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

PROTOCOL NO.: A4061027

PROTOCOL TITLE: A Phase 2 Study of the Anti-Angiogenesis Agent AG-013736 in Patients With Metastatic or Unresectable Locally-Advanced Thyroid Cancer Refractory to, or Not Suitable Candidates for ^{131}I Treatment

Study Centers: Twenty (20) centers took part in the study and randomized subjects; 6 in the United States (US), 4 in China, 2 each in Canada, Italy, Poland and Spain, and 1 each in the United Kingdom (UK), and the Czech Republic.

Study Initiation and Final Completion Dates: 19 December 2006 to 24 September 2012

Phase of Development: Phase 2

Study Objectives: The primary objective of this study was to determine the objective response rate (ORR).

Secondary objectives were to:

- Determine the safety profile of axitinib
- Determine the progression-free survival (PFS)
- Determine the duration of response (DR)
- Determine overall survival (OS)
- Obtain blood samples for population pharmacokinetic (POPPK) analyses
- Obtain blood samples to conduct exploratory studies monitoring circulating endothelial cells (CEC) as markers of drug response and/or disease
- Obtain blood samples for uridine diphosphate glucuronyltransferase UDP glucuronosyltransferase 1A1 (UGT1A1) mutation correlation with safety and efficacy outcomes
- Explore patient-reported outcomes (PROs) of symptom severity and interference in this study population.

METHODS

Study Design: This was a multicenter, Phase 2, single-arm, open-label study of the anti-angiogenesis agent axitinib in subjects with ^{131}I-refractory, ^{131}I-inappropriate, or doxorubicin-refractory metastatic or unresectable locally-advanced thyroid cancer of anaplastic, papillary, follicular, Hurthle-cell thyroid or medullary histology 1) who had failed prior ^{131}I treatment; or 2) had negative radioactive iodine uptake by 1 or more tumors; or had ^{131}I-inappropriate therapy (anaplastic or medullary histology); or 3) who were also refractory to, or intolerant of, or had clinical contraindication to doxorubicin treatment.

A single-stage design was used to treat a total target sample size of 50 subjects with axitinib at a starting dose of 5 mg twice daily (BID) administered with food to evaluate the clinical efficacy of axitinib in this subject population. Subjects had periodic safety evaluations and dose modifications were made as appropriate for their treatment. Radiologic tumor assessment for efficacy evaluations were performed at screening and every 8 weeks (according to RECIST 1.0). RECIST-defined response required confirmation $\geq$ 4 weeks after first documentation. Treatment continued until tumor progression, unmanageable toxicity, or the subject withdrew consent. Subsequent therapy was at the discretion of the Investigator.

The schedule of events is provided in Table 1.

Table 1. Schedule of Activities

Observation	Screening Day 14 to Day 0	Day 1 (Predose)	Every 2 Weeks × 4, then Every 4 Weeks*	Every 8 Weeks	Follow-Up Day 28 After Last Dose
Informed consent[a]	Day -28 to Day 0				
Medical history[b]	X				
Concomitant treatment[c]	X	X	X		X
Physical examination[d]	X	X**	X		X
Weight, height, and temperature[e]	X	X	X		X
Blood pressure[f]	X	X	X		X
Home blood pressure monitoring[g]		Twice a day, prior to taking each dose of axitinib			
ECOG performance status[h]	X	X	X (every 4 weeks)		X
Hematology[i]	X	X**	X (every 4 weeks)		X
Chemistry[j]	X	X**	X (every 4 weeks)		X
Blood sample for UGT1A1 genotype test[k]	X				
Urinalysis[l]	X		X (every 4 weeks)		X
12-lead electrocardiogram[m]	X		X (once at 4 weeks)		X
Tumor assessments, including CT/MRI[n]	Day -28 to Day 0			X	X
Circulating endothelial cell sample[o]	X		X (samples at 4, 8, and 12 weeks only)		
De-identified blood sample for pharmacogenomics[p]	X (optional)				
De-identified proteomic blood sample[q]	X (optional)		X (sample only at Week 4)		
De-identified transcriptomic blood sample[r]	X (optional)		X (sample only at Week 4)		
Tumor specimen (archived and/or fresh frozen) for pharmacogenomics (optional)[p]	X (optional)				
Thyroid function tests and thyroglobulin[s]	X		X		
Pharmacokinetic plasma samples for axitinib[t]		X	X (every 2 weeks with dose titration [4 hour serial PK sampling]; then population PK every 8 weeks)		
Safety assessment (adverse events)[u]		Throughout the study period			X
Survival[v]		Until at least 2 years after the initial dose for the last treated subject			
Serum or urine pregnancy test[w]	Day -3 to 0				
Patient reported outcomes: MDASI		X	X		X

* Cycle length was 4 weeks.

