
Complete response	0	0
Partial response	70 (19.4)	34 (9.4)
Stable disease (≥20 weeks)	96 (26.6)	77 (21.3)
Stable disease (<20 weeks)	84 (23.3)	120 (33.1)
Progressive disease	78 (21.6)	76 (21.0)
Not assessed	0	0
Indeterminate	22 (6.1)	42 (11.6)
Overall confirmed objective response rate (CR + PR)	70 (19.4)	34 (9.4)
95% exact CI[a]	15.4%-23.9%	6.6%-12.9%
Treatment comparison (axitinib vs sorafenib)		
Risk ratio[b]	2.056	
95% CI of risk ratio[b]	1.408-3.003	
p-Value[c]	0.0001	
Stratification Category: Prior Sunitinib-Containing Regimen (N)	**194**	**195**
Subjects with baseline assessment	194 (100)	195 (100)
Subjects with measureable disease at Baseline	188 (96.9)	189 (96.9)
Best overall response		
Complete response	0	0
Partial response	22 (11.3)	15 (7.7)
Stable disease (≥20 weeks)	49 (25.3)	26 (13.3)
Stable disease (<20 weeks)	53 (27.3)	70 (35.9)
Progressive disease	51 (26.3)	51 (26.2)
Not assessed	0	0
Indeterminate	13 (6.7)	27 (13.8)
Overall confirmed objective response rate (CR + PR)	22 (11.3)	15 (7.7)
95% exact CI[a]	7.2%-16.7%	4.4%-12.4%
Treatment comparison (axitinib vs sorafenib)		
Risk ratio[b]	1.477	
95% CI of risk ratio[b]	0.792-2.754	
p-Value[d]	0.1085	

Table 6. Summary of Best Overall Response by Treatment and Stratification Factor; Stratified Analysis; IRC Assessment; Full Analysis Set

Best Overall Response Parameter	Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Stratification Category: Prior Cytokine-Containing Regimen (N)	**126**	**125**
Subjects with baseline assessment	126 (100)	123 (98.4)
Subjects with measureable disease at Baseline	123 (97.6)	120 (96.0)
Best overall response		
Complete response	0	0
Partial response	41 (32.5)	17 (13.6)
Stable disease (≥20 weeks)	39 (31.0)	44 (35.2)
Stable disease (<20 weeks)	20 (15.9)	33 (26.4)
Progressive disease	16 (12.7)	15 (12.0)
Not assessed	0	0
Indeterminate	7 (5.6)	11 (8.8)
Overall confirmed objective response rate (CR + PR)	41 (32.5)	17 (13.6)
95% exact CI[a]	24.5%-41.5%	8.1%-20.9%
Treatment comparison (axitinib vs sorafenib)		
Risk ratio[b]	2.392	
95% CI of risk ratio[b]	1.434-3.992	
p-Value[d]	0.0002	

% = (n/N) × 100.
Data cutoff date: 31 August 2010.
CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; IRC = Independent Review Committee; N = number of subjects; n = number of subjects meeting prespecified criteria; PR = partial response.

a. Using exact method based on F-distribution.
b. Risk ratio and CI based on the Mantel-Haenszel estimator; risk ratio is adjusted for same stratification factors as Cochran-Mantel-Haenszel test.
c. For the overall stratified analysis, the p-value was from a 1-sided Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior treatment.
d. p-Value is from a 1-sided Cochran-Mantel-Haenszel test stratified by ECOG performance status.

Duration of Response: The data cutoff date for the blinded IRC assessment of DR was 31 August 2010. Table 7 presents a summary of the median DR among responders by treatment based on IRC assessment for the FAS.

Table 7. Summary of Duration of Tumor Response Among Responders by Treatment; IRC Assessment

Duration of Response Parameter	Axitinib N=70 n (%)	Sorafenib N=34 n (%)
Overall Stratified Analysis (N)	**70**	**34**
Subject observed to have progressed or died due to any cause while on-study[a]	19 (27.1)	10 (29.4)
Type of event		
Objective progression	18 (94.7)	9 (90.0)
Increase in existing lesion (target or nontarget)	11 (61.1)	6 (66.7)
New lesion	2 (11.1)	2 (22.2)
Increase and a new lesion	2 (11.1)	1 (11.1)
Other	3 (16.7)	0
Death without objective progression	1 (5.3)	1 (10.0)
Subject did not progress or die due to any cause while on-study[a]	51 (72.9)	24 (70.6)
Reason for censorship		
No baseline or on-study assessments	0	0
Alive, on-study, and progression-free at the time of the analysis	50 (98.0)	23 (95.8)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on-study	1 (2.0)	0
PD or death occurred after ≥2 consecutive, missed assessments	0	1 (4.2)
PD occurred after given new anti-tumor treatment	0	0
Withdrew consent for follow-up	0	0
Lost to follow-up	0	0
Kaplan-Meier estimates of duration of response (months)		
Quartile (95% CI)[b]		
25%	6.9 (5.2, 11.0)	7.2 (5.1, 11.1)
50%	11.0 (7.4, NE)	10.6 (8.8, 11.5)
75%	NE	11.1 (10.6, 11.5)
Stratification Category: Prior Sunitinib-Containing Regimen (N)	**22**	**15**
Subject observed to have progressed or died due to any cause while on-study[a]	9 (40.9)	4 (26.7)
Type of event		
Objective progression	8 (88.9)	4 (100)
Increase in existing lesion (target or nontarget)	4 (50.0)	2 (50.0)
New lesion	2 (25.0)	2 (50.0)
Increase and a new lesion	1 (12.5)	0
Other	1 (12.5)	0
Death without objective progression	1 (11.1)	0
Subject did not progress or die due to any cause while on-study[a]	13 (59.1)	11 (73.3)
Reason for censorship		
No baseline or on-study assessments	0	0
Alive, on-study, and progression-free at the time of the analysis	13 (100)	11 (100)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on-study	0	0
PD or death occurred after ≥2 consecutive, missed assessments	0	0
PD occurred after given new anti-tumor treatment	0	0
Withdrew consent for follow-up	0	0
Lost to follow-up	0	0

