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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: INLYTA®/Axitinib (AG-013736)

PROTOCOL NO.: A4061032

PROTOCOL TITLE: Axitinib (AG-013736) as second line therapy for metastatic renal cell cancer: Axis trial

Study Center(s): There were 175 sites in 22 countries that enrolled patients. Of these, there were 5 sites in Australia, 2 sites in Austria, 4 sites each in Brazil, and Poland, 6 sites each in Canada, and Republic of Korea, 7 sites each in China, Germany, and Russian Federation, 10 sites each in France, and United Kingdom, 2 sites in Greece, 5 sites in India, 1 site each in Ireland, and Singapore, 13 sites in Italy, 18 sites in Japan, 3 sites each in Slovakia, and Sweden, 8 sites in Spain, 4 sites in Taiwan, 48 sites in United States, an additional 19 sites were shipped study drug (including 4 sites in The Netherlands), but did not enroll any patients.

Study Initiation Date and Primary Completion and Final Completion Dates:

Study Initiation Date = 15 September 2008
Primary Completion Date = 31 August 2010
Final Completion Date = 25 February 2016

Phase of Development: Phase 3

Study Objectives:

The primary objective of this study was to:

- Compare the Progression Free Survival (PFS) of patients with metastatic renal cell carcinoma (mRCC) receiving AG-013736 (Axitinib) vs Sorafenib following failure of prior systemic first-line regimen containing one or more of the following: sunitinib, bevacizumab + IFN-α, temsirolimus or cytokine(s).

The secondary objectives were to:

- Compare the Overall Survival (OS) of patients in each arm;
- Compare the Objective Response Rate (ORR) of patients in each arm;
- Evaluate the safety and tolerability of AG-013736 (Axitinib);
- Estimate the Duration of Response (DR) of patients in each arm;

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- Compare the kidney specific symptoms, and health status of patients in each arm as measured by the FACT-Advanced Kidney Cancer Symptom Index (FKSI), and EuroQol-5D (EQ-5D).

METHODS

Study Design:

This was a 2-arm, randomized, open-label, multicenter, Phase 3 study of Axitinib vs Sorafenib in patients 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 patients were planned to be 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 patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and by prior therapy (i.e., 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. A schedule of activities is provided in Table 1.

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Table 1 Schedule of Activities

Page 1 of 5

Observation	Screening Day –14 to D0	D1 (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 D28 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	

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.

Abbreviations: BP = blood pressure, C = Cycle, D = Day, RECIST = Response Evaluation Criteria in Solid Tumors, 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 adverse events.

[e] Height did not need to be collected after the first measurement.

[f] BP was to be measured with the patient in the seated position after the patient had been sitting quietly for 5 minutes.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 2 of 5

Observation	Screening Day –14 to D0	D1 (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	Post Treatment: Follow-up D28 After Last Dose
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	

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.

Abbreviations: BP = blood pressure, C = Cycle, CO_2 = carbon dioxide, D = Day, ECOG = Eastern Cooperative Oncology Group, Hgb = hemoglobin, INR = International Normalized Ratio, mm Hg = millimeters of mercury, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase, T_3 = tri-iodothyronine, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cell, Wks = weeks

[g] All patients (in both study arms) were provided a BP monitoring device. Patients were to measure their BP at least twice daily before taking each dose of medication, and BP was recorded in a patient diary. Patients were instructed by the study staff to contact their physician immediately for guidance if their systolic BP rose above 150 mm Hg, diastolic BP rose above 100 mm Hg, or if they developed symptoms perceived to be related to elevated BP (e.g., 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 patients 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 patients (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 (e.g., urine dipstick), protein was to be quantified by 24-hour urine collection. Dose adjustment could have been required (adjustment of the dose once patient was on-study; this did not depend on baseline proteinuria).

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 3 of 5

Observation	Screening Day –14 to D0	D1 (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 D28 After Last Dose
12-Lead ECG[m]		X[l]	X (D15, C1 only)[l]			
Tumor assessments including CT/MRI and bone scan[m]	X (D –28 to D0)			X	X	
CT or MRI of brain[n]	X (D –28 to D0)					

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.

Abbreviations: C = Cycle, CR = complete response, CT = computed tomography, D = Day, ECG = electrocardiogram, MRI = magnetic resonance imaging, PR = partial response, QTc = corrected QT interval, RECIST = Response Evaluation Criteria in Solid Tumors, Wks = weeks

[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 patients randomized to Axitinib only). For all remaining patients (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 patient'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 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 repeated. For all patients, 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 performed by calendar as scheduled until progression of disease by RECIST or death, regardless of whether the patient was receiving study medication or not until permanent discontinuation of study treatment. All radiographic images and bone scans for tumor assessments were submitted for the independent review committee.

[n] CT or MRI of brain was required at baseline and the images were sent to the independent review committee for retrospective confirmation. Patients 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 4 of 5

Observation	Screening Day –14 to D0	D1 (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 D28 After Last Dose
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 (AEs)[s]	Throughout the study period					
Survival[t]	Until at least 3 years after the randomization of the last patient					
Patient-reported outcomes: FKSI and EQ-5D[u]		X	X (every 4 weeks)		X	X

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.

*** If for some reason the sample was not collected at Cycle 1 Day 1, it may have been collected at any time during study.

Abbreviations: AE = adverse event, C = Cycle, D = Day, EQ-5D = EuroQol Group's Self-Reported Health Status Measure, FKSI = Functional Assessment of Cancer Therapy-Kidney Symptom Index, IEC = Independent Ethics Committee, IRB = Institutional Research Board, PK = pharmacokinetics, UGT1A1 = UDP-glucuronosyltransferase 1A1, Wks = weeks

[o] Patients 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] Patient number, randomization, and Axitinib bottle number assignments were obtained via centralized randomization. Required information: site and patient identifiers, demographic information, and stratification variables (including ECOG performance status [0 vs 1] and prior therapy). Study treatment began within 7 days of randomization.

[q] Population PK samples for Axitinib were to be obtained from patients at selected sites on C1, D1; C2, D1; and C3, D1. For patients 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 (i.e., 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 patients 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 patient provided an informed consent as described in protocol Section 8 of Appendix A1.

[t] All patients were followed for survival at least every 3 months after discontinuing study treatment until at least 3 years after randomization of the last patient.

[u] FKSI and EQ-5D (patient-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).

Page 5 of 5						
Observation	**Screening Day –14 to D0**	**D1 (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 D28 After Last Dose**
Additional Research Component (Optional to Sites and Patients)						
De-identified blood sample for pharmacogenomics		X *** (Optional)				
De-identified archival tumor sample		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.
*** If, for some reason, the sample was not collected at C1, D1, it could have been collected at any time during the study.
Abbreviations: C = Cycle, D = Day, ECG = electrocardiogram, Wks = weeks

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Number of Patients (Planned and Analyzed):

Six-hundred and fifty patients were planned to be randomized 1:1 ratio to receive either Axitinib or Sorafenib. A total of 723 patients were randomized in the study between 15 September 2008 and 23 July 2010; 361 patients were randomized to Axitinib, of whom 359 patients received treatment, and 362 patients were randomized to Sorafenib, of whom 355 patients received treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

- Histologically or cytologically confirmed mRCC with a component of clear cell subtype
- Evidence of unidimensionally measurable disease with conventional computed tomography (CT) scan or magnetic resonance imaging (MRI) scan
- Must have failed one prior systemic first-line regimen for mRCC

Exclusion Criteria:

- Prior treatment for mRCC with more than one systemic first-line therapy
- Major surgery less than 4 weeks or radiation less than 2 weeks of starting study drug

Study Treatment:

In this study, patients 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 patient. Axitinib was to be taken beginning on Day 1 of the study. Doses were to be taken approximately 12 hours apart as continuous dosing. Patients 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)

Objective Response Rate (ORR)

Duration of Response (DR)

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0), timing, seriousness, and relatedness of AEs, and laboratory abnormalities.

Patient Reported Outcomes: Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15) and Euro Quality of Life Questionnaire- 5 Dimension (EQ-5D).

Safety Evaluations:

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:

1. The Full Analysis set (FAS) included all patients who were randomized, with study drug assignment designated according to initial randomization, regardless of whether patients 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 patient characteristics.

2. The safety analysis (SA) set consisted of all patients 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 (i.e., all patients who were randomized) using Kaplan-Meier methods and displayed graphically, where appropriate. 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 (i.e., 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 patient characteristics (e.g., 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.

MSKCC risk groups were derived using the following 4 risk factors: high lactate dehydrogenase (>1.5 × upper limit of normal [ULN]), low serum hemoglobin (less than the lower limit of normal [LLN]), high corrected serum calcium (>10 mg/dL), and absence of prior nephrectomy. Risk groups were defined as favorable (0 factors), intermediate (1 or 2 factors), or poor (≥3 factors).

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FKSI-15 was the sum of the scores from the 15 FKSI questions. FKSI-15 was summarized using means (with standard deviations) and medians at each assessment point, based on the observed values as well as changes from baseline both within group and between groups (with 95% CIs for mean changes). Comparisons of the 2 treatments were based on a repeated measures analysis using a mixed effects model. The variables in the model were treatment, time, and treatment-by-time, with baseline as a covariate and time assumed linear. FKSI-DRS was measured as the sum of the scores from the 9 FKSI-DRS questions. Analysis of FKSI-DRS, EQ-5D index, and EQ-VAS followed the same methodology as FKSI-15.

Genotype variables were treated as categorical variables. For the TA repeat polymorphism in the *UGT1A1* promoter only within each of the 3 possible genotype subsets for the most common variants , median event time and a 2-sided 95% CI were provided for the following efficacy endpoints: PFS, OS, and best overall tumor response. Kaplan-Meier method was used to display the data graphically for PFS and OS.