** Unnecessary to repeat before first dose if screening assessment was performed within 7 days prior to first dose.

Table 1. Schedule of Activities

Tests and procedures performed on schedule ±4 days allowable for holidays, vacations and other administrative reasons.
CR = complete response; CT = computed tomography; EC = Ethics Committee; ECOG = Eastern Cooperative Oncology Group; IRB = Institutional Review Board; MDASI = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid stimulating hormone.

a. Any time prior to any procedures performed solely for this study.
b. Including use of nicotine products.
c. Should have been collected from screening to the follow-up period.
d. After the initial complete examination, targeted examinations based on signs and symptoms may have been performed.
e. Height did not have to be collected after the first measurement.
f. Blood pressure was to be measured with the subject in the seated position after the subject had been sitting quietly for 5 minutes.
g. Subjects receiving axitinib received blood pressure monitoring devices. Subjects were to take blood pressure at least twice daily prior to taking each dose of medication and blood pressure was to be recorded in a subject diary. All subject diaries were to be collected as source documents. Subjects were to be instructed by the study staff to contact their physician immediately for guidance if their systolic blood pressure rose above 150 mm Hg, diastolic blood pressure rose above 100 mm Hg, or if they developed symptoms perceived to be related to elevated blood pressure (eg, headache, visual disturbance).
h. Performance status grade – 0: Fully active; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2: Ambulatory and capable of all self-care but unable to carry out any work activities; 3: Capable of only limited self-care; 4: Completely disabled; 5: Dead.
i. Hemoglobin, hematocrit, white blood cells with differential, and platelets. Prothrombin time and partial thromboplastin time were to be done prior to the first dose and then as clinically indicated.
j. Blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, total bilirubin, and glucose.
k. One (2 mL) blood sample was to be collected for genotyping of drug metabolizing enzymes only including UGT1A1.
l. Protein, glucose, and blood. If protein ≥1+ by semiquantitative method (eg, dipstick), then quantitated by 24 hour urine collection. Dose adjustment may have been required. Screening urinalysis was to include microscopic examination of the sediment.
m. At screening and once at fourth week, 1-2 hours after dosing (may have been repeated when clinically indicated).
n. Eligibility based on objective evidence of disease progression required 2 sets of CT/MRI (or 2 sets of chest x-rays, bone scans, or x-rays of bone lesion), performed any time within the time window beginning 1-month prior to the first dose of the prior therapy and ending at 12-months after the last dose showing objective evidence of disease progression as defined by RECIST criteria. These pre-study scans or x-rays documenting disease progression must have been reviewed and verified by the study investigator. Baseline tumor assessments required CT/MRI (no chest x-ray) of the neck, chest, and upper abdomen (including the liver). The baseline CT/MRI must have been reviewed by the study investigator and verified before the subject could receive treatment with axitinib. For all subjects, tumor assessments using CT/MRI were required every 8 weeks during the study. Response (CR/PR) required confirmation with CT/MRI at least 4 weeks after the response was first noted. Bone scans were not required unless it was clinically indicated. If the most recent tumor evaluation at the time of study drug discontinuation showed unconfirmed PR or CR, confirmatory tumor evaluation must have been performed as close to 4 weeks as possible but no less than 4 weeks after the date of the unconfirmed PR or CR as a part of the end of study procedures.
o. Circulating endothelial cells.
p. As per the pharmacogenomics supplement.
q. As per the proteomics blood sample procedure.

Table 1. Schedule of Activities

r.	As per the transcriptomic blood sample procedure.
s.	TSH, free triiodothyronine (T_3; or total T_3) and free thyroxine (T_4) every 2 weeks x 4, then every 8 weeks thereafter. Thyroglobulin in all subjects and serial measurements if subject had elevated serum concentrations at baseline.
t.	During dose titration, 4 hour serial PK sampling was to be performed the day prior to the first dose increase and 2 weeks after each dose increase. The collecting time points for the 4 hour serial PK sampling were: predose (prior to the morning dose taken in the clinic), and 1, 2, 3, and 4 hours postdose. Following the end of the dose titration, the population PK samples (peak and trough levels) should have been obtained every 8 weeks. Plasma samples (7 mL blood/sample) for axitinib were to be obtained 15 minutes prior to the morning dose (taken in the clinic) and 1 to 2 hours after that dose. For all collections the time of clinic tablet dosing, as well as actual times of all pharmacokinetic collections, were to be recorded in the source documents. The date and time of the last study dose taken prior to the morning clinic dose was also to be recorded in the source documents.
u.	Adverse events were to be collected from the time of consent and throughout the study period until at least 28 days after the last dose of study drug and followed until resolution or stabilization.
v.	All subjects were to be followed for survival at least every 3 months after discontinuing study treatment until at least 2 years after the initial dose for the last treated subject.
w.	Subjects of childbearing potential must have had a negative pregnancy test within 3 days prior to treatment and must have been using appropriate birth control or practicing abstinence. Pregnancy test was to be repeated during the study if requested by the EC/IRB or as required by local regulation.