Table 7. Summary of Duration of Tumor Response Among Responders by Treatment; IRC Assessment

Duration of Response Parameter	Axitinib N=70 n (%)	Sorafenib N=34 n (%)
Kaplan-Meier estimates of duration of response (months)		
Quartile (95% CI)[b]		
25%	3.7 (3.3, 11.0)	11.1 (3.8, 11.1)
50%	11.0 (5.2, NE)	11.1 (NE, NE)
75%	NE (11.0, NE)	11.1 (NE, NE)
Stratification Category: Prior Cytokine-Containing Regimen (N)	**41**	**17**
Subject observed to have progressed or died due to any cause while on-study[a]	8 (19.5)	5 (29.4)
Type of event		
Objective progression	8 (100)	4 (80.0)
Increase in existing lesion (target or nontarget)	5 (62.5)	3 (75.0)
New lesion	0	0
Increase and a new lesion	1 (12.5)	1 (25.0)
Other	2 (25.0)	0
Death without objective progression	0	1 (20.0)
Subject did not progress or die due to any cause while on-study[a]	33 (80.5)	12 (70.6)
Reason for censorship		
No baseline or on-study assessments	0	0
Alive, on-study, and progression-free at the time of the analysis	32 (97.0)	11 (91.7)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on-study	1 (3.0)	0
PD or death occurred after ≥2 consecutive, missed assessments	0	1 (8.3)
PD occurred after given new anti-tumor treatment	0	0
Withdrew consent for follow-up	0	0
Lost to follow-up	0	0
Kaplan-Meier estimates of duration of response (months)		
Quartile (95% CI)[b]		
25%	7.4 (6.9, NE)	6.5 (5.1, 11.5)
50%	11.0 (7.4, NE)	10.6 (5.9, 11.5)
75%	NE (11.0, NE)	11.5 (7.2, 11.5)

% = (n/N) × 100.
The denominator for reason for censorship was based on the number of subjects who did not progress or die due to any cause while on-study. Data cutoff date: 31 August 2010.
CI = confidence interval; IRC = Independent Review Committee; N = number of subjects; n = number of subjects meeting specified criteria; NE = not estimable; PD = progressive disease.
a. On study included treatment plus 28-day follow-up period.
b. Based on the Brookmeyer and Crowley method.

Safety Results: Treatment-emergent nonserious adverse events (all causalities) by system organ class are summarized in Table 8.

Table 8. Treatment-Emergent Nonserious Adverse Events (All Causalities) in ≥5% of Subjects

System Organ Class Preferred Term	Axitinib n (%)	Sorafenib n (%)
Number (%) of subjects: evaluable for AEs	359	355
Number (%) of subjects: with AEs	330 (91.9)	341 (96.1)
Blood and lymphatic system disorders	13 (3.6)	40 (11.3)
Anaemia	13 (3.6)	40 (11.3)
Endocrine disorders	68 (18.9)	29 (8.2)
Hypothyroidism	68 (18.9)	29 (8.2)
Gastrointestinal disorders	268 (74.7)	251 (70.7)
Abdominal pain	50 (13.9)	38 (10.7)
Abdominal pain upper	29 (8.1)	14 (3.9)
Constipation	72 (20.1)	71 (20.0)
Diarrhoea	197 (54.9)	188 (53.0)
Dyspepsia	36 (10.0)	8 (2.3)
Flatulence	19 (5.3)	8 (2.3)
Nausea	116 (32.3)	77 (21.7)
Stomatitis	54 (15.0)	44 (12.4)
Vomiting	84 (23.4)	60 (16.9)
General disorders and administration site conditions	230 (64.1)	190 (53.5)
Asthenia	73 (20.3)	49 (13.8)
Chest pain	19 (5.3)	15 (4.2)
Fatigue	138 (38.4)	112 (31.5)
Mucosal inflammation	54 (15.0)	44 (12.4)
Oedema peripheral	17 (4.7)	20 (5.6)
Pain	18 (5.0)	11 (3.1)
Pyrexia	20 (5.6)	36 (10.1)
Investigations	97 (27.0)	91 (25.6)
Lipase increased	9 (2.5)	19 (5.4)
Weight decreased	89 (24.8)	74 (20.8)
Metabolism and nutrition disorders	123 (34.3)	101 (28.5)
Decreased appetite	123 (34.3)	101 (28.5)
Musculoskeletal and connective tissue disorders	128 (35.7)	124 (34.9)
Arthralgia	54 (15.0)	39 (11.0)
Back pain	50 (13.9)	44 (12.4)
Musculoskeletal pain	19 (5.3)	21 (5.9)
Myalgia	25 (7.0)	10 (2.8)
Pain in extremity	44 (12.3)	48 (13.5)
Nervous system disorders	95 (26.5)	71 (20.0)
Dizziness	30 (8.4)	15 (4.2)
Dysgeusia	38 (10.6)	29 (8.2)
Headache	50 (13.9)	40 (11.3)
Psychiatric Disorders	29 (8.1)	18 (5.1)
Insomnia	29 (8.1)	18 (5.1)
Renal and urinary disorders	39 (10.9)	26 (7.3)
Proteinuria	39 (10.9)	26 (7.3)
Respiratory, thoracic and mediastinal disorders	172 (47.9)	138 (38.9)
Cough	55 (15.3)	59 (16.6)
Dysphonia	111 (30.9)	48 (13.5)
Dyspnoea	50 (13.9)	42 (11.8)
Epistaxis	22 (6.1)	15 (4.2)
Oropharyngeal pain	20 (5.6)	19 (5.4)

Table 8. Treatment-Emergent Nonserious Adverse Events (All Causalities) in ≥5% of Subjects

System Organ Class Preferred Term	Axitinib n (%)	Sorafenib n (%)
Skin and subcutaneous tissue disorders	158 (44.0)	273 (76.9)
Alopecia	14 (3.9)	115 (32.4)
Dry skin	36 (10.0)	38 (10.7)
Erythema	8 (2.2)	36 (10.1)
Palmar-plantar erythrodysaesthesia syndrome	98 (27.3)	181 (51.0)
Pruritus	24 (6.7)	44 (12.4)
Rash	45 (12.5)	111 (31.3)
Vascular disorders	156 (43.5)	105 (29.6)
Hypertension	145 (40.4)	102 (28.7)
Hypotension	18 (5.0)	6 (1.7)

Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary of Regulatory Activities; n = number of subjects with AEs.

