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

PROTOCOL NO.: A4061035

PROTOCOL TITLE: Phase 2 Study of AG-013736 as Second-Line Treatment in Patients with Metastatic Renal Cell Cancer

Study Centers: A total of 18 centers in Japan took part in the study and enrolled subjects.

Study Initiation Date, Primary Completion and Final Completion Dates:
First Subject First Visit (FSFV): 12 December 2007
Primary Completion date: 26 February 2010
Last Subject Last Visit (LSLV): 09 August 2013

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- Evaluate objective tumor response of AG-013736 (axitinib) for metastatic renal cell cancer (mRCC).

Secondary Objectives:

- Evaluate the progression-free survival (PFS);
- Evaluate time to tumor progression (TTP);
- Evaluate duration of response (DR);
- Evaluate overall survival (OS);
- Evaluate the safety profile of axitinib;
- Investigate the changes of the plasma concentration profiles of soluble vascular endothelial growth factor receptor 1 (s-VEGFR1), soluble vascular endothelial growth factor receptor 2 (s-VEGFR2), soluble vascular endothelial growth factor receptor 3 (s-VEGFR3), soluble stem cell factor receptor (s-KIT) and vascular endothelial growth factor (VEGF).

METHODS

Study Design: This study was an axitinib single agent, open-label, non-randomized, multicenter Phase 2 study in subjects with mRCC.

Axitinib 5 mg was administered orally twice daily (BID) on a continuous schedule. Cycle length was 28 days. If the drug was well tolerated at 5 mg BID, the dose of axitinib was to be titrated to 7 mg BID and then to a maximum of 10 mg BID. Treatment was continued until the subject met the discontinuation criteria. The schedule of tests and procedures is given in Table 1.

Table 1. Schedule of Tests and Procedures

Observation	Screening	Cycle 1 (Days ± Acceptable range)[a]				Cycle 2-4 (Days ± Acceptable Range) [a]		Cycle 5 or Later[a] (Days ± Acceptable Range)	Post Treatment (Days ± Acceptable Range)	
	Within 14 Days Predosing	Day 1 (Predosing) - 4 days	Day 8 ± 4 Days	Day 15 ± 4 Days	Day 22 ± 4 Days	Day 1 ± 4 Days	Day 15 ± 4 Days	Day 1 ± 4 Days	At End of Treatment/ Discontinuation[b] + 4 days	Follow Up 28 days After Last Dose[c]
Informed consent	X[d]									
Subject background[e]	X									
Body weight, body temperature, pulse rate	X	X	X	X	X	X	X	X	X	
Blood pressure[f]	X	X	X	X	X	X	X	X	X	
Home blood pressure monitoring[g]		Throughout the study period								
ECOG performance status	X	X	X	X	X	X	X	X	X	
Hematology[h]	X	X[i]	X	X	X	X	X	X	X	
Coagulation test[j]	X	X[i]	X	X	X	X	X	X	X	
Chemistry[k]	X	X[i]	X	X	X	X	X	X	X	
Thyroid function test[l]	X	X[i]	X	X	X	X (Cycles 2,3 only)		X (Odd number cycles only	X	
Urine analysis[m]	X[n]	X[i]	X	X	X	X	X	X	X	
12-lead ECG[o]	X			X[p]						
Blood sampling for genotyping		X								
Blood sampling for PK (for population PK analysis)[q]		X				X[q] (Cycles 3 only)		X[q] (Cycles 5,7 only)		
Blood sampling for PK (when dose is increased)[r]				When dose was titrated						

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Blood sampling for pharmacodynamic markers[s]		X				X		X (Until Cycle 7)	X	
Pregnancy test	X[t]									
Tumor assessment[u]	X[v]					X[w] (Cycles 3 only)		X[w] (Odd number cycles only)		X[x]
Bone scintigraphy	X[v]									
Brain CT / MRI[y]	X[v]									
Drug compliance		←	—	—	—	—	—	—	→	
Concomitant medications / therapies	←	—	—	—	—	—	—	—	—	→
Adverse events		←	—	—	—	—	—	—	→	
Serious adverse events	←	—	—	—	—	—	—	—	—	→
Survival[z]		←	—	—	—	—	—	—	→	

CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; PK = pharmacokinetic.

a. A cycle length was 28 days.
b. If the tests and procedures were performed after last dose, these were not repeated.
c. Adverse event was assessed at the visit after 28 days or later from last dose.
d. Within 28 days prior to registration on the study.
e. Including the smoking status.
f. Blood pressure was measured twice, separated by at least 1 hour, at each clinic visit (including screening visit). Blood pressure measurements were made with the subject in the seated position after the subject had been seated quietly for 5 minutes.
g. Blood pressure measurements were made at least twice daily prior to each axitinib dosing on an outpatient basis and recorded in a Subject Diary

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		- 4 days	± 4 Days	± 4 Days	± 4 Days	± 4 Days	± 4 Days	± 4 Days	+ 4 days	

during outpatient period, using blood pressure cuff provided by the sponsor for home monitoring. Subjects were instructed by the study staff to temporarily hold doses and contact their investigator immediately for guidance if their systolic blood pressure was elevated above 150 mm Hg, or diastolic blood pressure was elevated above 100 mm Hg, or if they developed symptoms perceived to be related to elevated blood pressure (eg, headache, visual disturbance). If subjects were unable to contact their investigator for guidance, subjects were to restart dosing when systolic blood pressure fell below 140 mm Hg and diastolic blood pressure fell below 90 mm Hg, and all symptoms related to elevated blood pressure were resolved.

h. Red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count (WBC) and differential, platelet count.

i. If the tests at screening were performed within 7 days prior to treatment period, the tests on Cycle 1 Day 1 were not repeated.

j. Prothrombin time (PT) and activated partial thromboplastin time (APTT).

k. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total protein, albumin, calcium (Ca), sodium (Na), potassium (K), chloride (Cl), total birilubin, blood urea nitrogen (BUN), creatinine, and glucose.