Number of Subjects (Planned and Analyzed): A total of 50 subjects were planned for the study and 52 subjects were randomized, treated and analyzed (4 in Canada, 6 in China, 2 in Czech Republic, 15 in Italy, 5 in Poland, 3 in Spain, 1 in UK and 16 in US). All 52 subjects discontinued from the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 years or older with ECOG 0-1; radioactive iodine (^{131}I)-refractory metastatic or unresectable locally-advanced thyroid cancer of anaplastic, papillary, follicular, Hurthle-cell thyroid or medullary histology 1) who had failed prior ^{131}I treatment; or 2) had negative radioactive iodine uptake by 1 or more tumors or had ^{131}I inappropriate histology (anaplastic or medullary); or 3) who were also refractory to, or intolerant of, or had clinical contraindication to, doxorubicin treatment; and at least 1 measurable target lesion, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) were included in the study.

Exclusion Criteria: Subjects with thyroid lymphoma, previous treatment with anti-angiogenesis agents or subjects having myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, deep vein thrombosis or pulmonary embolism or history of hemorrgaic or thrombotic events within 12 months prior to study drug administration and use of strong cytochrome P450 3A4 inhibitors/inducers were excluded from the study.

Study Treatment: All subjects received axitinib tablets orally daily. Treatment continued until tumor progression, unmanageable toxicity, or the subject withdrew consent. Subsequent therapy was at the discretion of the Investigator. The recommended starting dose of axitinib was 5 mg BID administered orally with food. Doses were taken as close to 12 hours apart as possible and at approximately the same times each day. Subjects who tolerated axitinib with no adverse events (AEs) related to axitinib above Common Terminology Criteria for Adverse Events version (v) 3.0 Grade 2 for consecutive 2 week periods had their dose increased by 1 dose level unless the subject's blood pressure was >150/90 mm Hg or the subject was receiving antihypertensive medication. A summary of axitinib dose levels is provided in Table 2.

Table 2. Axitinib Dose Levels

Dose Level	Dose	Dispensed As
+2	10 mg BID	2 × 5 mg tablets BID
+1	7 mg BID	1 × 5 mg tablet + 2 × 1 mg tablets BID
0 (Starting Dose)	5 mg BID	1 × 5 mg tablet BID
-1	3 mg BID	3 × 1 mg tablets BID
-2	2 mg BID	2 × 1 mg tablets BID

BID = Twice daily.

Efficacy, Safety and Outcomes Research Endpoints:

Primary Endpoint: ORR according to RECIST.

Secondary Endpoints:

- Safety profile of axitinib
- PFS
- DR
- OS
- PRO

Safety Evaluations: Safety evaluations included clinical monitoring, blood pressure assessments, 12-lead electrocardiograms (ECGs), (AEs), and safety laboratory tests.

Statistical Methods:

Intent-to-Treat (ITT) Population: The ITT population included all subjects who enrolled in the study and received at least 1 dose of study medication. This was the primary population for all efficacy and safety analyses, as well as subject characteristics.

The primary endpoint, ORR, was calculated for the ITT population and a 2-sided 95% exact confidence interval (CI) was provided. DR, PFS, and OS were analyzed using Kaplan-Meier methods. DR was summarized for the subgroups of ITT subjects who achieved confirmed objective response, while PFS and OS were summarized for the ITT population overall. Supportive analyses for the time-to event endpoints such as PFS and DR were performed in the ITT population based on the Investigator's assessment. In addition, analyses were performed for ORR in the ITT population based on the investigator's assessment. Stable disease (SD) was summarized by less than 16 weeks vs equal or greater than 16 weeks. Tumor response based on the Investigator's assessment was determined from overall tumor assessment data (where data meet the criteria for confirmed CR or PR).

ORR was defined as the proportion of subjects with confirmed CR or PR according to RECIST, relative to the total population of subjects who received at least 1 dose of study medication.

PFS was defined as the time from start of study treatment to first documentation of objective tumor progression or to death due to any cause, whichever came first.

DR was defined as the time from the first documentation of objective tumor response (unconfirmed CR or unconfirmed PR, whichever occurred first) that is subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first.

OS was defined as the time from the start of study treatment to date of death due to any cause. For subjects not expiring, their survival times were censored at the last date they were known to be alive.

PROs were assessed using the MD Anderson Symptom Inventory (MDASI) questionnaire, including the summary subscales of symptom severity and interference with life.

RESULTS

Subject Disposition and Demography: A summary of subject disposition and data sets analyzed are provided in Table 3. A total of 52 subjects were treated in the study; all 52 subjects discontinued from the study. The main reason for discontinuation was objective progression or relapse (26 [50.0%] subjects). All 52 subjects were evaluated for safety and efficacy. A total of 51 (98.1%) subjects were evaluated for PROs (1 subject did not complete any question on the questionnaire at Baseline).