Descriptive statistics were provided for each hematology, biochemistry, and urinalysis test result and for change from baseline by visit.

Triplicate, 12-lead ECGs were planned to be performed at screening and at Cycle 1, Day 15 for the first 50 patients randomized to Axitinib only. At each time point, triplicate data were averaged and all summary statistics and data presentations used the triplicate averaged data.

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RESULTS

Patient Disposition:

Overall summary of patient disposition by treatment is presented in Table 2. A total of 116 patients (32.1%) in the Axitinib arm and 77 patients (21.3%) in the Sorafenib arm had started at least 15 cycles of treatment. The most common reason for discontinuation from treatment in both treatment arms was objective progression or relapse (265 patients [73.4%] and 246 patients [68.0%] in the Axitinib and Sorafenib arms, respectively). Cumulatively, the most common reason for discontinuation from the study start in both treatment arms was death (280 patients [78.0%] in the Axitinib arm and 276 patients [77.7%] in the Sorafenib arm).

Table 2 Overall Summary of Patient Disposition by Treatment; Full Analysis Set

Page 1 of 2

	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	16 (4.4)	31 (8.6)
2	42 (11.6)	55 (15.2)
3	28 (7.8)	32 (8.8)
4	18 (5.0)	21 (5.8)
5	21 (5.8)	23 (6.4)
6	15 (4.2)	22 (6.1)
7	25 (6.9)	25 (6.9)
8	10 (2.8)	16 (4.4)
9	15 (4.2)	17 (4.7)
10	13 (3.6)	9 (2.5)
11	6 (1.7)	10 (2.8)
12	11 (3.0)	6 (1.7)
13	10 (2.8)	3 (0.8)
14	13 (3.6)	8 (2.2)
≥15	116 (32.1)	77 (21.3)
Primary reason for discontinuation from study treatment		
Adverse event	32 (8.9)	52 (14.4)
Patient died	19 (5.3)	14 (3.9)
Protocol violation	4 (1.1)	3 (0.8)
Lost to follow-up	2 (0.6)	3 (0.8)
Other	10 (2.8)	13 (3.6)
Study terminated by sponsor	0	0
Objective progression or relapse	265 (73.4)	246 (68.0)
Global deterioration of health status	14 (3.9)	12 (3.3)
Patient refused continued treatment for reason other than adverse event	13 (3.6)	12 (3.3)

% = (n/N) × 100

Abbreviations: N = number of patients; n = number of patients meeting specified criteria

[a] Full Analysis Set includes all patients who were randomized, with study treatment assignment designated according to initial randomization, regardless of whether patients received study treatment or received a different drug from that to which they were randomized.

[b] Safety Analysis Set consists of all patients who received at least 1 dose of study drug with treatment assignments designated according to actual study treatment received.

[c] A patient was considered to have started a cycle if the patient took at least 1 dose of Axitinib or Sorafenib

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 2 of 2

	Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Primary reason for discontinuation from study		
Adverse event	0	6 (1.7)
Patient died	280 (77.6)	269 (74.3)
Protocol violation	0	0
Lost to follow-up	15 (4.2)	13 (3.6)
Other	56 (15.5)	53 (14.6)
Study terminated by sponsor	1 (0.3)	2 (0.6)
Objective progression or relapse	3 (0.8)	8 (2.2)
Global deterioration of health status	0	0
Patient refused continued treatment for reason other than adverse event	4 (1.1)	4 (1.1)

% = (n/N) × 100
Abbreviations: N = number of patients; n = number of patients meeting specified criteria
[a] Full Analysis Set includes all patients who were randomized, with study treatment assignment designated according to initial randomization, regardless of whether patients received study treatment or received a different drug from that to which they were randomized.
[b] Safety Analysis Set consists of all patients who received at least 1 dose of study drug with treatment assignments designated according to actual study treatment received.
[c] A patient was considered to have started a cycle if the patient took at least 1 dose of Axitinib or Sorafenib.

Patient Demography:

The data cutoff date for Demographic and baseline characteristics was 31 Aug 2010. Demographic and baseline characteristics are summarized in Table 3. The demographic and baseline characteristics were similar between the treatment arms. The majority of patients in each treatment arm were <65 years of age (238 [65.9%] patients in the Axitinib arm; 238 [65.7%] patients in the Sorafenib arm), male (265 [73.4%] patients in the Axitinib arm; 258 [71.3%] patients in the Sorafenib arm), and white (278 [77.0%] patients in the Axitinib arm; 269 [74.3%] patients in the Sorafenib arm). Approximately half of the patients in each treatment arm had an ECOG PS score of 0 (195 [54.0%] patients in the Axitinib arm; 200 [55.2%] patients in the Sorafenib arm) and were in the intermediate MSKCC risk group (199 [55.1%] patients in the Axitinib arm; 210 (58.0%] patients in the Sorafenib arm).

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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)
		Indian Subcontinent Asian	11 (3.0)	13 (3.6)
		Southeast Asian	1 (0.3)	0
		Japanese	26 (7.2)	29 (8.0)
		Korean	11 (3.0)	16 (4.4)
		Chinese	28 (7.8)	23 (6.4)
	Other		5 (1.4)	8 (2.2)
		Mulatto	1 (0.3)	0
		Hispanic	3 (0.8)	8 (2.2)
		Mixed	1 (0.3)	0
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
	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		100 (27.7)	101 (27.9)
	Intermediate		134 (37.1)	130 (35.9)
	Poor		118 (32.7)	120 (33.1)
	Not applicable[c]		9 (2.5)	11 (3.0)

Data cutoff date: 31 Aug 2010.
Countries included in each geographic region are as follows: Asia: China, India, Japan, Korea, Singapore, and Taiwan; European Union: Austria, Germany, France, Great Britain, Greece, Ireland, Italy, Poland, Russia, Slovakia, Spain, and Sweden; North America: Canada and United States; and Other: Australia and Brazil.
Abbreviations: ECOG = Eastern Cooperative Oncology Group, MSKCC = Memorial Sloan-Kettering Cancer Center, N = number of patients, n = number of patients 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 Categorization Based on Criteria for Previously Treated Patients With RCC Using ECOG Performance Status of 1 as a Risk Factor. Using MSKCC risk factors for previously treated patients (hemoglobin, corrected calcium, and ECOG status). ECOG status 0 vs 1. ECOG performance status taken from case report forms and was the last measure taken prior to dosing.
[c] These patients were missing data on some or all of the risk factors (hemoglobin, corrected calcium, and ECOG status) that were used to derive the MSKCC risk groups.

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Primary endpoint Results:

Progression-Free Survival (PFS)

The data cutoff date for PFS was 31 Aug 2010. Table 4 presents a summary of PFS by treatment (stratified analysis) based on IRC assessment for the FAS.

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

Page 1 of 3

Progression-Free Survival Parameter	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Overall stratified analysis (n)	361	362
Patient 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[b]	180 (93.8)	200 (95.2)
Increase in existing lesion (target or nontarget)[c]	83 (46.1)	97 (48.5)
New lesion [c]	51 (28.3)	47 (23.5)
Increase and a new lesion [c]	32 (17.8)	45 (22.5)
Other [c]	14 (7.8)	11 (5.5)
Death without objective progression[b]	12 (6.3)	10 (4.8)
Patient did not progress or die due to any cause while on-study[a]	169 (46.8)	152 (42.0)
Reason for censorship[d]		
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)
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)[e]		
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[f]	0.665	
95% CI of hazard ratio	0.544-0.812	
P-value[g]	<0.0001	

% = (n/N) × 100

The efficacy tables in the body of this document contain those patients with prior sunitinib and cytokine regimens. Presentation of PFS for subgroups based on prior bevacizumab and temsirolimus regimens were not included in this document based on the low number of patients with these prior regimens (59 and 24 patients, respectively), and which resulted in wide confidence intervals. Data cutoff date: 31 Aug 2010.

Abbreviations: CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, IRC = Independent Review Committee, N = number of patients, n = number of patients meeting prespecified criteria, NE = not evaluable, PFS = progression-free survival

[a] On-study included treatment plus 28-day follow-up period.

[b] The denominator for type of event (Objective progression and Death without objective progression) was based on the number of patients observed to have progressed or died due to any cause while on-study.

[c] The denominator for reason of objective progression was based on the number of patients with Objective progression

[d] The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.

[e] Based on the Brookmeyer and Crowley method.

[f] 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.

[g] 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 2 of 3		
Progression-Free Survival Parameter	**Axitinib (N=361)**	**Sorafenib (N=362)**
	n (%)	**n (%)**
Stratification category: prior sunitinib-containing regimen (n)	194	195
Patient 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[b]	109 (93.2)	114 (95.0)
Increase in existing lesion (target or nontarget)[c]	46 (42.2)	55 (48.2)
New lesion[c]	35 (32.1)	27 (23.7)
Increase and a new lesion[c]	20 (18.3)	25 (21.9)
Other[c]	8 (7.3)	7 (6.1)
Death without objective progression[b]	8 (6.8)	6 (5.0)
Patient did not progress or die due to any cause while on-study[a]	77 (39.7)	75 (38.5)
Reason for censorship[d]		
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)[e]		
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[f]	0.741	
95% CI of hazard ratio	0.573-0.958	
P-value[g]	0.0107	

% = (n/N) × 100

The efficacy tables in the body of this document contain those patients with prior sunitinib and cytokine regimens. Presentation of PFS for subgroups based on prior bevacizumab and temsirolimus regimens were not included in this document based on the low number of patients with these prior regimens (59 and 24 patients, respectively), and which resulted in wide confidence intervals. Data cutoff date: 31 Aug 2010.