A total of 325 (90.5%) of the 359 subjects in the axitinib arm experienced 4087 treatment-related AEs, and 336 (94.6%) of the 355 subjects in the sorafenib arm experienced 3459 treatment-related AEs. The 2 most frequent treatment-related AEs in the axitinib arm were diarrhea and hypertension, with 478 events and 265 events reported for 184 (51.3%) and 141 (39.3%) subjects, respectively, compared with 361 events and 151 events reported for 179 (50.4%) and 103 (29.0%) subjects in the sorafenib arm, respectively (Table 9).

Table 9. Summary of Adverse Events by Treatment, MedDRA Preferred Term Experienced by ≥5% of Subjects Overall by Treatment (Treatment Related); Safety Analysis Set

Preferred Term[a]	Axitinib N=359	Sorafenib N=355
	n (%)	n (%)
Any AE	325 (90.5)	336 (94.6)
Diarrhea	184 (51.3)	179 (50.4)
Hypertension	141 (39.3)	103 (29.0)
Fatigue	125 (34.8)	93 (26.2)
Nausea	103 (28.7)	65 (18.3)
Decreased appetite	102 (28.4)	88 (24.8)
Dysphonia	101 (28.1)	42 (11.8)
Palmar-plantar erythrodysesthesia syndrome	98 (27.3)	181 (51.0)
Hypothyroidism	66 (18.4)	24 (6.8)
Asthenia	63 (17.5)	44 (12.4)
Vomiting	60 (16.7)	44 (12.4)
Weight decreased	59 (16.4)	54 (15.2)
Mucosal inflammation	54 (15.0)	43 (12.1)
Stomatitis	52 (14.5)	42 (11.8)
Constipation	44 (12.3)	45 (12.7)
Rash	42 (11.7)	109 (30.7)
Headache	38 (10.6)	24 (6.8)
Proteinuria	37 (10.3)	23 (6.5)
Dysgeusia	37 (10.3)	29 (8.2)
Dry skin	36 (10.0)	35 (9.9)
Pain in extremity	32 (8.9)	35 (9.9)
Arthralgia	31 (8.6)	17 (4.8)
Abdominal pain	30 (8.4)	16 (4.5)
Dyspepsia	28 (7.8)	6 (1.7)
Dyspnea	25 (7.0)	13 (3.7)
Abdominal pain upper	22 (6.1)	7 (2.0)
Pruritus	21 (5.8)	43 (12.1)
Dizziness	20 (5.6)	5 (1.4)
Myalgia	19 (5.3)	7 (2.0)
Cough	19 (5.3)	16 (4.5)
Epistaxis	19 (5.3)	10 (2.8)
Alopecia	12 (3.3)	112 (31.9)
Anemia	10 (2.8)	20 (5.6)
Erythema	8 (2.2)	35 (9.9)
Lipase increased	8 (2.2)	18 (5.1)

% = (n/N) × 100
Data in this table are from the AE case report form page. Data cutoff date: 31 August 2010.
AEs and SAEs are not separated out in this table.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects, n = number of subjects fitting specified criteria.
a. MedDRA (version 13.1) coding dictionary applied.

Treatment-emergent serious adverse events (all causalities) by system organ class are summarized in Table 10.

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Axitinib n (%)	Sorafenib n (%)
Number (%) of subjects: evaluable for adverse events	359	355
Number (%) of subjects: with AEs	108 (30.1)	110 (31.0)
Blood and lymphatic system disorders	1 (0.3)	5 (1.4)
Anaemia	0	4 (1.1)
Leukocytosis	1 (0.3)	0
Splenic infarction	0	1 (0.3)
Cardiac disorders	4 (1.1)	6 (1.7)
Acute coronary syndrome	0	1 (0.3)
Angina pectoris	0	1 (0.3)
Atrial fibrillation	1 (0.3)	0
Atrioventricular block	0	1 (0.3)
Bradycardia	1 (0.3)	0
Cardiac failure	0	1 (0.3)
Cardiopulmonary failure	2 (0.6)	0
Congestive cardiomyopathy	0	1 (0.3)
Myocardial infarction	0	2 (0.6)
Endocrine disorders	2 (0.6)	1 (0.3)
Hypothyroidism	1 (0.3)	0
Secondary hypothyroidism	1 (0.3)	0
Thyroiditis	0	1 (0.3)
Eye disorders	2 (0.6)	0
Retinal artery occlusion	1 (0.3)	0
Retinal vein occlusion	1 (0.3)	0
Retinal vein thrombosis	1 (0.3)	0
Gastrointestinal disorders	21 (5.8)	21 (5.9)
Abdominal pain	1 (0.3)	0
Ascites	0	1 (0.3)
Colitis ulcerative	0	1 (0.3)
Constipation	2 (0.6)	1 (0.3)
Diarrhoea	7 (1.9)	5 (1.4)
Duodenal ulcer haemorrhage	0	1 (0.3)
Enterocolitis	0	1 (0.3)
Gastric haemorrhage	1 (0.3)	0
Gastric ulcer	1 (0.3)	0
Gastritis	0	1 (0.3)
Gastrointestinal haemorrhage	0	3 (0.8)
Gastrointestinal perforation	1 (0.3)	0
Inguinal hernia	2 (0.6)	0
Intestinal obstruction	2 (0.6)	1 (0.3)
Lower gastrointestinal haemorrhage	1 (0.3)	1 (0.3)
Melaena	1 (0.3)	0
Nausea	1 (0.3)	1 (0.3)
Pancreatitis	0	1 (0.3)
Retroperitoneal haemorrhage	0	1 (0.3)
Small intestinal obstruction	1 (0.3)	0
Subileus	0	1 (0.3)
Upper gastrointestinal haemorrhage	0	1 (0.3)
Vomiting	3 (0.8)	1 (0.3)