Table 3. Subject Disposition and Data Sets Analyzed

Number (%) of Subjects	Axitinib n (%)
Screened	52
Assigned to study treatment	52
Treated	52
Discontinued	52 (100.0)
Subject died	4 (7.7)
Related to study drug	6 (11.5)
Adverse event	6 (11.5)
Not related to study drug	42 (80.8)
Adverse event	1 (1.9)
Global deterioration of health status	4 (7.7)
Lost to follow-up	2 (3.8)
Objective progression or relapse	26 (50.0)
Other[a]	6 (11.5)
Subject refused continued treatment for reason other than adverse event	3 (5.8)
Analyzed for safety	52 (100.0)
Adverse events	52 (100.01)
Laboratory data	51 (98.1)
Analyzed for efficacy	52 (100.0)
Analyzed for patient reported outcomes	51 (98.1)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
Discontinuation from study refers to discontinuation from treatment.
CNS = central nervous system; n = number of subjects.

a. Other reasons included subject withdrew consent (1 subject), subject withdrew because of clinical progression (1 subject), decided by investigator (1 subject), subject rolled over to extension study (2 subjects), and protocol violation (metastases in central nervous system [CNS]; 1 subject).

A summary of demographic characteristics and baseline ECOG performance status is provided in Table 4. A total of 28 men and 24 women participated in the study; the study participants had a mean age of 57.6 years (range, 28 to 81 years), had a mean weight of 71.8 kg (range, 43.0 to 124.0 kg), and were predominantly white (84.6%). ECOG performance status was 0 for 20 (38.5%) subjects and 1 for 32 (61.5%) subjects.

Table 4. Demographic Characteristics and Baseline ECOG Performance Status

	Axitinib		
	Male	**Female**	**Total**
Age (years), n (%)			
<18	0	0	0
18-44	3 (10.7)	7 (29.2)	10 (19.2)
45-64	15 (53.6)	10 (41.7)	25 (48.1)
≥65	10 (35.7)	7 (29.2)	17 (32.7)
Mean (SD)	60.7 (10.4)	54.0 (13.2)	57.6 (12.1)
Range	41-81	28-73	28-81
Race, n (%)			
White	23 (82.1)	21 (87.5)	44 (84.6)
Asian	4 (14.3)	3 (12.5)	7 (13.5)
Other	1 (3.6)	0	1 (1.9)
Weight (kg)			
Median	76.3	62.0	69.5
Mean (SD)	78.1 (16.1)	64.4 (16.7)	71.8 (17.6)
Range	47.0-112.3	43.0-124.0	43.0-124.0
Height (cm)			
n (%)	27 (96.4)	23 (95.8)	50 (96.2)
Median	170.5	160.0	169.0
Mean (SD)	172.1 (5.9)	161.6 (7.2)	167.3 (8.4)
Range	160.0-188.0	147.0-174.0	147.0-188.0
Baseline ECOG Performance Status[a] n (%)			
0	NA	NA	20 (38.5)
1			32 (61.5)

SD = standard deviation; n = number of subjects; NA = not applicable; ECOG = Eastern Cooperative Oncology Group.
a. Baseline was defined as screening visit if available, otherwise baseline was Cycle 1, Day 1.

Efficacy Results:

Primary Efficacy Results: A summary of ORR is provided in Table 5. The ORR was 34.6% (95% CI: 22.0%, 49.1%). No subject had a CR and 18 (34.6%) subjects had a PR.

Table 5. Objective Response Rate

	Axitinib (N=52)
Response, n (%)	
CR	0
PR	18 (34.6)
SD	18 (34.6)
PD	5 (9.6)
IND	8 (15.4)
Missing	3 (5.8)
ORR[a]	18 (34.6)
95% CI[b]	(22.0, 49.1)

Population includes all treated subjects who had the correct histological cancer type. Only includes assessments given within 28 days after last dose of study medication and before taking antitumor treatment. Subjects had to maintain SD for at least 16 weeks to have an ORR=SD.
CI = confidence interval; CR = complete response; IND = indeterminate; N = total number of subjects; n = number of subjects meeting specified criteria; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
a. ORR = CR + PR according to RECIST.
b. Exact CI for the ORR based on the F-distribution.

Secondary Efficacy Results:

Progression Free Survival: A summary of PFS is provided in Table 6. The median PFS was 70.14 weeks (95% CI: 64.14 weeks, 93.71 weeks). Of the 52 subjects, 32 (61.5%) subjects had disease progression or died and 20 (38.5%) subjects did not progress or die.