Abbreviations: CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, IRC = Independent Review Committee, N = number of patients, n = number of patients 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 type of event (Objective progression and Death without objective progression) was based on the number of patients observed to have progressed or died due to any cause while on-study.

[c] The denominator for reason of objective progression was based on the number of patients with Objective progression

[d] The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.

[e] Based on the Brookmeyer and Crowley method.

[f] 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.

[g] 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 3 of 3

Progression-Free Survival Parameter	**Axitinib (N=361)**	**Sorafenib (N=362)**
	n (%)	**n (%)**
Stratification category: prior cytokine-containing regimen (n)	126	125
Patient 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[b]	47 (94.0)	65 (94.2)
Increase in existing lesion (target or nontarget)[c]	28 (59.6)	33 (50.8)
New lesion[c]	9 (19.1)	15 (23.1)
Increase and a new lesion[c]	8 (17.0)	13 (20.0)
Other[c]	2 (4.3)	4 (6.2)
Death without objective progression[b]	3 (6.0)	4 (5.8)
Patient did not progress or die due to any cause while on-study[a]	76 (60.3)	56 (44.8)
Reason for censorship[d]		
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)[e]		
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[f]	0.464	
95% CI of hazard ratio	0.318-0.676	
P-value[g]	<0.0001	

% = (n/N) × 100

The efficacy tables in the body of this document contain those patients with prior sunitinib and cytokine regimens. Presentation of PFS for subgroups based on prior bevacizumab and temsirolimus regimens were not included in this document based on the low number of patients with these prior regimens (59 and 24 patients, respectively), and which resulted in wide confidence intervals. Data cutoff date: 31 Aug 2010.

Abbreviations: CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, IRC = Independent Review Committee, N = number of patients, n = number of patients 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 type of event (Objective progression and Death without objective progression) was based on the number of patients observed to have progressed or died due to any cause while on-study.

[c] The denominator for reason of objective progression was based on the number of patients with Objective progression

[d] The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.

[e] Based on the Brookmeyer and Crowley method.

[f] 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.

[g] 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.

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Secondary Endpoints Results:

Overall Survival (OS)

The data cutoff date for the final OS analysis was 01 Nov 2011. Following the final PFS analysis, patients remained in the treatment arms to which they had been randomized and were followed for evaluation of safety and efficacy, including OS. As of the 01 Nov 2011 cutoff date for the final OS analysis, there were 211 deaths (58.4%) in the Axitinib arm and 214 deaths (59.1%) in the Sorafenib arm. The final OS results for the overall study population were largely consistent with the interim results. Based on the final analysis, there was no significant difference in final OS between Axitinib and the active comparator, Sorafenib. A summary of OS by treatment (stratified analysis) for the FAS is presented in Table 5.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Table 5 Summary of Final Analysis of Overall Survival by Treatment and Stratification Factor; Stratified Analysis - Full Analysis Set

Page 1 of 5		
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[a]		
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[b]	150 (41.6)	148 (40.9)
Reason for censorship[c]		
Alive	136 (90.7)	134 (90.5)
Patients 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)[d]	67.1% (62.0%, 71.7%)	68.2% (63.1%, 72.7%)
Kaplan-Meier estimates of time to event (months)		
Quartile (95% CI)[e]		
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 vs Sorafenib		
Hazard ratio[f]	0.969	
95% CI of hazard ratio	0.800-1.174	
P-value[g]	0.3744	

CI = confidence interval; N = number of patients; n = number of patients meeting specified criteria; NE = not estimable
Data cutoff date: 31 Aug 2010.

[a] The denominator for cause of death was based on the number of patients who died.

[b] Patients who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.

[c] The denominator for reason of censorship was based on the number of patients censored.

[d] Calculated from the log(-log[12-month survival probability]) using a normal approximation and back transformation.

[e] Based on the Brookmeyer and Crowley method.

[f] 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.

[g] 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 2 of 5

Overall Survival Parameter	**Axitinib N=361 n (%)**	**Sorafenib N=362 n (%)**
Overall stratified analysis (n)	**361**	**362**
Stratification category: prior sunitinib-containing regimen (n)	194	195
Dead	131 (67.5)	131 (67.2)
Cause of death[a]		
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[b]	63 (32.5)	64 (32.8)
Reason for censorship[c]		
Alive	56 (88.9)	59 (92.2)
Patients 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)[d]	59.8% (52.5%, 66.3%)	61.8% (54.5%, 68.2%)
Kaplan-Meier estimates of time to event (months)		
Quartile (95% CI)[e]		
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 vs Sorafenib		
Hazard ratio[f]	0.997	
95% CI of hazard ratio	0.782-1.270	
P-value[g]	0.4902	

CI = confidence interval; N = number of patients; n = number of patients meeting specified criteria; NE = not estimable
Data cutoff date: 31 Aug 2010.

[a] The denominator for cause of death was based on the number of patients who died.

[b] Patients who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.

[c] The denominator for reason of censorship was based on the number of patients censored.

[d] Calculated from the log(-log[12-month survival probability]) using a normal approximation and back transformation.

[e] Based on the Brookmeyer and Crowley method.

[f] 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.

[g] 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 3 of 5

Overall Survival Parameter	**Axitinib N=361 n (%)**	**Sorafenib N=362 n (%)**
Overall stratified analysis (n)	**361**	**362**
Stratification category: prior cytokine-containing regimen (n)	126	125
Dead	51 (40.5)	57 (45.6)
Cause of death[a]		
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[b]	75 (59.5)	68 (54.4)
Reason for censorship[c]		
Alive	69 (92.0)	61 (89.7)
Patients 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)[d]	82.3% (74.4%, 87.9%)	80.5% (72.4%, 86.5%)
Kaplan-Meier estimates of time to event (months)		
Quartile (95% CI)[e]		
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 vs Sorafenib		
Hazard ratio[f]	0.813	
95% CI of hazard ratio	0.555-1.191	
P-value[g]	0.1435	

CI = confidence interval; N = number of patients; n = number of patients meeting specified criteria; NE = not estimable
Data cutoff date: 31 Aug 2010.

[a] The denominator for cause of death was based on the number of patients who died.

[b] Patients who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.

[c] The denominator for reason of censorship was based on the number of patients censored.

[d] Calculated from the log(-log[12-month survival probability]) using a normal approximation and back transformation.

[e] Based on the Brookmeyer and Crowley method.

[f] 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.

[g] 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 4 of 5

Overall Survival Parameter	**Axitinib N=361 n (%)**	**Sorafenib N=362 n (%)**
Overall stratified analysis (n)	**361**	**362**
Stratification category: prior bevacizumab-containing regimen (n)	29	30
Dead	22 (75.9)	15 (50.0)
Cause of death[a]		
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[b]	7 (24.1)	15 (50.0)
Reason for censorship[c]		
Alive	7 (100)	13 (86.7)
Patients no longer willing to participate	0	1 (6.7)
Lost to follow-up	0	1 (6.7)
Survival probability at Month 12 (95% CI)[d]	55.2 (36.1, 70.7)	72.2 (52.6, 84.9)
Kaplan-Meier estimates of time to event (months)		
Quartile (95% CI)[e]		
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 vs Sorafenib		
Hazard ratio[f]	1.825	
95% CI of hazard ratio	0.942-3.535	
P-value[g]	0.9648	

CI = confidence interval; N = number of patients; n = number of patients meeting specified criteria; NE = not estimable
Data cutoff date: 31 Aug 2010.

[a] The denominator for cause of death was based on the number of patients who died.

[b] Patients who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.

[c] The denominator for reason of censorship was based on the number of patients censored.

[d] Calculated from the log(-log[12-month survival probability]) using a normal approximation and back transformation.

[e] Based on the Brookmeyer and Crowley method.

[f] 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.

[g] 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 5 of 5		
Overall Survival Parameter	**Axitinib N=361 n (%)**	**Sorafenib N=362 n (%)**
Overall stratified analysis (n)	**361**	**362**
Stratification category: prior temsirolimus-containing regimen (n)	12	12
Dead	7 (58.3)	11 (91.7)
Cause of death[a]		
Disease under study	7 (100)	9 (81.8)
Study treatment toxicity	0	0
Unknown	0	1 (9.1)
Other	0	1 (9.1)
Alive[b]	5 (41.7)	1 (8.3)
Reason for censorship[c]		
Alive	4 (80.0)	1 (100)
Patients no longer willing to participate	0	0
Lost to follow-up	1 (20.0)	0
Survival probability at Month 12 (95% CI)[d]	55.6 (25.6, 77.6)	33.3 (11.7, 56.9)
Kaplan-Meier estimates of time to event (months)		
Quartile (95% CI)[e]		
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 vs Sorafenib		
Hazard ratio[f]	0.459	
95% CI of hazard ratio	0.165-1.278	
P-value[g]	0.0638	

CI = confidence interval; N = number of patients; n = number of patients meeting specified criteria; NE = not estimable
Data cutoff date: 31 Aug 2010.
[a] The denominator for cause of death was based on the number of patients who died.
[b] Patients who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
[c] The denominator for reason of censorship was based on the number of patients censored.
[d] Calculated from the log(-log[12-month survival probability]) using a normal approximation and back transformation.
[e] Based on the Brookmeyer and Crowley method.
[f] 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.
[g] 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 (ORR)

The data cutoff date for ORR was 31 Aug 2010. A summary of the best overall response by treatment (stratified analysis) is presented in Table 6.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

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

Page 1 of 2

Best Overall Response Parameter	Axitinib N=361 n (%)	Sorafenib N=362 n (%)
Overall stratified analysis (n)	361	362
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
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	

% = (n/N) × 100
Data cutoff date: 31 Aug 2010.
Abbreviations: CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, IRC = Independent Review Committee, N = number of patients, n = number of patients 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.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 2 of 2		
Stratification category: prior cytokine-containing regimen (n)	126	125
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 Aug 2010.
Abbreviations: CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, IRC = Independent Review Committee, N = number of patients, n = number of patients 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 (DR)

The data cutoff date for the blinded IRC assessment of DR was 31 Aug 2010. Table 7 presents a summary of the median DR among responders (Complete Responders or Partial Responders) by treatment based on IRC assessment for the FAS.