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Axitinib n (%)	Sorafenib n (%)
General disorders and administration site conditions	38 (10.6)	33 (9.3)
Asthenia	2 (0.6)	1 (0.3)
Chest pain	0	2 (0.6)
Chills	1 (0.3)	0
Death	1 (0.3)	4 (1.1)
Device dislocation	0	1 (0.3)
Disease progression	23 (6.4)	13 (3.7)
Fatigue	4 (1.1)	0
General physical health deterioration	3 (0.8)	4 (1.1)
Hernia	1 (0.3)	0
Inflammation	0	1 (0.3)
Mucosal inflammation	1 (0.3)	0
Pain	1 (0.3)	4 (1.1)
Pyrexia	5 (1.4)	3 (0.8)
Hepatobiliary disorders	1 (0.3)	4 (1.1)
Biliary dilatation	0	1 (0.3)
Cholangitis	1 (0.3)	1 (0.3)
Cholecystitis	0	1 (0.3)
Cholelithiasis	0	1 (0.3)
Hepatic function abnormal	0	1 (0.3)
Immune system disorders	1 (0.3)	0
Hypersensitivity	1 (0.3)	0
Infections and infestations	12 (3.3)	16 (4.5)
Abdominal abscess	1 (0.3)	0
Appendicitis	1 (0.3)	0
Cellulitis	0	1 (0.3)
Diverticulitis	0	1 (0.3)
Gastroenteritis	1 (0.3)	0
Herpes zoster	0	1 (0.3)
Infection	3 (0.8)	0
Intervertebral discitis	0	1 (0.3)
Lower respiratory tract infection	0	3 (0.8)
Lower respiratory tract infection bacterial	1 (0.3)	0
Lung infection	0	1 (0.3)
Muscle abscess	0	1 (0.3)
Pneumonia	4 (1.1)	3 (0.8)
Pulmonary tuberculosis	0	1 (0.3)
Pyelonephritis	0	1 (0.3)
Sepsis	1 (0.3)	2 (0.6)
Urinary tract infection	1 (0.3)	2 (0.6)
Injury, poisoning and procedural complications	6 (1.7)	4 (1.1)
Fall	1 (0.3)	2 (0.6)
Femoral neck fracture	1 (0.3)	0
Gastrointestinal anastomotic leak	1 (0.3)	0
Lumbar vertebral fracture	1 (0.3)	0
Radiation pneumonitis	1 (0.3)	0
Rib fracture	0	1 (0.3)
Soft tissue injury	0	1 (0.3)
Spinal compression fracture	1 (0.3)	0

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Axitinib n (%)	Sorafenib n (%)
Investigations	2 (0.6)	3 (0.8)
Alanine aminotransferase increased	0	1 (0.3)
Aspartate aminotransferase increased	0	2 (0.6)
Blood alkaline phosphatase increased	0	1 (0.3)
Blood creatinine increased	2 (0.6)	1 (0.3)
Blood lactate dehydrogenase increased	0	1 (0.3)
C-reactive protein increased	0	1 (0.3)
Gamma-glutamyltransferase increased	0	1 (0.3)
Metabolism and nutrition disorders	15 (4.2)	7 (2.0)
Decreased appetite	3 (0.8)	0
Dehydration	9 (2.5)	1 (0.3)
Hypercalcaemia	1 (0.3)	1 (0.3)
Hyperkalaemia	2 (0.6)	1 (0.3)
Hypocalcaemia	0	1 (0.3)
Hypoglycaemia	1 (0.3)	0
Hyponatraemia	1 (0.3)	3 (0.8)
Hypovolaemia	1 (0.3)	0
Musculoskeletal and connective tissue disorders	4 (1.1)	7 (2.0)
Arthralgia	1 (0.3)	1 (0.3)
Back pain	1 (0.3)	2 (0.6)
Flank pain	0	1 (0.3)
Musculoskeletal chest pain	0	1 (0.3)
Pain in extremity	2 (0.6)	0
Polyarthritis	0	1 (0.3)
Spinal column stenosis	0	1 (0.3)
Spondylolisthesis	0	1 (0.3)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	2 (0.6)	2 (0.6)
Neoplasm progression	1 (0.3)	0
Renal cell carcinoma	0	1 (0.3)
Squamous cell carcinoma	0	1 (0.3)
Tumour associated fever	1 (0.3)	0
Nervous system disorders	15 (4.2)	6 (1.7)
Aphasia	1 (0.3)	0
Cerebral haemorrhage	1 (0.3)	0
Cerebral ischaemia	0	1 (0.3)
Cerebrovascular accident	1 (0.3)	1 (0.3)
Dizziness	3 (0.8)	0
Hemicephalalgia	1 (0.3)	0
Hemiparesis	0	1 (0.3)
Ischaemic stroke	0	1 (0.3)
Lethargy	0	1 (0.3)
Leukoencephalopathy	1 (0.3)	0
Loss of consciousness	1 (0.3)	0
Meningeal disorder	1 (0.3)	0
Monoplegia	0	1 (0.3)
Presyncope	1 (0.3)	0
Spinal cord compression	1 (0.3)	0
Syncope	1 (0.3)	0
Transient ischaemic attack	3 (0.8)	0