l. Thyroid function test for Free-T3, Free-T4, and thyroid stimulating hormone (TSH) was performed at screening, Cycle 1 Day 1, Day 8, Day 15, Day 22, Cycle 2 Day 1, Cycle 3 Day 1 and subsequently Day 1 of odd number cycles. Hypothyroidism was to be treated per standard medical practice to maintain euthyroid state.

m. Urine protein, urine glucose, urine occult blood (quantitative or semiquantitative for all), and urinary sediment (urinary sediment was performed at screening and only Day 1 of each cycle). If urinalysis (semiquantitative testing, eg, dipstick) showed ≥2+ proteinuria, a 24-hour urine collection was to be performed. In urinary sediment, erythrocyte morphology, and RBC cast were observed by microscopy.

n. If urinalysis (semiquantitative testing, eg, dipstick) showed ≥2+ proteinuria, a 24-hour urine collection was to be performed; subjects with total protein <2 g/24 hours could be enrolled.

o. Three consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine mean QTc interval. The ECGs were performed at screening, approximately 1 to 3 hours following a dose of axitinib on Cycle 1 Day 15, and at end of treatment (EOT)/discontinuation. If the mean QTc interval was prolonged (>500 msec), then the results of ECG were to be re-read by a cardiologist at the site for confirmation. Additional ECGs were performed as clinically indicated.

p. ECG at Cycle 1 Day 15 was performed 1 to 3 hours post-treatment.

q. Blood sampling for PK (population PK analysis) was conducted on Day 1 of Cycles 1, 3, 5, and 7. Blood samples were collected at 2 hours postdose (taken in clinic) in the morning on Day 1 of Cycle 1, and prior to the morning dose (taken in clinic) and 2 hours after a dose of axitinib on Day 1 of

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	Within 14 Days Predosing	Day 1 (Predosing)	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	At End of Treatment/ Discontinuation[b]	Follow Up 28 days After Last Dose[c]
		- 4 days	± 4 Days	± 4 Days	± 4 Days	± 4 Days	± 4 Days	± 4 Days	+ 4 days	

Cycles 3, 5 and 7. If blood samples could not be collected for some reasons such as that the subject had inadvertently taken their morning dose prior to arriving at hospital, or dose interruption/dose reduction had been performed during 3 days before blood collection, blood collection was to be rescheduled to the next visit.

r. Only for the subjects undergoing dose titration on Cycle 1 Day 15 or later, 4-hour serial PK sampling was performed at the visit 5 days or more after dose increase (the day prior to next dose increase). The collection time points for the 4-hour serial PK sampling were: predose (prior to the morning dose taken in the clinic), 1, 2, 3 and 4 hours postdose. If 4-hour serial pharmacokinetic sampling was performed once at a particular dose, it was not required to perform another 4-hour serial PK sampling when the subject received the same dose following dose increase.

s. Plasma concentrations of s-VEGFR1, s-VEGFR2, s-VEGFR3, s-KIT, and VEGF were determined on Day 1 of each cycle until Cycle 7 and at EOT/discontinuation.

t. Pregnancy test was conducted within 7 days prior to the initiation of treatment.

u. At a minimum, CT/MRI of the chest, abdomen and pelvis and bone scan were required at baseline.

v. If tumor assessments were performed within 28 days (42 days for Bone scintigraphy) before starting the study treatment, the results could be used as the screening assessment.

w. Tumor assessments were done on Day 1 of odd number cycles following Cycle 3 Day 1 (acceptable range was 7 days). If baseline scan showed bone metastases, bone scan was required every 8 weeks. If responses (CR/PR) were observed, all assessments (CT/MRI and bone scan) were to be performed immediately after 4 weeks had passed since a response was first noted to confirm the response. If the confirmation assessments were performed, subsequent tumor assessments could be rescheduled at even number cycles.

x. If subject discontinued study treatment without progressive disease (PD) in accordance with Response Evaluation Criteria in Solid Tumors (RECIST), tumor assessments were to be performed after 28 days from last dosing (acceptable range is 7 days). If subject started a new anticancer treatment within 28 days from last dosing, this tumor assessment was not necessary.

y. If the symptoms related to brain metastases were clinically indicated, subsequent brain CT/MRI were to be performed.

z. Survival follow-up was performed at least every 6 months from EOT/discontinuation. All subjects were followed for survival until at least 3 years after the last subject started the study treatment.

Number of Subjects (Planned and Analyzed): It was planned to enroll 63 subjects in the study. Sixty-four (64) subjects were actually enrolled into the study. All 64 subjects were enrolled in Japan and all were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 20 years and older who were histologically diagnosed with mRCC with a component of clear cell cancer, refractory to cytokine therapy as 1st line, had experienced nephrectomy, had at least 1 target lesion, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) and who had no uncontrolled hypertension were eligible for inclusion in this study. Subjects with gastrointestinal abnormalities, current use or anticipated inability to avoid potent CYP3A4 inhibitors or CYP1A2/3A4 inducers, active seizure disorder or evidence of brain metastases, or with hemoptysis were excluded.

Study Treatment: The axitinib tablets were film-coated tablets that contained 1 mg or 5 mg of axitinib. The starting dose of axitinib was 5 mg BID administered orally with food. Doses were to be taken as close to 12 hours apart as possible, and at approximately the same time each day. One cycle was 28 days, and the treatment could be continued until the subject met the discontinuation criteria.

Subjects who tolerated axitinib with no adverse events (AEs) related to axitinib above Grade 2 (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) for consecutive 2-week periods could have their dose titrated to 7 mg BID and then to a maximum of 10 mg BID unless systolic blood pressure (sBP) was >150 mmHg or diastolic blood pressure (dBP) was >90 mmHg, or the subject was receiving antihypertensive medication. The dose could have been titrated every 2 weeks or longer interval. The clinical judgment of the treating physician was to be exercised regarding axitinib dose.