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

Page 1 of 3

Duration of Response Parameter	**Axitinib N=70 n (%)**	**Sorafenib N=34 n (%)**
Overall stratified analysis (n)	70	34
Patient 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[b]	18 (94.7)	9 (90.0)
Increase in existing lesion (target or nontarget)[c]	11 (61.1)	6 (66.7)
New lesion[c]	2 (11.1)	2 (22.2)
Increase and a new lesion[c]	2 (11.1)	1 (11.1)
Other[c]	3 (16.7)	0
Death without objective progression[b]	1 (5.3)	1 (10.0)
Patient did not progress or die due to any cause while on-study[a]	51 (72.9)	24 (70.6)
Reason for censorship[d]		
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)[e]		
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)

% = (n/N) × 100.
Data cutoff date: 31 Aug 2010.
The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.
Abbreviations: CI = confidence interval, IRC = Independent Review Committee, N = number of patients, n = number of patients meeting specified criteria, NE = not estimable, PD = progressive disease
[a] On-study included treatment plus 28-day follow-up period.
[b] The denominator for type of event (Objective progression and Death without objective progression) was based on the number of patients observed to have progressed or died due to any cause while on-study.
[c] The denominator for reason of objective progression was based on the number of patients with Objective progression
[d] The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.
[e] Based on the Brookmeyer and Crowley method.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 2 of 3

Stratification category: Prior sunitinib-containing regimen (n)	22	15
Patient 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[b]	8 (88.9)	4 (100)
Increase in existing lesion (target or nontarget)[c]	4 (50.0)	2 (50.0)
New lesion[c]	2 (25.0)	2 (50.0)
Increase and a new lesion[c]	1 (12.5)	0
Other[c]	1 (12.5)	0
Death without objective progression[b]	1 (11.1)	0
Patient did not progress or die due to any cause while on-study[a]	13 (59.1)	11 (73.3)
Reason for censorship[d]		
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
Kaplan-Meier estimates of duration of response (months)		
Quartile (95% CI)[e]		
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)

% = (n/N) × 100.
Data cutoff date: 31 Aug 2010.
The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.
Abbreviations: CI = confidence interval, IRC = Independent Review Committee, N = number of patients, n = number of patients meeting specified criteria, NE = not estimable, PD = progressive disease
[a] On-study included treatment plus 28-day follow-up period.
[b] The denominator for type of event (Objective progression and Death without objective progression) was based on the number of patients observed to have progressed or died due to any cause while on-study.
[c] The denominator for reason of objective progression was based on the number of patients with Objective progression
[d] The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.
[e] Based on the Brookmeyer and Crowley method.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 3 of 3

Stratification category: Prior cytokine-containing regimen (n)	41	17
Patient 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[b]	8 (100)	4 (80.0)
Increase in existing lesion (target or nontarget)[c]	5 (62.5)	3 (75.0)
New lesion[c]	0	0
Increase and a new lesion[c]	1 (12.5)	1 (25.0)
Other[c]	2 (25.0)	0
Death without objective progression[b]	0	1 (20.0)
Patient did not progress or die due to any cause while on-study[a]	33 (80.5)	12 (70.6)
Reason for censorship[d]		
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)[e]		
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.
Data cutoff date: 31 Aug 2010.
The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.
Abbreviations: CI = confidence interval, IRC = Independent Review Committee, N = number of patients, n = number of patients meeting specified criteria, NE = not estimable, PD = progressive disease
[a] On-study included treatment plus 28-day follow-up period.
[b] The denominator for type of event (Objective progression and Death without objective progression) was based on the number of patients observed to have progressed or died due to any cause while on-study.
[c] The denominator for reason of objective progression was based on the number of patients with Objective progression
[d] The denominator for reason for censorship was based on the number of patients who did not progress or die due to any cause while on-study.
[e] Based on the Brookmeyer and Crowley method.

Percentage of Participants with Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

The safety results include the cumulative safety results for all patients until 25 Feb 2016. The Safety Analysis Set consisted of all patients who received at least 1 dose of study drug with treatment assignments designated according to actual study treatment received. More than 95% of patients in either treatment arms experienced at least 1 all causality AE. Percentage of Participants with Treatment-Emergent AEs and SAEs is shown in Table 8.

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Table 8 Overall Summary of Adverse Events (All Causality) by Treatment; Safety Analysis Set

	Axitinib N=359	Sorafenib N=355
Number of AEs	4493	4029
	n (%)	**n (%)**
Patients with AEs	345 (96.1)	348 (98.0)
Patients with SAEs	146 (40.7)	127 (35.8)
Patients with Grade 3 or 4 AEs	252 (70.2)	253 (71.3)
Patients with Grade 5 AEs	50 (13.9)	33 (9.3)
Patients discontinued due to AEs	56 (15.6)	62 (17.5)
Patients with dose reduced due to AEs	100 (27.9)	82 (23.1)
Patients with temporary discontinuation due to AEs	228 (63.5)	231 (65.1)

% = (n/N)*100
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; n = number of patients meeting specified criteria.
Includes data up to 28 days after last dose of study treatment.
Except for the number of adverse events, patients are counted only once per treatment in each row.
CTCAE Grade Version 3.0.
MedDRA (v18.1) coding dictionary applied.

Percentage of Participants with Adverse Events (All Causality) by Severity

This includes the cumulative results for all patients until 25 Feb 2016. Percentage of Participants with AEs by Severity is shown in Table 9.

Table 9 Percentage of Participants with Adverse Events (All Causality) by Severity

	Axitinib N=359	Sorafenib N=355
Patients evaluable for AEs	359	355
Number of AEs	4493	4029
	n (%)	**n (%)**
Grade 1	14 (3.9)	11 (3.1)
Grade 2	72 (20.1)	77 (21.7)
Grade 3	171 (47.6)	186 (52.4)
Grade 4	38 (10.6)	41 (11.5)
Grade 5	50 (13.9)	33 (9.3)

% = (n/N)*100
Abbreviations: AE = adverse event
CTCAE Grade Version 3.0
MedDRA (v18.1) coding dictionary applied.

Percentage of Participants with Treatment-Related Adverse Events and Serious Adverse Events

This includes the cumulative results for all patients until 25 Feb 2016. A summary of Treatment-Related Adverse Events and SAE is presented in Table 10.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Table 10 Percentage of Participants with Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs); Safety Analysis Set

	Axitinib N=359	**Sorafenib N=355**
Patients evaluable for AEs	359	355
Number of AEs	2984	2659
	n (%)	**n (%)**
Patients with AEs	331 (92.2)	338 (95.2)
Patients with serious AEs	55 (15.3)	49 (13.8)
Patients with Grade 3 or 4 AEs	192 (53.5)	205 (57.7)
Patients with Grade 5 AEs	4 (1.1)	2 (0.6)
Patients discontinued treatment due to AEs	24 (6.7)	36 (10.1)
Patients with dose reduced due to AEs	92 (25.6)	75 (21.1)
Patients with temporary discontinuation due to AEs	194 (54.0)	207 (58.3)

% = (n/N)*100
Abbreviations: AE = adverse event
CTCAE Grade Version 3.0
MedDRA (v18.1) coding dictionary applied

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Number of Participants with Clinically Significant Laboratory Abnormalities: Hematology

The data cutoff date for the clinically significant laboratory abnormalities in hematology was 31 Aug 2010. Similar proportions of patients in the Axitinib and Sorafenib arms experienced Grade 3 or 4 hematology laboratory values; the exception to this was decreased hemoglobin, with a lower number of patients in the Axitinib arm compared with patients in the Sorafenib arm with Grade 3 values.

Participants with Clinically Significant Laboratory Abnormalities: Hematology is shown in Table 11.

Table 11 Participants with Clinically Significant Laboratory Abnormalities: Hematology; Safety Analysis Set

Hematology Parameter (All Cycles)[a]	Axitinib					Sorafenib				
	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hemoglobin (decreased)	320	93 (29.1)	19 (5.9)	1 (0.3)	0	316	112 (35.4)	41 (13.0)	11 (3.5)	1 (0.3)
Lymphocytes (absolute)	317	7 (2.2)	89 (28.1)	10 (3.2)	0	309	7 (2.3)	93 (30.1)	11 (3.6)	0
Neutrophils (absolute)	316	13 (4.1)	4 (1.3)	2 (0.6)	0	308	20 (6.5)	4 (1.3)	2 (0.6)	0
Platelets	312	47 (15.1)	0	1 (0.3)	0	310	41 (13.2)	3 (1.0)	0	0
White blood cells	320	32 (10.0)	4 (1.3)	0	0	315	36 (11.4)	12 (3.8)	1 (0.3)	0

CTCAE Grade Version 2 used for this analysis. Data cutoff date: 31 Aug 2010. Data source: central laboratory.
% = (n/N)*100, where N=number of patients with baseline measurement and at least 1 postbaseline value.
Abbreviations: CTCAE = Common Terminology for Adverse Events, N/n = number of patients
[a] Does not include baseline.

Number of Participants with Clinically Significant Laboratory Abnormalities: Biochemistry

The data cutoff date for clinically significant laboratory abnormalities in biochemistry was 31 Aug 2010. In general, similar proportions of patients in the Axitinib and Sorafenib arms experienced Grade 3 or 4 biochemistry laboratory values. For lipase and hypophosphatemia, there were a lower number of patients in the Axitinib arm compared with patients in the Sorafenib arm with Grade 3 biochemistry results or Grade 4 biochemistry results.