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Axitinib n (%)	Sorafenib n (%)
Psychiatric disorders	2 (0.6)	1 (0.3)
Anxiety	0	1 (0.3)
Confusional state	1 (0.3)	0
Mental status changes	1 (0.3)	0
Renal and urinary disorders	5 (1.4)	3 (0.8)
Acute prerenal failure	1 (0.3)	0
Haematuria	1 (0.3)	0
Oliguria	0	1 (0.3)
Renal failure acute	3 (0.8)	2 (0.6)
Urinary retention	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	19 (5.3)	13 (3.7)
Cough	0	1 (0.3)
Dyspnoea	5 (1.4)	3 (0.8)
Dyspnoea exertional	1 (0.3)	0
Haemoptysis	1 (0.3)	2 (0.6)
Haemothorax	0	1 (0.3)
Interstitial lung disease	1 (0.3)	0
Lung disorder	1 (0.3)	0
Pleural effusion	3 (0.8)	4 (1.1)
Pleurisy	0	1 (0.3)
Pneumothorax	4 (1.1)	1 (0.3)
Pulmonary embolism	6 (1.7)	1 (0.3)
Pulmonary haemorrhage	0	1 (0.3)
Respiratory distress	1 (0.3)	0
Skin and subcutaneous tissue disorders	1 (0.3)	5 (1.4)
Erythema multiforme	0	3 (0.8)
Hyperhidrosis	1 (0.3)	0
Palmar-plantar erythrodysaesthesia syndrome	0	1 (0.3)
Rash	0	2 (0.6)
Urticaria	1 (0.3)	0
Surgical and medical procedures	1 (0.3)	2 (0.6)
Malignant tumour excision	1 (0.3)	0
Pain management	0	1 (0.3)
Vertebroplasty	0	1 (0.3)
Vascular disorders	6 (1.7)	8 (2.3)
Accelerated hypertension	1 (0.3)	0
Deep vein thrombosis	1 (0.3)	0
Haemorrhage	0	1 (0.3)
Hypertension	1 (0.3)	2 (0.6)
Hypertensive crisis	1 (0.3)	0
Hypotension	1 (0.3)	4 (1.1)
Infarction	0	1 (0.3)
Jugular vein thrombosis	1 (0.3)	0
Subclavian vein thrombosis	1 (0.3)	0

Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary of Regulatory Activities; n = number of subjects with AEs.

Table 11 presents a summary of treatment-related SAEs by SOC and preferred term for the SA set. Overall, 44 (12.3%) subjects in the axitinib arm experienced 61 treatment-related SAEs and 43 (12.1%) subjects in the sorafenib arm experienced 70 treatment-related SAEs. The most frequently reported treatment-related SAEs in the axitinib arm were dehydration and diarrhea, experienced by 7 (1.9% [7 events]) subjects and 6 (1.7% [6 events]) subjects, respectively. The most frequently reported treatment-related SAEs in the sorafenib arm were anemia, diarrhea, pyrexia, and erythema multiforme, each experienced by 3 (0.8%) subjects (3 events each).

Table 11. Summary of Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Axitinib N=359		Sorafenib N=355	
	n (%)	No. of Events	n (%)	No. of Events
Any treatment-related serious AE	44 (12.3)	61	43 (12.1)	70
Blood and lymphatic system disorders				
Anemia	0 (0.0)	0	3 (0.8)	4
Splenic infarction	0 (0.0)	0	1 (0.3)	1
Cardiac disorders				
Angina pectoris	0 (0.0)	0	1 (0.3)	1
Myocardial infarction	0 (0.0)	0	1 (0.3)	1
Endocrine disorders				
Hypothyroidism	1 (0.3)	1	0 (0.0)	0
Secondary hypothyroidism	1 (0.3)	1	0 (0.0)	0
Thyroiditis	0 (0.0)	0	1 (0.3)	1
Eye disorders				
Retinal artery occlusion	1 (0.3)	1	0 (0.0)	0
Retinal vein occlusion	1 (0.3)	1	0 (0.0)	0
Retinal vein thrombosis	1 (0.3)	1	0 (0.0)	0
Gastrointestinal disorders				
Colitis ulcerative	0 (0.0)	0	1 (0.3)	1
Diarrhea	6 (1.7)	6	3 (0.8)	3
Enterocolitis	0 (0.0)	0	1 (0.3)	1
Gastric hemorrhage	1 (0.3)	1	0 (0.0)	0
Gastric ulcer	1 (0.3)	1	0 (0.0)	0
Gastrointestinal hemorrhage	0 (0.0)	0	1 (0.3)	1
Nausea	0 (0.0)	0	1 (0.3)	1
Pancreatitis	0 (0.0)	0	1 (0.3)	1
Retroperitoneal hemorrhage	0 (0.0)	0	1 (0.3)	1
Upper gastrointestinal hemorrhage	0 (0.0)	0	1 (0.3)	1
Vomiting	1 (0.3)	1	0 (0.0)	0
Lower gastrointestinal hemorrhage	1 (0.3)	1	0 (0.0)	0
General disorders and administration site conditions				
Asthenia	1 (0.3)	1	0 (0.0)	0
Chills	1 (0.3)	1	0 (0.0)	0
Fatigue	3 (0.8)	3	0 (0.0)	0
Mucosal inflammation	1 (0.3)	1	0 (0.0)	0
Pyrexia	1 (0.3)	1	3 (0.8)	5
General physical health deterioration	1 (0.3)	1	2 (0.6)	2
Hepatobiliary disorders				
Cholecystitis	0 (0.0)	0	1 (0.3)	1
Hepatic function abnormal	0 (0.0)	0	1 (0.3)	1
Infections and infestations				
Infection	1 (0.3)	1	0 (0.0)	0
Pneumonia	2 (0.6)	2	0 (0.0)	0
Sepsis	1 (0.3)	1	0 (0.0)	0
Muscle abscess	0 (0.0)	0	1 (0.3)	1
Intervertebral discitis	0 (0.0)	0	1 (0.3)	1
Lower respiratory tract infection	1 (0.3)	1	0 (0.0)	0
Injury, poisoning and procedural complications				
Fall	0 (0.0)	0	1 (0.3)	1
Radiation pneumonitis	1 (0.3)	1	0 (0.0)	0