Efficacy, Safety and Pharmacodynamic Endpoints:

Primary Endpoint

- Objective response rate (ORR)

Secondary Endpoints

- PFS
- TTP
- DR
- OS
- Adverse events and abnormal change of laboratory test results
- Plasma concentration of s-VEGFR1, s-VEGFR2, s-VEGFR3, s-KIT and VEGF

Safety Evaluations: Safety was assessed by monitoring AEs, and through laboratory test results, blood pressure measurements, and electrocardiograms (ECGs).

Statistical Methods: The intent to treat (ITT) population was defined as all subjects enrolled in the study who received at least 1 dose of study medication. This ITT population was used for all efficacy and safety analyses.

In the analyses of ORR, PFS and TTP, subjects who had no baseline tumor assessment and who had inadvertently enrolled in this study were to be excluded from analyses, and were replaced with new subjects. The analyses of DR were conducted for all subjects who achieved complete response (CR) or partial response (PR).

ORR was estimated with a 2-sided 95% confidence interval (CI) using the exact method based on F distribution. PFS, TTP, DR and OS were summarized using the Kaplan-Meier method. Median and 95% CI for each of the durations were calculated using the method of Brookmeyer and Crowley. The primary analyses of ORR, PFS, TTP and DR were based on the Independent Review Committee (IRC) assessments, and the investigator assessments were used for secondary analyses.

If a subject received subsequent therapy after discontinuation of study treatment, the data collected after initiation of subsequent therapy was not used for efficacy analysis (except for OS).

Plasma concentrations of s-VEGFR1, s-VEGFR2, s-VEGFR3, s-KIT, and VEGF were summarized using descriptive statistics.

RESULTS

The results presented here are based on data at the time of study completion (LSLV: 09 August 2013).

Subject Disposition and Demography: A total of 64 subjects were enrolled and treated with axitinib. The majority of subjects (59 subjects, 92.2%) out of 64 subjects who were treated with axitinib discontinued the study. The commonest reason for discontinuation was "objective progression or relapse" in 42 subjects (65.6%), followed by "treatment-related AEs" in 16 subjects (25.0%). After the 3-year OS observation period (ie, end of study), 5 subjects who were still on the study were prescribed axitinib off-study. These 5 subjects were recorded to have completed the study. Subject disposition is shown in Table 2.

Table 2. Subject Disposition

Subject Category Number of Subjects (%)	Axitinib
Assigned to study treatment	64
Treated	64
Replaced	0
Completed	5 (7.8)
Discontinued	59 (92.2)
Reason for discontinuation	
Related to study drug	16 (25.0)
Adverse event	16 (25.0)
Not related to study drug	43 (67.2)
Global deterioration of health status	1 (1.6)
Objective progression or relapse	42 (65.6)

Demographic characteristics are summarized in Table 3.

Table 3. Demographic Characteristics

	Axitinib		
	Male	**Female**	**Total**
Number (%) of subjects	44	20	64
Age (years)			
<18	0	0	0
18-44	4	2	6
45-64	21	9	30
≥65	19	9	28
Mean	62.1	61	61.8
SD	11	10.7	10.8
Range	37-80	34-77	34-80
Race			
Asian	44	20	64
Weight (kg)			
Mean	66.8	53.1	62.5
SD	11.8	8.7	12.6
Range	47.7-105.4	37.0-72.0	37.0-105.4
N	44	20	64
Height (cm)			
Mean	166.3	152.8	162.1
SD	5.9	6.7	8.8
Range	152.5-178.0	139.2-165.0	139.2-178.0
N	44	20	64
Smoking			
Never smoked	6	16	22
Smoker	5	0	5
Ex-smoker	33	4	37
Allergy			
Yes	7	3	10
No	37	17	54

N = number of evaluable subjects; SD = standard deviation.

All 64 subjects were analyzed for efficacy and safety.

Efficacy and Pharmacodynamic Results:

Primary Endpoint: According to the IRC assessment, no subject had a CR, 33/64 subjects (51.6%) had a PR including 1 subject who had a response after the primary analysis; the overall ORR was 51.6% (95% CI: 38.7 % to 64.2%). Among the non-responders, 28 subjects (43.8%) had a best response of stable disease (SD), 1 subject (1.6%) had a best response of PD, and 2 subjects (3.1%) were indeterminate (no on-study disease assessment). Best overall response is given in Table 4.

Table 4. Best Overall Response (Independent Review Committee Assessment)

Number of Subjects (%)	Axitinib N = 64
Complete response (CR)	0
Partial response (PR)	33 (51.6)
Stable/No response	28 (43.8)
Objective progression	1 (1.6)
Symptomatic deterioration	0
Early death	0
Indeterminate	2 (3.1)
Objective response rate (CR+PR)	33 (51.6)
95% CI[a]	[38.7, 64.2]

CI = confidence interval; N = total number of subjects.
a. Using exact method based on binomial distribution.