Participants with Clinically Significant Laboratory Abnormalities: Biochemistry is shown in Table 12.

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Table 12 Participants with Clinically Significant Laboratory Abnormalities: Biochemistry; Safety Analysis Set

Biochemistry Parameter (All Cycles)[a]	Axitinib					Sorafenib				
	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Alanine aminotransferase	331	65 (19.6)	8 (2.4)	1 (0.3)	0	313	57 (18.2)	6 (1.9)	2 (0.6)	3 (1.0)
Alkaline phosphatase	336	88 (26.2)	8 (2.4)	4 (1.2)	0	319	92 (28.8)	15 (4.7)	3 (0.9)	0
Amylase	338	64 (18.9)	12 (3.6)	7 (2.1)	0	319	76 (23.8)	21 (6.6)	6 (1.9)	1 (0.3)
Aspartate aminotransferase	331	59 (17.8)	5 (1.5)	1 (0.3)	0	311	67 (21.5)	7 (2.3)	4 (1.3)	0
Bicarbonate	314	127 (40.4)	11 (3.5)	0	1 (0.3)	291	115 (39.5)	10 (3.4)	0	0
Bilirubin (total)	336	16 (4.8)	8 (2.4)	1 (0.3)	0	318	12 (3.8)	2 (0.6)	1 (0.3)	0
Creatinine	336	155 (46.1)	30 (8.9)	0	0	318	121 (38.1)	9 (2.8)	1 (0.3)	0
Hypercalcemia	336	15 (4.5)	4 (1.2)	0	0	319	4 (1.3)	1 (0.3)	0	0
Hyperglycemia	336	41 (12.2)	45 (13.4)	7 (2.1)	0	319	28 (8.8)	37 (11.6)	7 (2.2)	0
Hyperkalemia	333	0	42 (12.6)	9 (2.7)	0	314	0	22 (7.0)	8 (2.5)	0
Hypernatremia	338	34 (10.1)	19 (5.6)	3 (0.9)	0	319	23 (7.2)	14 (4.4)	1 (0.3)	2 (0.6)
Hypoalbuminemia	337	37 (11.0)	11 (3.3)	1 (0.3)	0	319	25 (7.8)	31 (9.7)	2 (0.6)	0
Hypocalcemia	336	108 (32.1)	20 (6.0)	2 (0.6)	2 (0.6)	319	113 (35.4)	70 (21.9)	3 (0.9)	2 (0.6)
Hypoglycemia	336	23 (6.8)	12 (3.6)	1 (0.3)	0	319	9 (2.8)	16 (5.0)	1 (0.3)	0
Hypokalemia	333	22 (6.6)	0	0	0	314	21 (6.7)	0	5 (1.6)	0
Hyponatremia	338	33 (9.8)	0	11 (3.3)	1 (0.3)	319	27 (8.5)	0	6 (1.9)	1 (0.3)
Hypophosphatemia	336	4 (1.2)	33 (9.8)	6 (1.8)	0	318	8 (2.5)	99 (30.8)	51 (16.0)	0
Lipase	338	53 (15.7)	22 (6.5)	14 (4.1)	2 (0.6)	319	76 (23.8)	25 (7.8)	40 (12.5)	7 (2.2)

CTCAE Grade Version 2 used for this analysis. Data cutoff date: 31 Aug 2010. Data source: central laboratory.
% = (n/N)*100, where N=number of patients with baseline measurement and at least 1 postbaseline value.
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, N/n = number of patients
[a] Does not include baseline.

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Number of Participants with Clinically Significant Laboratory Abnormalities: Urinalysis; Safety Analysis Set

The data cutoff date for Urinalysis was 31 Aug 2010. Similar proportions of patients in the Axitinib arm and the Sorafenib arm had 3+ or 4+ protein in urine on-study. A summary of urinalysis results by treatment is presented in Table 13.

Table 13 Participants with Clinically Significant Laboratory Abnormalities: Urinalysis

Urinalysis Parameter (All Cycles)[a]	Axitinib					Sorafenib				
	N	1+ n (%)	2+ n (%)	3+ n (%)	4+ n (%)	N	1+ n (%)	2+ n (%)	3+ n (%)	4+ n (%)
Urine blood/ hemoglobin	304	45 (14.8)	1 (0.3)	0	0	272	35 (12.9)	0	0	0
Urine glucose	322	12 (3.7)	0	0	1 (0.3)	286	13 (4.5)	3 (1.0)	0	1 (0.3)
Urine protein	326	105 (32.2)	31 (9.5)	27 (8.3)	9 (2.8)	289	91 (31.5)	27 (9.3)	21 (7.3)	7 (2.4)

The denominator for the percent was the number of all treated patients with baseline values and at least 1 postbaseline value for the given parameter. For number of patients, each patient was counted once with maximum severity within each urinalysis test. Data cutoff date: 31 Aug 2010.
Abbreviations: N = number of patients, n = number of patients meeting prespecified criteria,
Note: 1+/2+/3+/4+ = indicates the amount of blood/hemoglobin, glucose and protein in urine.
[a] Does not include baseline.

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Patient Related Outcomes:

Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15) Score

The data cutoff date for FKSI-15 score assessment was 31 Aug 2010. At baseline, 312 (86.4%) of 361 patients in the Axitinib arm and 305 (85.9%) of 355 patients in the Sorafenib arm who were eligible completed all items of the FKSI-15.

A repeated measures mixed-effects model showed the difference between the 2 treatment arms for FKSI-15 observed summary scores by treatment cycle, and are presented together with the medians, SDs, and 95% CIs in Table 14. The sample sizes decreased over time. At Cycle 13, 99 patients remained in the Axitinib arm compared with only 65 patients in the Sorafenib arm. The mean FKSI-15 values were almost identical at baseline (43.199 and 43.339 for Axitinib and Sorafenib, respectively) and remained similar though the study; however, fewer patients remained in the Sorafenib arm over time.

Table 14 FKSI-15 Observed Summary Results; Full Analysis Set

Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Median	Minimum, Maximum	Mean	95% CI	p-value
Baseline	346	43.199 (8.416)	43.465	(16.15,59.00)	342	43.339 (8.162)	43.965	(16.00,60.00)	-0.140	(-1.38, 1.10)	0.8244
Cycle 2/ Day 1	319	42.351 (8.305)	43.000	(15.00,60.00)	296	41.668 (7.696)	42.000	(12.00,58.00)	0.683	(-0.59, 1.99)	0.2918
Cycle 3/ Day 1	279	42.590 (7.729)	43.000	(18.00,58.00)	246	42.424 (7.888)	42.000	(14.00,59.00)	0.166	(-1.18, 1.51)	0.8083
Cycle 4/ Day 1	257	42.791 (8.180)	43.000	(21.00,59.00)	221	43.424 (7.345)	44.000	(18.00,57.00)	-0.632	(-2.04, 0.77)	0.3777
Cycle 5/ Day 1	238	42.968 (8.152)	43.930	(11.00,60.00)	203	42.907 (7.255)	43.000	(22.00,58.00)	0.061	(-1.39, 1.52)	0.9345
Cycle 6/ Day 1	213	42.949 (7.842)	43.000	(10.00,60.00)	179	43.057 (7.724)	43.000	(16.00,59.00)	-0.108	(-1.66, 1.44)	0.8912
Cycle 7/ Day 1	206	42.747 (7.621)	43.000	(15.00,58.00)	158	43.578 (7.621)	44.000	(24.00,59.00)	-0.830	(-2.42, 0.75)	0.3035
Cycle 8/ Day 1	177	43.580 (7.578)	43.000	(20.00,58.00)	136	44.074 (7.757)	45.000	(24.00,59.00)	-0.494	(-2.21, 1.22)	0.5719
Cycle 9/ Day 1	163	43.191 (8.300)	44.000	(18.00,60.00)	118	44.518 (6.511)	44.000	(29.00,59.00)	-1.327	(-3.14, 0.48)	0.1498

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Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Median	Minimum, Maximum	Mean	95% CI	p-value
Cycle 10/ Day 1	146	43.312 (8.564)	43.000	(15.00,59.00)	96	44.771 (7.155)	45.000	(22.00,59.00)	-1.459	(-3.54, 0.62)	0.1683
Cycle 11/ Day 1	122	44.119 (8.306)	43.000	(16.00,60.00)	85	44.438 (7.388)	45.000	(22.00,58.00)	-0.319	(-2.53, 1.89)	0.7764
Cycle 12/ Day 1	110	44.517 (8.212)	45.000	(24.00,60.00)	70	44.357 (7.247)	44.500	(28.00,59.00)	0.160	(-2.21, 2.53)	0.8944
Cycle 13/ Day 1	92	44.492 (7.972)	45.500	(22.00,59.00)	58	45.261 (7.840)	47.000	(19.00,58.00)	-0.769	(-3.39, 1.86)	0.5632
Cycle 14/ Day 1	81	44.485 (8.204)	45.000	(26.00,59.00)	54	44.898 (7.495)	45.500	(18.00,58.00)	-0.413	(-3.17, 2.34)	0.7671
Cycle 15/ Day 1	61	45.291 (7.095)	47.000	(28.00,59.00)	38	45.053 (6.682)	45.500	(32.00,58.00)	0.239	(-2.61, 3.09)	0.8682
Cycle 16/ Day 1	52	45.217 (7.656)	46.000	(29.00,60.00)	34	44.445 (7.160)	44.500	(29.00,58.00)	0.772	(-2.50, 4.05)	0.6404
Cycle 17/ Day 1	47	45.242 (7.344)	45.000	(30.00,60.00)	28	44.438 (7.683)	45.500	(24.00,58.00)	0.804	(-2.75, 4.36)	0.6534
Cycle 18/ Day 1	36	44.861 (7.769)	45.000	(28.00,59.00)	22	44.182 (7.228)	44.500	(29.00,58.00)	0.679	(-3.42, 4.78)	0.7415
Cycle 19/ Day 1	29	45.379 (6.662)	46.000	(29.00,59.00)	14	45.026 (7.705)	46.500	(30.00,57.00)	0.354	(-4.25, 4.96)	0.8776
Cycle 20/ Day 1	20	47.050 (5.375)	47.000	(37.00,59.00)	12	44.780 (6.689)	45.500	(34.00,58.00)	2.270	(-2.12, 6.66)	0.2997
Cycle 21/ Day 1	15	45.850 (5.209)	46.000	(36.00,52.00)	7	44.494 (6.153)	47.000	(34.00,51.00)	1.356	(-3.90, 6.62)	0.5968
End of treatment	163	38.328 (9.472)	38.570	(10.00,59.00)	191	38.457 (8.787)	38.000	(13.00,57.00)	-0.129	(-2.04, 1.78)	0.8945
Follow-up	80	41.919 (8.318)	42.500	(18.00,59.00)	110	40.028 (9.048)	41.000	(13.00,57.00)	1.891	(-0.65, 4.43)	0.1430