Table 6. Progression-Free Survival

	Axitinib (N=52)
Status, n (%)	
Subject progressed or died	32 (61.5)
Subject did not progress or die	20 (38.5)
Percentiles and 95% CIs	
25th percentile of PFS[a] (weeks)	26.14
95% CI of 25th percentile of PFS[b]	(18.71, 65.00)
Median PFS[a] (weeks)	70.14
95% CI of median PFS[b]	(64.14, 93.71)
75th percentile of PFS[a] (weeks)	127.29
95% CI of 75th percentile of PFS[b]	(90.14, 168.00)

Population included all treated subjects who had a baseline assessment of disease and had the correct histological cancer type.
PFS = (first date that criteria for disease progression was met or the subject died due to any cause) – (first active therapy date) +1.
Subjects lacking an evaluation of tumor response after first dose date had their event times censored at 1 day. Subjects not experiencing disease progression during the treatment period and who did not die during the treatment period had their event time censored on the last study date that objective tumor assessments verified lack of disease progression.
CI = confidence interval; N = total number of subjects; n = number of subjects meeting specified criteria;
PFS = progression-free survival.
a. Estimated from Kaplan-Meier curve.
b. Based on Brookmeyer and Crowley method.

Duration of Response: A summary of DR among responding subjects is provided in Table 7. Of the 18 subjects who responded, 15 (83.3%) were known to have died or progressed and

3 (16.7%) did not progress or die. The median DR was 74.71 weeks (95% CI: 59.14 weeks, 112.29 weeks).

Table 7. Duration of Objective Response Among Responders

	Axitinib N=18
Status, n (%)	
Subject progressed or died	15 (83.3)
Subject did not progress or die	3 (16.7)
Percentiles and 95% CIs	
25th percentile of DR[a] (weeks)	57.71
95% CI of 25th percentile of DR[b]	(16.43, 65.14)
Median DR[a] (weeks)	74.71
95% CI of median DR[b]	(59.14, 112.29)
75th percentile of DR[a] (weeks)	113.93
95% CI of 75th percentile of DR[b]	(84.29, NE)

Population included all treated subjects who had a baseline assessment of disease and had the correct histological cancer type.
Duration of response = (first date that criteria for progression was met or the subject died due to any cause) – (first date that criteria for PR or CR met) +1.
Subjects who achieved PR or CR and who did not experience disease progression during the treatment period and who did not die during the treatment period had their event times censored on the last study date that objective tumor assessments verified lack of disease progression.
CI = confidence interval; CR = complete response; DR = duration of response; N = total number of subjects; n = number of subjects meeting specified criteria; NE = not estimable; PR = partial response.
a. Estimated from Kaplan-Meier curve.
b. Based on Brookmeyer and Crowley method.

Overall Survival: A summary of OS is provided in Table 8. A total of 33 (63.5%) subjects were dead and 19 (36.5%) subjects were alive at the time of study closure. The reported median OS was 118.43 weeks (95% CI: 63.57 weeks, 174.57 weeks). The 1-year survival probability was 67.87% (95% CI: 53.19%, 78.83%).

Table 8. Overall Survival

	Axitinib N=52
Status, n (%)	
Dead	33 (63.5)
Alive	19 (36.5)
Percentiles and 95% CIs	
25th percentile of survival[a] (weeks)	37.57
95% CI of 25th percentile of survival[b]	(29.00, 89.57)
Median survival[a] (weeks)	118.43
95% CI of median survival[b]	(63.57, 174.57)
75th percentile of survival[a] (weeks)	238.14
95% CI of 75th percentile of survival[b]	(143.71, NE)
1-year survival (%)[a]	67.87
95% CI of 1-year survival (%)[c]	(53.19, 78.83)

If a subject had no record of the subject survival CRF page, then the last visit date from the other CRF pages was used as the last date of known contact that the subject was documented to be alive. Survival time was 1 plus the number of days between the date of first dose and the date of death.
CI = confidence interval; CRF = case report form; N = total number of subjects; n = number of subjects meeting specified criteria; NE = not estimable.
a. Estimated from Kaplan-Meier curve.
b. Based on Brookmeyer and Crowley method.
c. Calculated from the log (-log [1-year survival probability]) using normal approximation and back transformation.

Disease Progression: A summary of reasons for disease progression is provided in Table 9. A total of 27 (51.9%) subjects had progressive disease (PD). The reasons for PD were new lesion (10 [19.2%] subjects), progression in target lesion (19 [36.5%] subjects), and progression in nontarget lesion (17 [32.7%] subjects).

Table 9. Reason for Disease Progression

	Axitinib (N=52)
Progressive disease	27 (51.9)
New lesion	10 (19.2)
Progression in target lesions	19 (36.5)
Progression in non-target lesions	17 (32.7)

Only includes assessments given within 28 days after last dose of study medication and before taking antitumor treatment.
One subject might have more than 1 reason for disease progression.
N = number of subjects.