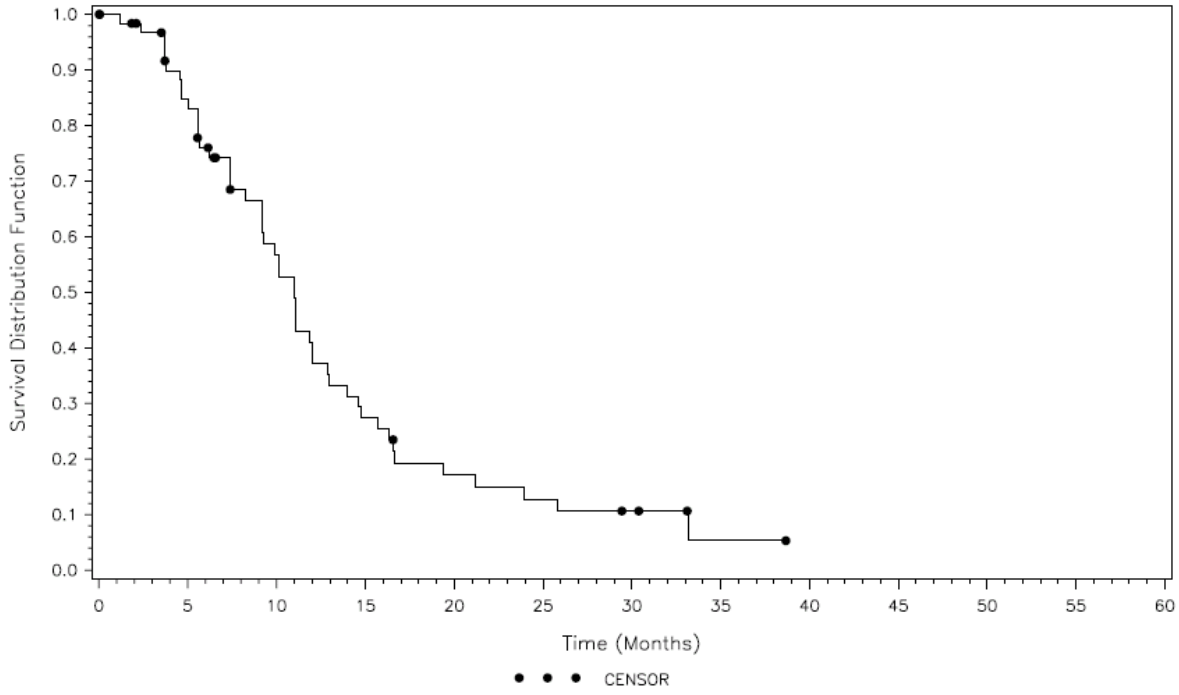
According to Investigator-assessment, no subject had a CR, 36/64 subjects (56.3%) had a PR including 1 subject who had a response after the primary analysis; the overall ORR was 56.3% (95% CI: 43.3% to 68.6%). Among the non-responders, 25 subjects (39.1%) had a best response of SD, 1 subject (1.6%) had a best response of PD, and 2 subjects (3.1%) were indeterminate (no on-study disease assessment).

Secondary Endpoints:

Progression-Free Survival (PFS)

At the study completion, there were 48 events among 64 subjects according to the IRC-assessment and the median PFS was 11 months (95% CI: 9.2 to 12.0 months). All the events were PD. A similar result was obtained based on the Investigator-assessment. The Kaplan-Meier plot for PFS is shown in Figure 1.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival (Independent Review Committee Assessment)



Time to Progression (TTP)

The TTP outcome was identical to the PFS outcome since no subject died prior to experiencing PD.

Duration of Objective Response (DR)

Of the 33 subjects with a response (confirmed PR) according to the IRC-assessment, 25 subjects (75.8%) subsequently progressed. The median DR was 11.1 months (95% CI: 8.2 to 13.7 months). Of the 36 subjects with a response according to the Investigator-assessment, 30 subjects (83.3%) subsequently progressed; the median DR was 12.8 months (95% CI: 7.7 to 17.5 months).

Overall Survival (OS)

A total of 43 deaths (67.2%) were reported at the study completion. All deaths were due to disease under the study. Survival probability at Month 12, Month 24, Month 36, and Month 48 were 92.1%, 68.3%, 55.6%, and 41.3%, respectively. The median OS was 37.3 months (95% CI: 28.6 to 49.9 months).

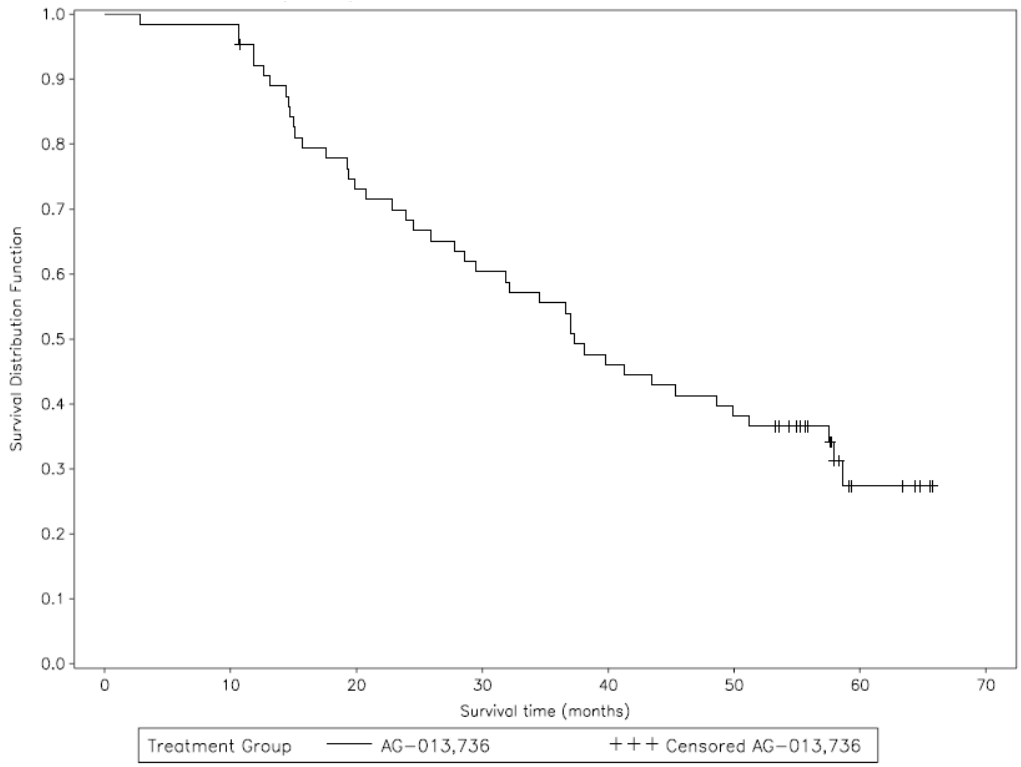
The summary of OS is shown in Table 5. The Kaplan-Meier plot for OS is shown in Figure 2.