Based on patients who completed >50% of the FKSI-15 questions (i.e., ≥8 of 15) as per scoring manual. Larger values are associated with better health states (individual questions were reverse coded as appropriate). P-value was based on 2 sample t-test (2-sided p-values). Data cutoff: 31 Aug 2010.

Abbreviations: CI = confidence interval, FKSI = Functional Assessment of Cancer Therapy Kidney Symptom Index, FKSI-15 = sum of the scores from the 15 FKSI questions, N = number of patients, n = number of patients meeting prespecified criteria, SD = standard deviation

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Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) Score

The data cutoff date for FKSI-DRS score assessment was 31 Aug 2010. Baseline FKSI-DRS assessments were available for 716 patients (i.e., 361 patients in the Axitinib arm and 355 patients in the Sorafenib arm). At baseline, 332 (92.0%) of 361 patients in the Axitinib arm and 327 (92.1%) of 355 patients in the Sorafenib arm completed all items of the FKSI-DRS.

A repeated measures mixed-effects model was used to compare the differences in FKSI-DRS scores between the Axitinib and the Sorafenib arms (Table 15). All results were similar to those obtained based on the full 15 items of FKSI-15 described previously.

Table 15 FKSI-DRS Observed Summary Results; Full Analysis Set

Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Median	Minimum, Maximum	Mean	95% CI	p-value
Baseline	346	28.874 (5.187)	30.000	(10.80,36.00)	341	28.975 (5.193)	29.000	(7.20,36.00)	-0.100	(-0.88, 0.68)	0.7999
Cycle 2/ Day 1	319	28.211 (4.920)	29.000	(12.00,36.00)	295	28.399 (5.064)	30.000	(7.00,36.00)	-0.188	(-0.98, 0.60)	0.6408
Cycle 3/ Day 1	279	28.640 (4.837)	29.000	(12.38,36.00)	244	28.640 (4.868)	29.000	(10.13,36.00)	0.000	(-0.84, 0.84)	1.0000
Cycle 4/ Day 1	257	28.822 (4.952)	30.000	(13.00,36.00)	220	29.130 (4.322)	30.000	(14.00,36.00)	-0.309	(-1.15, 0.53)	0.4723
Cycle 5/ Day 1	238	28.869 (4.880)	30.000	(10.00,36.00)	202	29.007 (4.379)	29.000	(13.00,36.00)	-0.138	(-1.01, 0.74)	0.7562
Cycle 6/ Day 1	213	29.159 (4.462)	30.000	(10.00,36.00)	178	29.098 (4.697)	30.000	(12.00,36.00)	0.060	(-0.85, 0.97)	0.8969
Cycle 7/ Day 1	206	29.042 (4.581)	30.000	(9.00,36.00)	157	29.361 (4.558)	30.000	(18.00,36.00)	-0.320	(-1.27, 0.63)	0.5097
Cycle 8/ Day 1	177	29.520 (4.346)	30.000	(13.00,36.00)	135	29.619 (4.386)	30.000	(18.00,36.00)	-0.099	(-1.08, 0.88)	0.8426
Cycle 9/ Day 1	163	29.194 (4.937)	30.000	(14.00,36.00)	117	29.884 (3.838)	31.000	(19.00,36.00)	-0.690	(-1.77, 0.39)	0.2082
Cycle 10/ Day 1	146	29.343 (4.907)	30.500	(12.00,36.00)	96	29.604 (3.959)	30.000	(18.00,36.00)	-0.261	(-1.44, 0.92)	0.6631
Cycle 11/ Day 1	122	29.762 (4.943)	31.000	(11.00,36.00)	85	29.366 (4.404)	30.000	(11.00,36.00)	0.396	(-0.92, 1.71)	0.5540

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Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Median	Minimum, Maximum	Mean	95% CI	p-value
Cycle 12/ Day 1	110	29.764 (4.507)	31.000	(16.00,36.00)	70	29.257 (4.299)	30.000	(18.00,36.00)	0.507	(-0.83, 1.84)	0.4546
Cycle 13/ Day 1	92	29.594 (4.205)	31.000	(15.00,36.00)	58	29.666 (4.710)	31.000	(16.00,36.00)	-0.072	(-1.53, 1.39)	0.9224
Cycle 14/ Day 1	81	29.711 (4.313)	31.000	(17.00,36.00)	54	29.820 (4.333)	31.000	(17.00,36.00)	-0.108	(-1.61, 1.39)	0.8869
Cycle 15/ Day 1	61	30.324 (3.582)	31.000	(21.00,36.00)	38	29.500 (3.454)	29.500	(21.00,35.00)	0.824	(-0.63, 2.27)	0.2621
Cycle 16/ Day 1	52	30.430 (3.443)	31.000	(22.00,36.00)	34	29.474 (4.146)	29.625	(20.00,36.00)	0.956	(-0.68, 2.59)	0.2491
Cycle 17/ Day 1	47	30.551 (3.331)	31.000	(23.00,36.00)	28	28.737 (4.930)	30.000	(15.00,35.00)	1.814	(-0.09, 3.72)	0.0613
Cycle 18/ Day 1	36	30.194 (3.992)	31.500	(21.00,36.00)	22	29.045 (4.520)	29.500	(19.00,36.00)	1.149	(-1.13, 3.42)	0.3161
Cycle 19/ Day 1	29	30.310 (3.636)	30.000	(21.00,36.00)	14	29.286 (4.795)	30.500	(18.00,35.00)	1.025	(-1.63, 3.68)	0.4402
Cycle 20/ Day 1	20	31.300 (2.736)	31.500	(26.00,36.00)	12	29.250 (4.025)	29.500	(22.00,35.00)	2.050	(-0.39, 4.49)	0.0961
Cycle 21/ Day 1	15	31.067 (3.173)	32.000	(26.00,36.00)	7	30.143 (4.100)	31.000	(23.00,36.00)	0.924	(-2.40, 4.24)	0.5681
End of treatment	163	26.288 (5.806)	26.000	(10.00,36.00)	191	26.517 (5.614)	27.000	(11.00,36.00)	-0.230	(-1.43, 0.97)	0.7060
Follow-up	80	28.263 (4.802)	29.000	(14.00,36.00)	110	27.516 (5.577)	28.000	(12.00,36.00)	0.747	(-0.78, 2.27)	0.3358

Based on patients who completed >50% of the FKSI-DRS questions (i.e., ≥5 of 9) as per scoring manual. Larger values are associated with better health states (individual questions were reverse coded as appropriate). P-value was based on 2 sample t-test (2-sided p-values). Data cutoff: 31 Aug 2010.

Abbreviations: CI = confidence interval, FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms, N = number of patients, n = number of patients meeting pre specified criteria, SD = standard deviation:

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Euro Quality of Life Questionnaire- 5 Dimension (EQ-5D): Health State Profile Utility Score

The data cutoff date for EQ-5D assessment was 31 Aug 2010. A repeated measures mixed-effects model was used to compare the differences in EQ-5D scores between Axitinib and Sorafenib arms. Table 16 presents the comparison in EQ-5D scores between the two arms. The overall between-treatment comparison for Axitinib vs Sorafenib based on the repeated measures mixed effects model was not statistically significant.