Patient Reported Outcomes: Overall, the PROs as per MDASI scores remained low (<4) throughout treatment, however, there were changes from baseline in MDASI items scores that did reach the meaningfully important difference (MID). The summary interference and symptom scores remain fairly constant throughout the treatment period (focusing on the first 24 cycles). In general, subjects were not considered to be having a significant deterioration in their quality of life or worsening in symptoms. A summary of MDASI derived symptom severity change scale and derived symptom interference change scale, by cycle is provided in Table 10 and Table 11.

Table 10. MD Anderson Symptom Inventory (MDASI): Items and Derived Symptom Severity Change Scale by Cycle (Evaluable Population)

Variable	Axitinib (N=52)							
	N[a]	Mean	SD	Mean 95 % CI	p-Value	Min	Median	Max
Symptom severity scale								
Cycle 1/Day 15	40	0.18	1.158	(-0.20, 0.60)	0.3218	-3	0.04	2.7
Cycle 2/Day 1	42	0.43	1.274	(0.00, 0.80)	0.0354	-2.1	0.12	4.8
Cycle 2/Day 15	37	0.52	1.407	(0.10, 1.00)	0.0296	-1.8	0.31	5.7
Cycle 3/Day 1	43	0.53	1.602	(0.00, 1.00)	0.0371	-2.8	0.38	6.5
Cycle 4/Day 1	39	0.58	1.199	(0.20, 1.00)	0.0046	-1.1	0.23	3.6
Cycle 5/Day 1	36	0.69	1.55	(0.20, 1.20)	0.0118	-3.5	0.38	3.8
Cycle 6/Day 1	36	0.53	1.484	(0.00, 1.00)	0.0377	-4.2	0.5	4.4
Cycle 7/Day 1	29	0.40	1.344	(-0.10, 0.90)	0.1246	-4.1	0.31	2.9
Cycle 8/Day 1	28	0.44	1.395	(-0.10, 1.00)	0.107	-4.1	0.38	3.3
Cycle 9/Day 1	27	0.56	1.516	(0.00, 1.20)	0.0661	-3.3	0.31	5.1
Cycle 10/Day 1	25	0.59	1.494	(0.00, 1.20)	0.0596	-3.9	0.46	3.3
Cycle 11/Day 1	25	0.63	1.669	(-0.10, 1.30)	0.0693	-3.8	0.46	4.0
Cycle 12/Day 1	24	0.59	1.584	(-0.10, 1.30)	0.0796	-3.7	0.31	4.4
Cycle 13/Day 1	24	0.60	1.281	(0.10, 1.10)	0.0316	-3.2	0.57	3.2
Cycle 14/Day 1	24	0.59	1.476	(0.00, 1.20)	0.0639	-4.2	0.46	2.9
Cycle 15/Day 1	24	0.76	1.654	(0.10, 1.50)	0.0343	-4.3	0.65	3.7
Cycle 16/Day 1	23	0.81	1.911	(0.00, 1.60)	0.0545	-4.2	0.31	5.1
Cycle 17/Day 1	20	0.73	1.816	(-0.10, 1.60)	0.0894	-4	0.58	6.0
Cycle 18/Day 1	20	0.60	1.729	(-0.20, 1.40)	0.1395	-3.9	0.46	5.5
Cycle 19/Day 1	18	0.40	1.201	(-0.20, 1.00)	0.1785	-2.6	0.23	2.2
Cycle 20/Day 1	16	0.50	0.864	(0.00, 1.00)	0.0348	-0.8	0.19	2.1
Cycle 21/Day 1	16	0.84	1.094	(0.30, 1.40)	0.008	-0.8	0.54	2.6
Cycle 22/Day 1	15	0.61	0.97	(0.10, 1.10)	0.0288	-0.8	0.54	2.3
Cycle 23/Day 1	14	0.87	1.086	(0.20, 1.50)	0.0105	-0.5	0.88	2.8
Cycle 24/Day 1	11	1.05	0.99	(0.40, 1.70)	0.0057	-0.1	0.69	2.4
Cycle 25/Day 1	11	0.87	1.016	(0.20, 1.60)	0.0172	-0.3	1.00	2.2
Cycle 26/Day 1	9	1.15	0.96	(0.40, 1.90)	0.0072	-0.2	1.23	2.4
Cycle 27/Day 1	9	1.19	1.244	(0.20, 2.10)	0.0207	-0.2	1.15	3.2
Cycle 28/Day 1	10	0.95	1.291	(0.00, 1.90)	0.0445	-0.3	0.65	3.2
Cycle 29/Day 1	10	0.98	1.08	(0.20, 1.80)	0.0181	-0.1	0.82	2.3
Cycle 30/Day 1	10	1.03	0.97	(0.30, 1.70)	0.0083	-0.2	1.15	2.2
Cycle 31/Day 1	9	1.14	1.1	(0.30, 2.00)	0.0145	-0.2	1.38	3.2
Cycle 32/Day 1	9	1.44	1.058	(0.60, 2.30)	0.0035	-0.1	1.23	2.8
Cycle 33/Day 1	9	1.32	1.233	(0.40, 2.30)	0.0124	-0.1	1.00	3.1
Cycle 34/Day 1	8	1.54	1.366	(0.40, 2.70)	0.0155	-0.2	1.42	3.4
Cycle 35/Day 1	6	1.29	1.233	(0.00, 2.60)	0.0509	0.2	0.92	2.8
Cycle 36/Day 1	6	1.27	1.61	(-0.40, 3.00)	0.1114	-0.2	0.69	3.3
Cycle 37/Day 1	5	1.48	1.347	(-0.20, 3.20)	0.0696	0.3	1.00	3.0
Cycle 38/Day 1	5	1.27	1.117	(-0.10, 2.70)	0.0643	0.2	0.85	2.5
Cycle 39/Day 1	5	1.49	1.288	(-0.10, 3.10)	0.0612	0.5	0.77	3.3
Cycle 40/Day 1	5	1.47	1.176	(0.00, 2.90)	0.0495	0.1	1.00	2.8
Cycle 41/Day 1	5	1.48	1.267	(-0.10, 3.00)	0.0597	-0.2	1.15	2.8
Cycle 42/Day 1	5	1.59	1.312	(0.00, 3.20)	0.0537	0.1	1.15	3.1
Cycle 43/Day 1	5	1.59	1.259	(0.00, 3.20)	0.0479	0	1.46	2.9
Cycle 44/Day 1	5	1.42	1.258	(-0.10, 3.00)	0.0655	-0.1	0.92	2.8
Cycle 45/Day 1	4	1.49	1.349	(-0.70, 3.60)	0.1143	-0.1	1.55	2.9
Cycle 46/Day 1	4	1.73	1.425	(-0.50, 4.00)	0.093	0	1.88	3.2
Cycle 47/Day 1	4	1.70	1.543	(-0.80, 4.20)	0.1154	0	1.81	3.2
Cycle 48/Day 1	3	1.90	1.377	(-1.50, 5.30)	0.1397	0.3	2.69	2.7
Cycle 49/Day 1	3	2.26	1.554	(-1.60, 6.10)	0.1284	0.5	3.15	3.2
Cycle 50/Day 1	3	2.38	1.425	(-1.20, 5.90)	0.1012	0.8	2.92	3.5
Cycle 51/Day 1	3	2.46	1.533	(-1.30, 6.30)	0.1086	0.7	3.31	3.4
Cycle 52/Day 1	1	3.38	-	-	-	3.4	3.38	3.4
Cycle 53/Day 1	1	3.54	-	-	-	3.5	3.54	3.5