Table 5. Overall Survival

	Axitinib N=64
Number of deaths n (%)	43 (67.2)
Cause of death n (%)	
Disease under study	43 (67.2)
Number censored n (%)	21 (32.8)
Reason for censorship n (%)	
Alive	20 (31.3)
Lost to follow-up	1 (1.6)
Survival probability at Month 6 [a] (95% CI [b])	98.4 (89.4, 99.8)
Survival probability at Month 12 [a] (95% CI [b])	92.1 (82.1, 96.6)
Survival probability at Month 24 [a] (95% CI [b])	68.3 (55.3, 78.3)
Survival probability at Month 36 [a] (95% CI [b])	55.6 (42.5, 66.8)
Survival probability at Month 48 [a] (95% CI [b])	41.3 (29.1, 53.1)
Kaplan-Meier Estimates of time to event (Month)	
Quartiles (95% CI) [c]	
25%	19.4 (14.6, 27.8)
50%	37.3 (28.6, 49.9)
75%	NE (51.2, NE)

CI = confidence interval; N =total number of subjects; n = number of subject; NE = not estimable.
a. Estimated from the Kaplan-Meier curve
b. Calculated from the product-limit method
c. Based on the Brookmeyer and Crowley Method

Figure 2. Kaplan-Meier Plot of Overall Survival



Pharmacodynamic results: Soluble protein plasma concentration percent change from Cycle 1 up to the end of study is presented in Table 6.

A decrease in median s-VEGFR1 was observed throughout the study with median percent change from Cycle 1 Day 1 of -12.78% to -30.95% (up to Cycle 7). The degree of change was smaller at end of treatment (EOT)/discontinuation compared to other visits with the median percent change of -9.75%.

A decrease in median s-VEGFR2 was observed throughout the study with median percent change from Cycle 1 Day 1 of -32.90% to -41.19% (up to Cycle 7). The degree of change was smaller at EOT/discontinuation compared to other visits with the median percent change of -27.18%.

A decrease in median s-VEGFR3 was observed throughout the study with median percent change from Cycle 1 Day 1 of -23.76% to -39.71% (up to Cycle 7). Increased median percent change of 5.37% from Cycle 1 Day 1 was observed at EOT/discontinuation.

The largest decrease in median s-KIT was observed at Cycle 2 Day 1, then a trend to revert to the baseline was observed and the median percent change was 3.49% at Cycle 7 Day 1 and 0.24% at EOT/discontinuation. An increase in median VEGF-A was observed throughout the study with median percent change from Cycle 1 Day 1 of 80.89% to 166.85% (up to Cycle 7). The degree of change was smaller at EOT/discontinuation compared to other visits with the median percent change of 54.00%.

Table 6. Soluble Protein Plasma Concentration Percent Change From Cycle 1 Day 1

		Axitinib	
		Percent Change From Baseline	
Soluble Protein	**Visit/Day**	**n**	**Median (Minimum, Maximum)**
s-VEGFR1	Cycle 1 Day 1	64	–
	Cycle 2 Day 1	63	-26.41 (-100.0, 23.4)
	Cycle 3 Day 1	60	-24.48 (-61.8, 507.8)
	Cycle 4 Day 1	59	-12.78 (-70.5, 90.6)
	Cycle 5 Day 1	57	-22.67 (-100.0, 101.6)
	Cycle 6 Day 1	52	-29.27 (-65.1, 48.9)
	Cycle 7 Day 1	48	-30.95 (-100.0, 29.2)
	At EOT/Discon	55	-9.75 (-100.0, 1705.2)
s-VEGFR2	Cycle 1 Day 1	64	–
	Cycle 2 Day 1	63	-33.50 (-71.6, 92.7)
	Cycle 3 Day 1	60	-32.90 (-68.4, 92.7)
	Cycle 4 Day 1	59	-34.81 (-61.5, 149.4)
	Cycle 5 Day 1	57	-35.39 (-63.4, 261.8)
	Cycle 6 Day 1	52	-38.89 (-71.5, 225.6)
	Cycle 7 Day 1	48	-41.19 (-60.7, 296.9)
	At EOT/Discon	55	-27.18 (-64.3, 165.6)
s-VEGFR3	Cycle 1 Day 1	64	–
	Cycle 2 Day 1	63	-39.69 (-80.8, 2.5)
	Cycle 3 Day 1	60	-39.71 (-76.8, 66.5)
	Cycle 4 Day 1	59	-25.63 (-100.0, 65.7)
	Cycle 5 Day 1	57	-23.76 (-100.0, 54.8)
	Cycle 6 Day 1	52	-25.92 (-83.0, 109.0)
	Cycle 7 Day 1	48	-35.75 (-100.0, 51.1)
	At EOT/Discon	55	5.37 (-100.0, 240.0)
s-KIT	Cycle 1 Day 1	64	–
	Cycle 2 Day 1	63	-12.10 (-38.7, 28.5)
	Cycle 3 Day 1	60	-8.10 (-39.8, 25.1)
	Cycle 4 Day 1	59	-9.20 (-43.2, 30.8)
	Cycle 5 Day 1	57	-2.20 (-37.4, 48.1)
	Cycle 6 Day 1	52	-1.15 (-43.5, 44.0)
	Cycle 7 Day 1	48	3.49 (-23.1, 65.3)
	At EOT/Discon	55	0.24 (-41.1, 63.3)
VEGF-A	Cycle 1 Day 1	64	–
	Cycle 2 Day 1	63	117.89 (-66.6, 996.8)
	Cycle 3 Day 1	60	91.81 (-54.2, 634.0)
	Cycle 4 Day 1	59	80.89 (-48.6, 656.0)
	Cycle 5 Day 1	57	114.89 (-66.0, 825.7)
	Cycle 6 Day 1	52	141.56 (-69.2, 900.0)
	Cycle 7 Day 1	48	166.85 (-39.7, 1163.8)
	At EOT/Discon	55	54.00 (-89.7, 415.6)

discon = study discontinuation; EOT = end of treatment; n = number of subjects with the given soluble protein at each visit; s-KIT = soluble stem cell factor receptor; s-VEGFR = soluble vascular endothelial growth factor receptor; VEGF-A = vascular endothelial growth factor A.