Table 16 EQ-5D: Health State Profile Utility Score; Full Analysis Set

Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Median	Minimum, Maximum	Mean	95% CI	p-value
Baseline	347	0.732 (0.275)	0.796	(-0.35, 1.00)	341	0.731 (0.25)	0.796	(-0.32, 1.00)	0.001	(-0.04, 0.04)	0.9732
Cycle2/Day1	326	0.716 (0.267)	0.76	(-0.35, 1.00)	307	0.696 (0.237)	0.725	(-0.29, 1.00)	0.02	(-0.02, 0.06)	0.3241
Cycle3/Day1	287	0.72 (0.243)	0.727	(-0.13, 1.00)	248	0.709 (0.239)	0.727	(-0.35, 1.00)	0.013	(-0.03, 0.05)	0.5301
Cycle4/Day1	262	0.730 (0.236)	0.752	(-0.32, 1.00)	226	0.716 (0.248)	0.727	(-0.35, 1.00)	0.014	(-0.03, 0.06)	0.5146
Cycle5/Day1	244	0.730 (0.237)	0.788	(-0.11, 1.00)	207	0.711 (0.243)	0.725	(-0.59, 1.00)	0.019	(-0.03, 0.06)	0.3907
Cycle6/Day1	221	0.734 (0.230)	0.743	(-0.18, 1.00)	178	0.704 (0.246)	0.725	(-0.18, 1.00)	0.03	(-0.02, 0.08)	0.2118
Cycle7/Day1	213	0.718 (0.267)	0.743	(-0.59, 1.00)	163	0.728 (0.228)	0.76	(-0.18, 1.00)	-0.011	(-0.06, 0.04)	0.6866
Cycle8/Day1	181	0.756 (0.236)	0.796	(-0.22, 1.00)	136	0.702 (0.259)	0.725	(-0.24, 1.00)	0.055	(-0.00, 0.11)	0.0516
Cycle9/Day1	169	0.760 (0.227)	0.796	(-0.35, 1.00)	120	0.730 (0.229)	0.725	(-0.07, 1.00)	0.031	(-0.02, 0.08)	0.2618
Cycle10/Day1	151	0.734 (0.243)	0.76	(-0.18, 1.00)	98	0.730 (0.233)	0.735	(-0.18, 1.00)	0.004	(-0.06, 0.07)	0.8967
Cycle11/Day1	126	0.764 (0.235)	0.796	(-0.18, 1.00)	87	0.724 (0.250)	0.743	(-0.18, 1.00)	0.04	(-0.03, 0.11)	0.2349
Cycle12/Day1	110	0.744 (0.244)	0.796	(-0.18, 1.00)	73	0.734 (0.232)	0.725	(-0.02, 1.00)	0.01	(-0.06, 0.08)	0.7921
Cycle13/Day1	96	0.760	0.788	(-0.17, 1.00)	61	0.753	0.76	(-0.02, 1.00)	0.007	(-0.06, 0.08)	0.8402

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Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Median	Minimum, Maximum	Mean	95% CI	p-value
Cycle14/Day1	80	0.723 (0.211)	0.725	(-0.11, 1.00)	57	0.752 (0.232)	0.743	(-0.24, 1.00)	-0.029	(-0.11, 0.05)	0.4623
Cycle15/Day1	63	0.730 (0.239)	0.796	(0.00, 1.00)	41	0.758 (0.211)	0.76	(0.18, 1.00)	-0.028	(-0.12, 0.06)	0.5433
Cycle16/Day1	54	0.749 (0.255)	0.762	(0.15, 1.00)	37	0.785 (0.191)	0.796	(0.52, 1.00)	-0.036	(-0.12, 0.05)	0.3924
Cycle17/Day1	48	0.779 (0.220)	0.796	(0.29, 1.00)	29	0.764 (0.158)	0.743	(0.19, 1.00)	0.016	(-0.07, 0.10)	0.7242
Cycle18/Day1	37	0.755 (0.186)	0.796	(0.26, 1.00)	20	0.755 (0.193)	0.735	(0.19, 1.00)	-0.001	(-0.11, 0.11)	0.9925
Cycle19/Day1	29	0.734 (0.204)	0.796	(-0.02, 1.00)	14	0.804 (0.208)	0.822	(0.52, 1.00)	-0.07	(-0.22, 0.08)	0.3624
Cycle20/Day1	21	0.794 (0.253)	0.812	(0.19, 1.00)	12	0.771 (0.184)	0.796	(0.52, 1.00)	0.023	(-0.13, 0.18)	0.7623
Cycle21/Day1	16	0.700 (0.220)	0.761	(0.08, 1.00)	7	0.771 (0.182)	0.725	(0.52, 1.00)	-0.071	(-0.31, 0.17)	0.5397
END OF TREATM	169	0.608 (0.273)	0.689	(-0.43, 1.00)	196	0.612 (0.186)	0.689	(-0.59, 1.00)	-0.004	(-0.07, 0.06)	0.9036
Follow-up	76	0.682 (0.316)	0.725	(-0.33, 1.00)	106	0.666 (0.310)	0.718	(-0.24, 1.00)	0.016	(-0.07, 0.10)	0.7224
						(0.294)					
						(0.295)					

Based on patients who completed ALL of the EQ-5D questions as per the scoring manual.
Larger values are associated with better health states
P-value is based on two sample t-test (2 sided P-values)
Data cutoff date: 31 Aug 2010
Abbreviations: CI = confidence interval, N = number of patients, n = number of patients meeting pre specified criteria, SD = standard deviation:

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Euro Quality of Life Questionnaire- 5 Dimension (EQ-5D): Visual Analog Scale (VAS); Full Analysis Set

The data cutoff date for EQ-5D VAS assessment was 31 Aug 2010. A repeated measures mixed effects model was used to compare differences between treatment arms, as reported in Table 17.

Table 17 EQ-5D VAS; Full Analysis Set

Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Media n	Minimum, Maximum	Mean	95% CI	p-value
Baseline	341	70.560 (19.187)	75	(0.00,100.0)	339	70.351 (17.403)	70	(7.00,100.0)	0.209	(-2.55, 2.97)	0.8817
Cycle2/Day1	317	69.003 (20.195)	72	(6.00,100.0)	302	67.606 (18.265)	70	(1.00,100.0)	1.397	(-1.65, 4.44)	0.3678
Cycle3/Day1	280	69.843 (17.927)	70	(10.00,100.0)	250	69.712 (18.429)	70	(7.00,100.0)	0.131	(-2.97, 3.24)	0.9341
Cycle4/Day1	261	69.180 (18.636)	70	(8.00,100.0)	224	70.759 (17.189)	75	(6.00,100.0)	-1.579	(-4.80, 1.64)	0.3355
Cycle5/Day1	244	69.705 (18.330)	70	(7.00,100.0)	205	71.888 (16.999)	75	(5.00,100.0)	-2.183	(-5.49, 1.12)	0.1946
Cycle6/Day1	220	69.900 (18.168)	70	(20.00,100.0)	178	71.365 (17.019)	72	(8.00,100.0)	-1.465	(-4.97, 2.04)	0.4111
Cycle7/Day1	209	69.919 (18.063)	75	(20.00,100.0)	163	72.282 (17.521)	75	(7.00,100.0)	-2.364	(-6.03, 1.30)	0.2053
Cycle8/Day1	180	70.756 (19.183)	75	(15.00,100.0)	139	71.475 (18.523)	75	(7.00,100.0)	-0.719	(-4.92, 3.48)	0.7363
Cycle9/Day1	168	70.667 (18.556)	74	(12.00,100.0)	121	73.380 (17.473)	77	(7.00,100.0)	-2.713	(-6.96, 1.54)	0.2099
Cycle10/Day1	151	70.629 (18.680)	72	(15.00,100.0)	98	75.102 (14.854)	76	(30.00,100.0)	-4.473	(-8.89,-0.06)	0.0471
Cycle11/Day1	126	72.103 (18.064)	75	(20.00,100.0)	87	74.586 (15.161)	75	(30.00,100.0)	-2.483	(-7.14, 2.17)	0.2942
Cycle12/Day1	111	71.730 (17.276)	75	(20.00,99.00)	73	73.959 (15.852)	75	(23.00,100.0)	-2.229	(-7.20, 2.74)	0.3777
Cycle13/Day1	94	70.723 (19.147)	75	(15.00,100.0)	61	75.639 (14.571)	80	(30.00,100.0)	-4.916	(-10.6, 0.77)	0.0895
Cycle14/Day1	81	69.420	73	(0.00,96.00)	58	75.362	80	(27.00,100.0)	-5.942	(-12.3, 0.38)	0.0651

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Time	Axitinib N = 361				Sorafenib N=362				Axitinib - Sorafenib		
	n	Mean (SD)	Median	Minimum, Maximum	n	Mean (SD)	Median	Minimum, Maximum	Mean	95% CI	p-value
Cycle15/Day1	62	73.016 (20.286)	75	(30.00,98.00)	42	75.357 (15.875)	80	(45.00,100.0)	-2.341	(-8.42, 3.74)	0.4469
Cycle16/Day1	52	70.269 (15.325)	71	(26.00,97.00)	37	73.676 (15.368)	80	(37.00,97.00)	-3.406	(-11.1, 4.24)	0.3782
Cycle17/Day1	48	71.375 (19.272)	75	(33.00,95.00)	30	73.767 (15.699)	77	(40.00,97.00)	-2.392	(-10.4, 5.61)	0.5535
Cycle18/Day1	37	70.459 (17.840)	75	(26.00,98.00)	23	73.870 (16.298)	80	(45.00,97.00)	-3.41	(-13.1, 6.23)	0.4818
Cycle19/Day1	29	71.034 (18.853)	72	(29.00,97.00)	14	70.571 (16.904)	71	(40.00,97.00)	0.463	(-10.9,11.82)	0.9348
Cycle20/Day1	21	73.143 (16.963)	74	(45.00,97.00)	12	66.917 (17.956)	59.5	(44.00,97.00)	6.226	(-5.76,18.21)	0.2977
Cycle21/Day1	16	74.563 (15.347)	73.5	(45.00,96.00)	7	64.714 (17.758)	58	(48.00,87.00)	9.848	(-5.32,25.01)	0.1912
END OF TREATM	166	61.759 (16.054)	63.5	(9.00,100.0)	197	61.690 (16.183)	65	(5.00,100.0)	0.069	(-4.34, 4.48)	0.9756
Follow-up	76	64.382 (21.668)	69	(9.00,98.00)	109	66.037 (20.973)	70	(10.00,100.0)	-1.655	(-7.68, 4.37)	0.5886

Larger values are associated with better health states
P-value is based on two sample t-test (2 sided P-values)
Data cutoff date: 31 Aug 2010
Abbreviations: CI = confidence interval, N = number of patients, n = number of patients meeting pre specified criteria, SD = standard deviation

Additional Safety Results:

SAEs: This includes the cumulative results for all patients until 25 Feb 2016. All causality and treatment-related serious AEs are presented in Table 18. General disorders and administration side conditions and gastrointestinal disorders were the most commonly reported SAEs among patients.