Table 11. Summary of Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Axitinib N=359		Sorafenib N=355	
	n (%)	No. of Events	n (%)	No. of Events
Investigations				
Alanine aminotransferase increased	0 (0.0)	0	1 (0.3)	4
Aspartate aminotransferase increased	0 (0.0)	0	1 (0.3)	3
Blood creatinine increased	0 (0.0)	0	1 (0.3)	1
Blood lactate dehydrogenase increased	0 (0.0)	0	1 (0.3)	1
C-reactive protein increased	0 (0.0)	0	1 (0.3)	1
Gamma-glutamyl transferase increased	0 (0.0)	0	1 (0.3)	3
Blood alkaline phosphatase increased	0 (0.0)	0	1 (0.3)	1
Metabolism and nutrition disorders				
Dehydration	7 (1.9)	7	0 (0.0)	0
Hyperkalemia	0 (0.0)	0	1 (0.3)	1
Hyponatremia	0 (0.0)	0	1 (0.3)	1
Decreased appetite	2 (0.6)	2	0 (0.0)	0
Musculoskeletal and connective tissue disorders				
Pain in extremity	1 (0.3)	1	0 (0.0)	0
Polyarthritis	0 (0.0)	0	1 (0.3)	1
Spinal column stenosis	0 (0.0)	0	1 (0.3)	1
Neoplasms benign, malignant, and unspecified (including cysts and polyps)				
Neoplasm progression	1 (0.3)	1	0 (0.0)	0
Nervous system disorders				
Aphasia	1 (0.3)	1	0 (0.0)	0
Cerebral hemorrhage	1 (0.3)	1	0 (0.0)	0
Leukoencephalopathy	1 (0.3)	1	0 (0.0)	0
Loss of consciousness	1 (0.3)	1	0 (0.0)	0
Presyncope	1 (0.3)	1	0 (0.0)	0
Syncope	1 (0.3)	1	0 (0.0)	0
Transient ischemic attack	3 (0.8)	3	0 (0.0)	0
Ischemic stroke	0 (0.0)	0	1 (0.3)	1
Hemicephalgia	1 (0.3)	1	0 (0.0)	0
Renal and urinary disorders				
Oliguria	0 (0.0)	0	1 (0.3)	2
Renal failure acute	1 (0.3)	1	1 (0.3)	1
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0.0)	0	1 (0.3)	1
Hemoptysis	0 (0.0)	0	2 (0.6)	2
Lung disorder	1 (0.3)	1	0 (0.0)	0
Pneumothorax	1 (0.3)	1	1 (0.3)	1
Pulmonary embolism	2 (0.6)	2	1 (0.3)	1
Skin and subcutaneous tissue disorders				
Erythema multiforme	0 (0.0)	0	3 (0.8)	3
Palmar-plantar erythrodysesthesia syndrome	0 (0.0)	0	1 (0.3)	1
Rash	0 (0.0)	0	2 (0.6)	4

Table 11. Summary of Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Axitinib N=359		Sorafenib N=355	
	n (%)	No. of Events	n (%)	No. of Events
Vascular disorders				
Accelerated hypertension	1 (0.3)	1	0 (0.0)	0
Hypertension	1 (0.3)	1	2 (0.6)	2
Hypertensive crisis	1 (0.3)	1	0 (0.0)	0
Hypotension	0 (0.0)	0	2 (0.6)	2
Jugular vein thrombosis	1 (0.3)	1	0 (0.0)	0
Subclavian vein thrombosis	1 (0.3)	1	0 (0.0)	0
Deep vein thrombosis	1 (0.3)	1	0 (0.0)	0
Hemorrhage	0 (0.0)	0	1 (0.3)	1

% = (n/N)*100
Except for the number of AEs, subjects were counted only once per treatment in each cell. Data cutoff date: 31 August 2010.
MedDRA (version 13.1) coding dictionary applied.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, n = number of subjects fitting specified criteria, No. = number.

Discontinuation: In the axitinib arm, 199 (55.4%) subjects experienced 674 events leading to dose modification or temporary delay of treatment; 220 (62.0%) subjects in the sorafenib arm experienced 568 events leading to dose modification or temporary delay of treatment. The most frequent AEs leading to dose modification or temporary delay of treatment in the axitinib arm were diarrhea and hypertension, experienced by 52 (14.5% [97 events]) and 46 (12.8% [83 events]) subjects. The most frequent AEs leading to dose modification or temporary delay of treatment in the sorafenib arm were palmar-plantar erythrodysesthesia syndrome and diarrhea, experienced by 63 (17.7% [96 events]) and 33 (9.3% [40 events]) subjects.

Overall, 33 (9.2%) subjects in the axitinib arm experienced 35 events leading to discontinuation of the study, of which 14 (3.9%) subjects discontinued due to treatment-related AEs 46 (13.0%) subjects in the sorafenib arm experienced 48 events leading to discontinuation of the study, of which 29 (8.2%) subjects discontinued due to treatment-related AEs. The highest number of AEs by preferred term in the axitinib arm leading to discontinuation of the study were disease progression, fatigue, and transient ischemic attack, experienced by 9 (2.5% [9 events]) subjects, 4 (1.1% [4 events]) subjects, and 3 (0.8% [3 events] subjects), respectively. The highest number of AEs by preferred term in the sorafenib arm leading to discontinuation of the study were disease progression and palmar-plantar erythrodysesthesia syndrome (each experienced by 4 [1.1%] subjects [4 events each]), and diarrhea and asthenia (each experienced by 3 [0.8%] subjects [3 events each]).