Safety Results:

Treatment emergent AEs (all causalities and treatment related) are shown in Table 7.

Table 7. Treatment Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term[a]

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Axitinib (N=64)	
	All-Causality	Treatment-Related
	All Cycles	All Cycles
At least 1 adverse event	**64 (100)**	**63 (98.4)**
Any AEs	64 (100)	63 (98.4)
Blood and lymphatic system disorders	10 (15.6)	7 (10.9)
Anaemia	5 (7.8)	2 (3.1)
Ear and labyrinth disorders	12 (18.8)	12 (18.8)
Tinnitus	5 (7.8)	4 (6.3)
Endocrine disorders	31 (48.4)	31 (48.4)
Hypothyroidism	31 (48.4)	31 (48.4)
Gastrointestinal disorders	59 (92.2)	56 (87.5)
Abdominal pain	9 (14.1)	9 (14.1)
Abdominal pain upper	9 (14.1)	7 (10.9)
Cheilitis	6 (9.4)	5 (7.8)
Constipation	14 (21.9)	10 (15.6)
Dental caries	5 (7.8)	3 (4.7)
Diarrhoea	44 (68.8)	42 (65.6)
Dyspepsia	5 (7.8)	5 (7.8)
Gastritis	6 (9.4)	5 (7.8)
Haemorrhoids	4(6.3)	2(3.1)
Nausea	22 (34.4)	18 (28.1)
Stomatitis	15 (23.4)	15 (23.4)
Vomiting	14 (21.9)	12 (18.8)
General disorders and administration site conditions	49 (76.6)	48 (75.0)
Chest pain	10 (15.6)	9 (14.1)
Face oedema	4 (6.3)	3 (4.7)
Fatigue	36 (56.3)	36 (56.3)
Malaise	10 (15.6)	9 (14.1)
Mucosal inflammation	4 (6.3)	4 (6.3)
Oedema	6 (9.4)	5 (7.8)
Oedema peripheral	7 (10.9)	6 (9.4)
Pyrexia	10 (15.6)	5 (7.8)
Hepatobiliary disorders	14 (21.9)	11 (17.2)
Hepatic function abnormal	8 (12.5)	7 (10.9)
Infections and infestations	43 (67.2)	24 (37.5)
Cystitis	4 (6.3)	1 (1.6)
Gastroenteritis	4 (6.3)	2 (3.1)
Gingivitis	4 (6.3)	2 (3.1)
Herpes zoster	4 (6.3)	3 (4.7)
Nasopharyngitis	25 (39.1)	5 (7.8)
Periodontitis	9 (14.1)	9 (14.1)
Injury, poisoning and procedural complications	11 (17.2)	3 (4.7)
Fall	6 (9.4)	1 (1.6)
Investigations	48 (75.0)	46 (71.9)
Alanine aminotransferase increased	15 (23.4)	15 (23.4)
Aspartate aminotransferase increased	15 (23.4)	15 (23.4)

Table 7. Treatment Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term[a]

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Axitinib (N=64)	
	All-Causality	Treatment-Related
	All Cycles	All Cycles
Blood albumin decreased	7 (10.9)	6 (9.4)
Blood alkaline phosphatase increased	13 (20.3)	12 (8.8)
Blood creatinine increased	5 (7.8)	5 (7.8)
Blood lactate dehydrogenase increased	8 (12.5)	7 (10.9)
Blood thyroid stimulating hormone decreased	4 (6.3)	4 (6.3)
Blood thyroid stimulating hormone increased	21 (32.8)	21 (32.8)
Blood urea increased	6 (9.4)	6 (9.4)
Blood urine present	5 (7.8)	4 (6.3)
C-reactive protein increased	7 (10.9)	2 (3.1)
Haemoglobin decreased	5 (7.8)	4 (6.3)
Neutrophil count decreased	4 (6.3)	4 (6.3)
Platelet count decreased	8 (12.5)	7 (10.9)
Protein urine	5 (7.8)	5 (7.8)
Weight decreased	21 (32.8)	20 (31.3)
Metabolism and nutrition disorders	31 (48.4)	30 (46.9)
Decreased appetite	27 (42.2)	26 (40.6)
Hyperlipidaemia	6 (9.4)	5 (7.8)
Musculoskeletal and connective tissue disorders	40 (62.5)	27 (42.2)
Arthralgia	15 (23.4)	13 (20.3)
Back pain	13 (20.3)	7 (10.9)
Musculoskeletal pain	9 (14.1)	6 (9.4)
Musculoskeletal stiffness	5 (7.8)	4 (6.3)
Myalgia	4 (6.3)	3 (4.7)
Neck pain	5 (7.8)	4 (6.3)
Nervous system disorders	32 (50.0)	29 (45.3)
Dizziness	7 (10.9)	6 (9.4)
Dysgeusia	12 (18.8)	12 (18.8)
Headache	18 (28.1)	16 (25.0)
Hypoaesthesia	5 (7.8)	4 (6.3)
Psychiatric disorders	6 (9.4)	3 (4.7)
Insomnia	4 (6.3)	2 (3.1)
Renal and urinary disorders	35 (54.7)	35 (54.7)
Proteinuria	33 (51.6)	33 (51.6)
Respiratory, thoracic and mediastinal disorders	49 (76.6)	46 (71.9)
Cough	14 (21.9)	9 (14.1)
Dysphonia	34 (53.1)	34 (53.1)
Epistaxis	17 (26.6)	16 (25.0)
Oropharyngeal pain	9 (14.1)	7 (10.9)
Upper respiratory tract inflammation	4 (6.3)	2 (3.1)
Skin and subcutaneous tissue disorders	55 (85.9)	53 (82.8)
Alopecia	5 (7.8)	5 (7.8)
Hyperkeratosis	4 (6.3)	4 (6.3)
Palmar-plantar erythrodysaesthesia syndrome	48 (75.0)	48 (75.0)
Pruritus	6 (9.4)	5 (7.8)
Rash	17 (26.6)	13 (20.3)
Vascular disorders	56 (87.5)	56 (87.5)
Hypertension	56 (87.5)	56 (87.5)

Table 7. Treatment Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term[a]

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Axitinib (N=64)	
	All-Causality	Treatment-Related
	All Cycles	All Cycles

Adverse events and serious adverse events are not separated out.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects assessed.
a. According to incidence of all-causality adverse events in all cycles.