Table 18 Treatment-Emergent Serious Adverse Events by System Organ Class (All Causalities and Treatment-Related); Safety Analysis Set

System Organ Class	AG-013736 N=359		Sorafenib N=355	
	All Causalities	Treatment-Related	All Causalities	Treatment-Related
Blood and lymphatic system disorders	0	0	14	5
Cardiac disorders	26	10	14	4
Endocrine disorders	2	2	2	2
Eye disorders	4	4	1	0
Gastrointestinal disorders	32	12	30	10
General disorders and administration site conditions	62	11	47	7
Hepatobiliary disorders	3	0	5	2
Immune system disorders	1	0	0	0
Infections and infestations	24	7	26	3
Injury, poisoning and procedural complications	11	1	4	1
Investigations	4	1	15	14
Metabolism and nutrition disorders	21	11	8	2
Musculoskeletal and connective tissue disorders	6	1	8	1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	5	1	3	0
Nervous system disorders	21	13	8	1
Psychiatric disorders	3	0	2	0
Renal and urinary disorders	8	2	4	2
Reproductive system and breast disorders	2	0	1	1
Respiratory, thoracic and mediastinal disorders	29	5	22	7
Skin and subcutaneous tissue disorders	2	0	8	8
Surgical and medical procedures	0	0	2	0
Vascular disorders	7	6	8	5

Abbreviations: N = number of patients

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AEs: This includes the cumulative results for all patients until 25 Feb 2016. Gastrointestinal disorders and general disorders and administration site conditions were the most common treatment-emergent non-serious AEs occurring in ≥5% of patients. All causality and treatment-related non-serious AEs are presented in Table 19.

Table 19 Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in ≥5 % of patients; Safety Analysis Set

System Organ Class Preferred Term	AG-013736 (N=359)		Sorafenib (N=355)	
	All Causalities	Treatment-Related	All Causalities	Treatment-Related
Blood and lymphatic system disorders	28	15	106	48
Anemia	28	15	106	48
Endocrine disorders	89	86	36	32
Hypothyroidism	89	86	36	32
Gastrointestinal disorders	1551	1261	996	799
Abdominal pain	95	50	69	25
Abdominal pain upper	50	34	20	10
Constipation	116	54	101	56
Diarrhea	736	682	449	421
Dyspepsia	46	37	22	19
Flatulence	22	18	10	10
Nausea	212	164	138	107
Stomatitis	113	110	87	82
Vomiting	161	112	100	69
General disorders and administration site conditions	781	630	550	388
Asthenia	203	172	120	104
Chest pain	34	14	24	10
Fatigue	366	315	210	151
Mucosal inflammation	99	95	83	81
Edema peripheral	25	10	35	17
Pain	23	12	19	5
Pyrexia	31	12	59	20
Infections and infestations	33	5	13	3
Nasopharyngitis	33	5	13	3
Investigations	253	194	234	189
Blood thyroid stimulating hormone increased	22	20	16	14
Lipase increased	15	13	50	48
Weight decreased	216	161	168	127
Metabolism and nutrition disorders	305	233	171	130
Decreased appetite	279	215	161	125
Dehydration	26	18	10	5
Musculoskeletal and connective tissue disorders	387	165	283	118
Arthralgia	111	47	55	22
Back pain	96	17	65	10
Muscle spasms	14	8	30	16
Musculoskeletal pain	41	15	31	7
Myalgia	43	32	15	11
Pain in extremity	82	46	87	52

Abbreviations: N = number of patients

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

System Organ Class Preferred Term	AG-013736 (N=359)		Sorafenib (N=355)	
	All Causalities	Treatment-Related	All Causalities	Treatment-Related
Nervous system disorders	176	137	119	78
Dizziness	42	24	28	13
Dysgeusia	56	55	32	32
Headache	78	58	59	33
Psychiatric disorders	41	15	24	10
Insomnia	41	15	24	10
Respiratory, thoracic and mediastinal disorders	470	274	301	123
Cough	107	28	90	20
Dysphonia	158	144	51	45
Dyspnea	100	31	78	19
Dyspnea exertional	21	7	13	4
Epistaxis	37	33	20	14
Hemoptysis	10	4	21	5
Oropharyngeal pain	37	27	28	16
Skin and subcutaneous tissue disorders	522	505	955	931
Alopecia	20	18	145	138
Dry skin	47	47	47	43
Erythema	14	13	52	50
Palmar plantar erythrodysesthesia syndrome	339	339	484	483
Pruritus	30	26	59	57
Rash	72	62	168	160
Vascular disorders	338	308	181	171
Hypertension	318	303	174	169
Hypotension	20	5	7	2

Abbreviations: N = number of patients

PERMANENT DISCONTINUATION DUE TO ADVERSE EVENTS: This includes the cumulative results for all patients until 25 Feb 2016. Overall 17 (4.7%) patients in the Axitinib group and 28 (7.9%) patients in the Sorafenib group discontinued permanently from the study due to AEs related to study drug. In addition, 6 (1.7%) and 5 (1.4%) patients from Axitinib and Sorafenib groups, respectively permanently discontinued from the study due to AEs that were judged as not related to study drug.

DEATHS: This includes the cumulative results for all patients until 25 Feb 2016. In the Axitinib arm, 280 (78.0%) patients died in total; 48 (13.4%) patients died on-study and 232 (64.6%) patients died during follow-up. In the Sorafenib arm, 276 (77.7%) patients died in total; 32 (9.0%) patients died on-study and 244 (68.7%) patients died during follow-up. A summary of deaths reported is presented in Table 20.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Table 20 Death summary; Safety Analysis Set

Page 1 of 2

Variable	Axitinib N=359 n (%)	Sorafenib N=355 n (%)
Patients who died	280 (78.0)	276 (77.7)
Patients who died while on-study[a,b]	**48 (13.4)**	**32 (9.0)**
Disease under study	36 (10.0)	20 (5.6)
Study treatment toxicity	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	5 (1.4)	6 (1.7)
Other	8 (2.2)	4 (1.1)
Acute cerebrovascular accident	1 (0.3)	0
Acute myocardial infarction	1 (0.3)	0
Cardiac infarction	1 (0.3)	0
Cardiopulmonary failure	0	1 (0.3)
Coronary plaque - hemorrhage, coronary atherosclerosis	1 (0.3)	0
Duodenal ulcer hemorrhage	0	1 (0.3)
GI hemorrhage & poss. intra-abdominal bleed at site of kidney tumor	1 (0.3)	0
General weakness	1 (0.3)	0
Heart failure, GI bleeding of the stomach lining	0	1 (0.3)
Pulmonary embolus	1 (0.3)	0
Sepsis	1 (0.3)	0
Stroke	0	1 (0.3)

% = (n/N)*100
Abbreviations: N = number of patients; n = number of patients meeting specified criteria; GI = gastrointestinal; poss = possible.
[a] On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
[b] Death data were collected from 2 sources, the AE CRF (Grade 5 AEs) and Notice of Death CRF. Deaths reported in this table are based on dates reported in the Notice of Death CRF page.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

Page 2 of 2		
Variable	**Axitinib N=359 n (%)**	**Sorafenib N=355 n (%)**
Patients who died during follow-up[c]	**232 (64.6)**	**244 (68.7)**
Disease under study	204 (56.8)	202 (56.9)
Study treatment toxicity	0	0
Unknown	19 (5.3)	27 (7.6)
Other	9 (2.5)	15 (4.2)
Acute renal failure and acute myocardial infarction	1 (0.3)	0
Brain hemorrhage	0	1 (0.3)
Brain metastasis aggravation	0	1 (0.3)
Cardio-respiratory failure in the course of disease progression	1 (0.3)	0
Decreased consciousness due to slip down	0	1 (0.3)
Disease progression	0	1 (0.3)
Disease progression	0	1 (0.3)
Hypoxic respiratory failure	0	1 (0.3)
Interstitial lung disease	1 (0.3)	0
Intracerebral hemorrhage	1 (0.3)	0
Lung cancer	1 (0.3)	0
Massive intrapulmonary and intrabronchial bleeding	1 (0.3)	0
Multiple system organ failure	0	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)
Possible reason of death is cardiac failure due to infarction	0	1 (0.3)
Progression disease	1 (0.3)	4 (1.1)
Pseudomonas bronchopneumonia	0	1 (0.3)
Respiratory hemorrhage	1 (0.3)	0
Sepsis	0	1 (0.3)

% = (n/N)*100
Abbreviations: N = number of patients; n = number of patients meeting specified criteria; GI = gastrointestinal; poss = possible.
[c] Follow-up deaths are those that occurred more than 28 days after the last dose of study drug.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)

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 (HR = 0.665; p-value <0.0001) for the Axitinib arm vs the active comparator, Sorafenib, is clinically meaningful.

- The efficacy results are robust, as indicated by the sensitivity analyses that confirmed the primary analysis of the PFS endpoint. In addition, the secondary efficacy endpoint, ORR, also confirmed the superiority of Axitinib treatment over Sorafenib; another secondary endpoint, OS, was immature at the time of the final PFS analysis and the interim OS result will be updated at a later date.

- For the patients 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 patients 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 patients in the Axitinib arm compared with the Sorafenib arm, and an increased incidence of palmar plantar erythrodysesthesia syndrome, rash, and alopecia for patients in the Sorafenib arm compared with the Axitinib arm.

- In general, the patient-reported outcome data suggest that Axitinib provides patients with a benefit in PFS, while generally enabling them to maintain their quality of life as compared with Sorafenib. There was no difference in the overall FKSI-15 scores between the 2 treatment arms over time.

- No new important safety signals were observed.

090177e18bdbc6a1\Approved\Approved On: 04-May-2017 09:36 (GMT)