Table 12. Summary of Adverse Events That Led to Discontinuation by Treatment, MedDRA System Organ Class, and Preferred Term; Safety Analysis Set

System Organ Class Preferred Term	Axitinib N=359		Sorafenib N=355	
	n (%)	No. of Events	n (%)	No. of Events
Any AE	33 (9.2)	35	46 (13.0)	48
Blood and lymphatic system disorders	1 (0.3)	1	1 (0.3)	1
Anemia	1 (0.3)	1	1 (0.3)	1
Cardiac disorders	0 (0.0)	0	2 (0.6)	2
Angina pectoris	0 (0.0)	0	1 (0.3)	1
Myocardial infarction	0 (0.0)	0	1 (0.3)	1
Eye disorders	1 (0.3)	1	0 (0.0)	0
Retinal vein thrombosis	1 (0.3)	1	0 (0.0)	0
Gastrointestinal disorders	2 (0.6)	2	11 (3.1)	11
Ascites	1 (0.3)	1	0 (0.0)	0
Diarrhea	0 (0.0)	0	3 (0.8)	3
Duodenal ulcer hemorrhage	0 (0.0)	0	1 (0.3)	1
Enterocolitis	0 (0.0)	0	1 (0.3)	1
Gastrointestinal hemorrhage	0 (0.0)	0	1 (0.3)	1
Nausea	0 (0.0)	0	2 (0.6)	2
Periodontitis	0 (0.0)	0	1 (0.3)	1
Upper gastrointestinal hemorrhage	0 (0.0)	0	1 (0.3)	1
Vomiting	1 (0.3)	1	1 (0.3)	1
General disorders and administrative site conditions	15 (4.2)	15	8 (2.3)	8
Asthenia	2 (0.6)	2	3 (0.8)	3
Fatigue	4 (1.1)	4	1 (0.3)	1
Disease progression	9 (2.5)	9	4 (1.1)	4
Hepatobiliary disorders	0 (0.0)	0	2 (0.6)	2
Cholangitis	0 (0.0)	0	1 (0.3)	1
Hepatic function abnormal	0 (0.0)	0	1 (0.3)	1
Infections and infestations	0 (0.0)	0	1 (0.3)	1
Sepsis	0 (0.0)	0	1 (0.3)	1
Injury, poisoning and procedural complications	0 (0.0)	0	1 (0.3)	1
Fall	0 (0.0)	0	1 (0.3)	1
Investigations	1 (0.3)	1	2 (0.6)	2
Blood bilirubin increased	0 (0.0)	0	1 (0.3)	1
Blood creatinine increased	1 (0.3)	1	0 (0.0)	0
Weight decreased	0 (0.0)	0	1 (0.3)	1
Metabolism and nutrition disorders	3 (0.8)	3	0 (0.0)	0
Hypoglycemia	1 (0.3)	1	0 (0.0)	0
Decreased appetite	2 (0.6)	2	0 (0.0)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps	0 (0.0)	0	1 (0.3)	1
Renal cell carcinoma	0 (0.0)	0	1 (0.3)	1
Nervous system disorders	5 (1.4)	5	3 (0.8)	3
Altered state of consciousness	1 (0.3)	1	0 (0.0)	0
Cerebral hemorrhage	1 (0.3)	1	0 (0.0)	0
Hemiparesis	0 (0.0)	0	1 (0.3)	1
Hyperesthesia	0 (0.0)	0	1 (0.3)	1
Transient ischemic attack	3 (0.8)	3	0 (0.0)	0
Ischemic stroke	0 (0.0)	0	1 (0.3)	1

Table 12. Summary of Adverse Events That Led to Discontinuation by Treatment, MedDRA System Organ Class, and Preferred Term; Safety Analysis Set

System Organ Class Preferred Term	Axitinib N=359		Sorafenib N=355	
	n (%)	No. of Events	n (%)	No. of Events
Renal and urinary disorders	0 (0.0)	0	1 (0.3)	1
Renal failure acute	0 (0.0)	0	1 (0.3)	1
Respiratory, thoracic, and mediastinal disorders	5 (1.4)	5	3 (0.8)	3
Dyspnea	1 (0.3)	1	2 (0.6)	2
Dyspnea exertional	1 (0.3)	1	0 (0.0)	0
Pleural effusion	2 (0.6)	2	1 (0.3)	1
Pneumothorax	1 (0.3)	1	0 (0.0)	0
Skin and subcutaneous tissue disorders	1 (0.3)	1	11 (3.1)	11
Erythema multiforme	0 (0.0)	0	2 (0.6)	2
Palmar-plantar erythrodysesthesia syndrome	1 (0.3)	1	4 (1.1)	4
Pruritus	0 (0.0)	0	1 (0.3)	1
Rash	0 (0.0)	0	2 (0.6)	2
Rash generalized	0 (0.0)	0	1 (0.3)	1
Pruritus generalized	0 (0.0)	0	1 (0.3)	1
Vascular disorders	1 (0.3)	1	1 (0.3)	1
Hypertension	1 (0.3)	1	0 (0.0)	0
Hemorrhage	0 (0.0)	0	1 (0.3)	1

% = (n/N)*100
Data cutoff date: 31 August 2010.
MedDRA (version 13.1) coding dictionary applied.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, n = number of subjects meeting prespecified criteria, No. = number.

Deaths: Overall, 113 (31.5%) subjects in the axitinib arm died; 35 (9.7%) subjects in the SA set died on-study and 78 (21.7%) subjects in the SA set died during follow-up. In the sorafenib arm, 109 (30.7%) subjects in the SA set died; 23 (6.5%) subjects died on-study and 86 (24.2%) subjects in the SA set died during follow-up. The most frequently reported reason leading to death for subjects on-study and in follow-up was disease under study. Note that both deaths considered related to study treatment toxicity were reported in subjects in the sorafenib arm (Table 13).