Treatment emergent serious adverse events (all causality and treatment related) are shown in Table 8.

Table 8. Treatment Emergent Serious Adverse Events

Serial No.	Sex/ Age[a]	Dose at Onset of AE[b]	Adverse Event MedDRA version 16.0 Preferred Term	Grade[c]	Event Onset Day	Causality[d]	Study Drug Action	Outcome
1	M/73	5 mg	Cholecystitis	3	40	Not related	Temporarily withdrawn	Resolved
2	M/61	5 mg	Dehydration	2	42	Related	Temporarily withdrawn	Resolved
	M/62	5 mg	Pneumothorax	2	365	Related	Temporarily withdrawn	Resolved
3	M/56	5 mg	Proteinuria	2	71	Related	Temporarily withdrawn	Resolved
		3 mg	Decreased appetite	3	124	Related	Permanently withdrawn	Resolved
		3 mg	Malaise	3	124	Related	Permanently withdrawn	Resolved
4	M/64	5 mg	Diarrhoea	2	251	Related	Temporarily withdrawn	Resolved
		5 mg	Vomiting	2	252	Related	Temporarily withdrawn	Resolved
		5 mg	Dehydration	3	253	Related	Temporarily withdrawn	Resolved
5	F/75	5 mg	Diarrhoea	3	189	Related	Dose reduced	Resolved
		3 mg	Balance disorder	3	299	Related	Dose reduced	Resolved
		2 mg	Peptic ulcer	3	319	Related	Temporarily withdrawn	Resolved
		2 mg	Duodenal stenosis	3	340	Related	Temporarily withdrawn	Resolved
6	F/62	0 mg	Anaphylactic reaction[e]	3	1401	Not related	Post-therapy[f]	Resolved
7	M/60	5 mg	Myocardial Infarction[e]	4	1160	Related	Permanently withdrawn	Resolving
8	F/65	3 mg	Hyponatraemia	3	114	Related	Dose not changed	Resolved
9	F/46	0 mg	Diverticulitis[e]	3	1220	Not related	Post-therapy[g]	Resolved
10	M/77	0 mg	Disease progression[h]	5	64	Not related	Post-therapy[i]	Fatal
			Renal cell carcinoma[h]	5	64	Not related	Post-therapy[i]	Fatal
11	M/37	2 mg	Pneumonia	2	136	Related	Temporarily withdrawn	Resolving
12	M/50	5 mg	Appendicitis	4	692	Not related	Temporarily withdrawn	Resolved
		5 mg	Bile duct stone[e]	3	698	Not related	Temporarily withdrawn	Resolved
13	M/43	5 mg	Hypertension	4 3 2	7	Related	Permanently withdrawn	Resolving
		5 mg	Subarachnoid haemorrhage	2	13	Related	Permanently withdrawn	Resolving
		5 mg	Posterior reversible encephalopathy syndrome[j]	1	13	Related	Permanently withdrawn	Resolving
14	M/67	2 mg	Pneumonia[e]	2	753	Not related	Temporarily withdrawn	Resolved
15	F/64	3 mg	Cryptococcosis	3	113	Related	Dose not changed	Resolved
	F/65	2 mg	Hypertension	3	450	Related	Dose not changed	Resolved
	F/68	2 mg	Pyelonephritis[e]	2	1461	Not related	Temporarily withdrawn	Resolved
16	M/39	10 mg	Haemoptysis	2	312	Related	Temporarily withdrawn	Resolved
17	F/68	5 mg	Gastrointestinal haemorrhage	2	144	Related	Temporarily withdrawn	Resolved
		5 mg	Loss of consciousness	3	144	Related	Temporarily withdrawn	Resolved
18	M/50	3 mg	Duodenal ulcer	3	401	Not related	Temporarily withdrawn	Resolved
	M/51	3 mg	Diarrhoea[e]	2	813	Related	Temporarily withdrawn	Resolved
		3 mg	Renal failure acute[e, k]	3	821	Not related	Temporarily withdrawn	Resolved
		3 mg	Vomiting[e]	2	819	Related	Temporarily withdrawn	Resolved
19	M/62	3 mg	Angina unstable	3	621	Related	Temporarily withdrawn	Resolved
	M/64	0 mg	Angina unstable[e, l]		1208	Not related	Post-therapy[m]	Resolved
20	M/55	5 mg	Gastroenteritis	3	152	Related	Temporarily withdrawn	Resolved

Table 8. Treatment Emergent Serious Adverse Events

Serial No.	Sex/ Age[a]	Dose at Onset of AE[b]	Adverse Event MedDRA version 16.0 Preferred Term	Grade[c]	Event Onset Day	Causality[d]	Study Drug Action	Outcome
	M/56	5 mg	Upper gastrointestinal haemorrhage	3	356	Related	Temporarily withdrawn	Resolved
21	M/60	7 mg	Acute myocardial infarction[e]	4	528	Related	Temporarily withdrawn	Resolved
22	M/61	3 mg	Hyperthyroidism	4	142	Related	Permanently withdrawn	Resolved

AE = adverse event; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; No. = Number.

a. Age at adverse event onset.
b. Dose per administration at onset or the last dose prior to the onset of AE.
c. According to Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0
d. Investigator causality.
e. Newly reported after the primary analysis.
f. Therapy was stopped on Day 1400.
g. Therapy was stopped on Study Day 1176.
h. Single event term "disease progression" was entered in the project database.
i. Therapy was stopped on Study Day 62.
j. This event was entered as "Leukoencephalopathy" in the project database.
k. Reported as "renal failure" in the project database.
l. Angina was initially entered as non-serious in the project database. After the active reporting period, ie, >28 days after the last study drug administration, the angina became serious and it was entered as serious into the safety database only.
m. Therapy was stopped on Study Day 1149.