Table 10. MD Anderson Symptom Inventory (MDASI): Items and Derived Symptom Severity Change Scale by Cycle (Evaluable Population)

Variable	Axitinib (N=52)							
	N[a]	Mean	SD	Mean 95 % CI	p-Value	Min	Median	Max
Cycle 54/Day 1	1	3.00	-	-	-	3	3	3
Cycle 55/Day 1	1	3.38	-	-	-	3.4	3.38	3.4
Cycle 56/Day 1	1	3.15	-	-	-	3.2	3.15	3.2
Cycle 57/Day 1	1	3.62	-	-	-	3.6	3.62	3.6
Cycle 58/Day 1	1	3.23	-	-	-	3.2	3.23	3.2
Cycle 59/Day 1	1	3.08	-	-	-	3.1	3.08	3.1
Cycle 60/Day 1	1	3.85	-	-	-	3.8	3.85	3.8
Cycle 61/Day 1	1	3.31	-	-	-	3.3	3.31	3.3
Cycle 62/Day 1	1	3.46	-	-	-	3.5	3.46	3.5
Follow-up	12	0.37	0.939	(-0.20, 1.00)	0.1973	-0.9	0.12	1.8

Range of Symptom Severity Scale = -10 to 10. Symptom Severity Scale includes items 1-13 of the MDASI questionnaire.
Change from Baseline = Cycle (x) - Baseline.
Interpretation (Items and Scale Change Scores): A negative change score indicates the intensity of the symptom reduced (ie., the symptom improved).
A positive change score indicates that the symptom increased or got worse.
Unplanned visits for three subjects were excluded from the summary.
CI = confidence interval; min = minimum; max = maximum; N = subjects who have received at least 1 dose of study medication; SD = standard deviation.
a. (Subjects at each cycle) = evaluable subjects included subjects who received at least 1 dose of study medication, had Baseline data, and at least 1 post-Baseline measurement.