Table 13. Summary of Deaths by Treatment; Safety Analysis Set

Summary of Deaths	Axitinib N=359 n (%)	Sorafenib N=355 n (%)
Subjects who died	113 (31.5)	109 (30.7)
Subjects who died on-study[a]	35 (9.7)	23 (6.5)
Disease under study	28 (7.8)	15 (4.2)
Study treatment toxicity[b]	0	2 (0.6)
Coagulation deranged possibly due to sorafenib/Fragmin or tumor necrosis	0	1 (0.3)
GI bleed sorafenib	0	1 (0.3)
Unknown	2 (0.6)	3 (0.8)
Other	5 (1.4)	3 (0.8)
Acute cerebrovascular accident	1 (0.3)	0
Disease progression	0	1 (0.3)
Duodenal ulcer hemorrhage	0	1 (0.3)
GI hemorrhage and possible intra-abdominal bleed at site of kidney tumor	1 (0.3)	0
General weakness	1 (0.3)	0
Pulmonary embolus	1 (0.3)	0
Sepsis	1 (0.3)	0
Stroke	0	1 (0.3)
Subjects who died during follow-up[c]	78 (21.7)	86 (24.2)
Disease under study	65 (18.1)	72 (20.3)
Study treatment toxicity	0	0
Unknown	3 (0.8)	7 (2.0)
Other	10 (2.8)	7 (2.0)
Acute renal failure and acute myocardial infarction	1 (0.3)	0
Brain hemorrhage	0	1 (0.3)
Cardio-respiratory failure in the course of disease progression	1 (0.3)	0
Disease progresion[d]	0	1 (0.3)
Disease progression[d]	1 (0.3)	1 (0.3)
Hypoxic respiratory failure	0	1 (0.3)
Interstitial lung disease	1 (0.3)	0
Massive intrapulmonary and intrabronchial bleeding	1 (0.3)	0
Pneumonia	0	1 (0.3)
Progression disease	1 (0.3)	0
Progressive disease	3 (0.8)	0
Pseudomonas bronchopneumonia	0	1 (0.3)
Respiratory hemorrhage	1 (0.3)	0
Sepsis	0	1 (0.3)

% = (n/N) × 100.
Data cutoff date: 31 August 2010.
AE = adverse events, CRF = case report form, GI = gastrointestinal, N = number of subjects, n = number of subjects fitting specified criteria.

a. On-study deaths were those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
b. The reason for death was collected on the AE CRF therefore the categorization of death differed. For axitinib, 3/4 deaths related to axitinib was captured under 'Other' (1 each due to GI hemorrhage, general weakness, and sepsis) and 1/4 deaths was captured under 'Disease under study'. For sorafenib, 2/3 deaths due to sorafenib were captured under 'Study treatment toxicity' and 1/3 deaths were captured under 'Disease under study'.
c. Follow-up deaths were those that occurred more than 28 days after the last dose of study drug.
d. 'Disease progression' and 'disease progression' were both listed.

Other Safety Results: The data cutoff date for the other safety evaluations was 31 August 2010. In general, similar proportions of subjects in the axitinib and sorafenib arms experienced Grade 3 or 4 biochemistry laboratory values. For elevated lipase and decreased serum phosphate, there were lower numbers of subjects in similar proportions of subjects in the axitinib and sorafenib arm experienced Grade 3/4 hematology laboratory values; the exception to this was decreased hemoglobin, with a lower number of subjects in the axitinib versus sorafenib arm with Grade 3 values, and a higher number of subjects in the axitinib arm with elevated hemoglobin above the upper limit of normal. In general, similar proportions of subjects in the axitinib and sorafenib arms experienced Grade 3 or 4 biochemistry laboratory values. For elevated lipase and decreased serum phosphate, there were lower numbers of subjects in the sorafenib arm with Grade 4 biochemistry results.

A higher proportion of subjects in the axitinib arm compared with the sorafenib arm had an on-study pulse rate <50 bpm (15.9% vs 5.1%, respectively), an on-study pulse rate >120 bpm (6.7% vs 2.5%, respectively), pulse rate ≥30 bpm increase from Baseline (15.3% vs 9.3%, respectively), pulse rate ≥30 bpm decrease from Baseline (23.4% vs 18.9%, respectively), and ≥5% decrease in weight from Baseline (46.8% vs 42.7%, respectively). Four (1.1%) subjects in the sorafenib arm had an on-study temperature >38.3ºC during the study and 4 (1.1%) subjects had a ≥1.1ºC increase from Baseline temperature (when baseline was >36ºC).

Matched baseline and post-treatment triplicate ECGs were obtained from 86 subjects on the axitinib treatment arm; per protocol, ECGs were only to be performed for subjects on the axitinib treatment arm. Two of the subjects had Grade ≥3 corrected QT interval (QTc) prolongation (absolute QTc >500 msec) at Cycle 1 Day 15.

CONCLUSIONS:

- This Phase 3 study met the primary endpoint, demonstrating statistically significant improvement in the PFS, as determined by the IRC. The 33.5% reduction in the hazard of disease progression or death (hazard ratio [HR] = 0.665; p-value <0.0001) for the axitinib arm vs the active comparator, sorafenib, is clinically meaningful.

- The efficacy results are robust. In addition, the secondary efficacy endpoint, ORR, also confirmed the superiority of axitinib treatment over sorafenib.

- There was no difference between axitinib and the active comparator, sorafenib, in OS in the overall population (HR = 0.969 [95% CI: 0.800, 1.174]). In addition, there was no difference in OS between axitinib and sorafenib in the subgroup of subjects previously treated with a sunitinib-containing regimen (HR = 0.997 [95% CI: 0.782, 1.270]). In the subgroup of subjects previously treated with a cytokine-containing regimen, the HR (0.813 [95% CI: 0.555, 1.191]) favored axitinib. The results in the subgroups of subjects previously treated with bevacizumab or temsirolimus were difficult to interpret due to the low numbers of subjects in each treatment group (59 and 24 subjects, respectively) and the wide CIs, especially in the prior bevacizumab subgroup.

- For the subjects in the prior-sunitinib stratum, there was a 25.9% reduction in the hazard of disease progression or death (HR =0.741; p-value <0.0107) for the axitinib arm vs the active comparator, sorafenib.

- For the subjects in the prior-cytokine stratum, there was a 53.6% reduction in the hazard of disease progression or death (HR = 0.464; p-value <0.0001) for the axitinib arm versus the active comparator, sorafenib.

- AEs were generally tolerable and clinically manageable. There was an increased incidence of hypertension, nausea, dysphonia, and hypothyroidism for subjects in the axitinib arm compared with the sorafenib arm and an increased incidence of palmar-plantar erythrodysesthesia syndrome, rash, and alopecia for subjects in the sorafenib arm compared with the axitinib arm.