A total of 41 SAEs were reported in 22 subjects. A total of 30 SAEs reported in 16 subjects were considered treatment-related. SAEs that were reported in >1 subject included diarrhea, hypertension, dehydration, and vomiting. One death due to disease progression was reported and was not-related to the study drug.

Discontinuations due to AEs are presented in Table 9. A total of 16 subjects (25.0%) discontinued the study due to AEs. Protein in urine (Medical Dictionary for Regulatory Activities [MedDRA] term: proteinuria [7 subjects], protein urine [1 subject], protein urine present [1 subject]) was the most common AE leading to study discontinuation and was reported in 9 subjects (14.1%). Other AEs that resulted in discontinuation were polycythaemia, malaise, myocardial infarction, subarachnoid hemorrhage, anxiety, weight decreased, and hyperthyroidism (each reported in 1 subject).

Table 9. Discontinuations Due to Adverse Events

Serial No.	Sex/Age	Adverse Events MedDRA Version 16.0	Cycle (Day) Start/Stop	Study Day Start/Stop [a]	Grade	Causality
1	M/64	Polycythaemia	Cycle 1 (15)/ 2 (7)	15/35	2	Related
2	M/56	Malaise	Cycle 5 (12)/ 5 (19)	124/131	3	Related
3	M/60	Proteinuria	Cycle 9 (15)/ Follow-up (2)	239/(>645)	2	Related
4	M/70	Protein urine present	Cycle 6 (18)/ 6 (29)	158/169	3	Related
5	F/54	Proteinuria	Cycle 2 (1)/ Follow-up (2)	29/141	2	Related
6	M/74	Protein urine	Cycle 1 (8)/ 8 (50)	8/(>246)	2	Related
7	M/57	Myocardial infarction	Cycle 42 (33)/ Follow-up (12)	1181/(>1198)	2	Related
8	M/65	Proteinuria	Cycle 1 (22)/ 15 (29)	22/(>421)	2	Related
9	M/43	Subarachnoid haemorrhage	Cycle 1 (13)/ 1 (34)	13/(>34)	2	Related
10	M/63	Proteinuria	Cycle 42 (1)/ Follow-up (1)	1148/(>1372)	2	Related
11	M/77	Anxiety	Cycle 1 (15)/ Follow-up (20)	15/(>79)	2	Related
12	M/79	Weight decreased	Cycle 4 (1)/ Follow-up (10)	85/(>155)	2	Related
13	M/72	Proteinuria	Cycle 1 (8)/ 5 (15)	8/(>127)	2	Related
14	F/61	Proteinuria	Cycle 2 (14)/ 2 (36)	42/64	3	Related
15	M/79	Proteinuria	Cycle 1 (22)/ 7 (19)	22/187	2	Related
16	M/61	Hyperthyroidism	Cycle 6 (2)/ 6 (14)	142/154	4	Related

F = female; M = male; No. = number; MedDRA = Medical Dictionary for Regulatory Activities.
a. Day relative to start of study treatment. First day of study treatment = Day 1.

Nine (9) subjects (14.1%) had a dose reduction without temporary discontinuation due to AEs and 58 subjects (90.6%) had both dose reductions and temporary discontinuations or temporarily discontinuations only due to AEs

One death due to disease progression was reported and was not-related to the study drug.

A total of 62 subjects (97%) had ≥1 postdose abnormal laboratory test value regardless of the baseline abnormality. The most commonly reported laboratory abnormalities were thyroid stimulating hormone (TSH) increased >1.2 × upper limit of normal (ULN) (54 subjects, 84%) and urine protein (41 subjects, 64%). Both increases and decreases in TSH were measured in some subjects during the study treatment.

CONCLUSIONS:

- No subject had CR, 33/64 subjects (51.6%) had a PR, and the overall ORR based on IRC assessment was 51.6% (95% CI: 38.7 % to 64.2%). The ORR based on Investigator assessment was 56.3% (05% CI: 43.3% to 68.6%).

- The median PFS was 11 months (95% CI: 9.2 to 12.0 months). A total of 43 deaths (67.2%) were reported at the study completion. All deaths were due to disease under the study. Survival probability at Month 12, Month 24, Month 36, and Month 48 were 92.1%, 68.3%, 55.6%, and 41.3%, respectively. The median OS was 37.3 months (95% CI: 28.6 to 49.9 months).

- The most commonly-reported all-causality adverse events (≥50%) were hypertension, palmar-plantar erythrodysaesthesia syndrome, diarrhoea, and dysphonia. In general, treatment-emergent adverse events were clinically manageable with no unexpected

toxicities. There was no apparent increase of toxicity in subjects who underwent dose titration above a starting dose of 5 mg BID; however, the number of subjects who underwent dose titration was limited (7.8%).

- Elevation of TSH (with/without transient decrease) was frequently observed.
- Proteinuria was the most common adverse event leading to treatment discontinuation.
- Axitinib decreased s-VEGFR1, s-VEGFR2, s-VEGFR3, increased VEGF, and had little effect on s-KIT concentrations.
- Exploratory analysis suggested subjects with a larger degree of decrease in s-VEGFR2 were likely to show a higher ORR, longer PFS and longer OS. Also, subjects with diastolic BP ≥90 mmHg showed longer OS than subjects with diastolic BP <90 mmHg after Cycle 1 Day 1 to Cycle 2 Day 1.