Table 11. MD Anderson Symptom Inventory (MDASI): Derived Symptom Interference Change Scale by Cycle (Evaluable Population)

Variable	Axitinib (N=52)							
	N[a]	Mean	SD	Mean 95 % CI	p-Value	Min	Median	Max
Symptom interference scale								
Cycle 1/Day 15	40	-0.05	2.161	(-0.70, 0.60)	0.8749	-7	0	2.8
Cycle 2/Day 1	41	0.28	2.763	(-0.60, 1.20)	0.5231	-7.5	0.17	7.4
Cycle 2/Day 15	36	0.67	2.403	(-0.10, 1.50)	0.105	-7	0.58	5.2
Cycle 3/Day 1	42	0.46	2.669	(-0.40, 1.30)	0.2661	-8.3	0.25	7.7
Cycle 4/Day 1	37	0.47	2.311	(-0.30, 1.20)	0.2212	-6.3	0.17	5.3
Cycle 5/Day 1	36	0.5	2.377	(-0.30, 1.30)	0.2111	-7	0.25	6.8
Cycle 6/Day 1	36	0.65	2.605	(-0.20, 1.50)	0.1417	-7	0.67	7
Cycle 7/Day 1	29	0.19	2.386	(-0.70, 1.10)	0.6719	-7	0	5.8
Cycle 8/Day 1	28	0.22	2.242	(-0.60, 1.10)	0.6074	-7	0.33	4.7
Cycle 9/Day 1	27	0.46	2.45	(-0.50, 1.40)	0.3352	-6.3	0.33	6.7
Cycle 10/Day 1	25	0.35	2.386	(-0.60, 1.30)	0.4745	-7	0.5	3.8
Cycle 11/Day 1	25	0.51	2.784	(-0.60, 1.70)	0.3718	-7	0.17	7
Cycle 12/Day 1	23	0.32	2.593	(-0.80, 1.40)	0.5613	-7	0.17	4.8
Cycle 13/Day 1	24	0.42	2.346	(-0.60, 1.40)	0.3932	-6.2	0.25	4.8
Cycle 14/Day 1	24	0.42	2.624	(-0.70, 1.50)	0.4371	-7	0	4.8
Cycle 15/Day 1	24	0.69	2.902	(-0.50, 1.90)	0.2531	-7	0.08	6
Cycle 16/Day 1	23	0.73	3.179	(-0.60, 2.10)	0.2815	-7	0.33	7.8
Cycle 17/Day 1	20	0.26	2.92	(-1.10, 1.60)	0.6968	-7	0.17	7
Cycle 18/Day 1	20	0.35	2.638	(-0.90, 1.60)	0.5599	-7	0.67	5.2
Cycle 19/Day 1	18	-0.18	2.497	(-1.40, 1.10)	0.7686	-6.7	-0.08	4
Cycle 20/Day 1	15	0.3	2.124	(-0.90, 1.50)	0.593	-4.8	0	3.3
Cycle 21/Day 1	15	0.5	1.954	(-0.60, 1.60)	0.3384	-4.5	0.33	3
Cycle 22/Day 1	14	0.32	1.979	(-0.80, 1.50)	0.5538	-4.3	0	3
Cycle 23/Day 1	14	0.95	1.615	(0.00, 1.90)	0.046	-1.5	0.75	4.8
Cycle 24/Day 1	11	0.77	1.844	(-0.50, 2.00)	0.1948	-1.3	0	5.2
Cycle 25/Day 1	11	0.65	1.699	(-0.50, 1.80)	0.2322	-1.7	0.17	4
Cycle 26/Day 1	9	1.04	1.681	(-0.30, 2.30)	0.1013	-1.5	0.83	4.2
Cycle 27/Day 1	9	0.81	2.463	(-1.10, 2.70)	0.35	-1.8	0	5
Cycle 28/Day 1	10	0.67	1.956	(-0.70, 2.10)	0.3092	-1.8	0.25	4.8
Cycle 29/Day 1	10	0.88	1.926	(-0.50, 2.30)	0.1809	-1.8	0	4.2
Cycle 30/Day 1	10	1.03	1.846	(-0.30, 2.40)	0.1104	-1.8	0.83	3.3
Cycle 31/Day 1	9	1.19	1.91	(-0.30, 2.70)	0.0997	-1.8	1.83	4
Cycle 32/Day 1	9	1.52	1.87	(0.10, 3.00)	0.0408	-1.8	1.83	4.5
Cycle 33/Day 1	9	1.07	1.972	(-0.40, 2.60)	0.1409	-1.8	0.83	4.2
Cycle 34/Day 1	8	1.81	1.846	(0.30, 3.40)	0.0274	-0.8	1.25	4.2
Cycle 35/Day 1	6	1.17	1.517	(-0.40, 2.80)	0.1182	-0.8	1.25	3.2
Cycle 36/Day 1	6	0.97	1.572	(-0.70, 2.60)	0.1902	-1	1	3
Cycle 37/Day 1	5	1.4	1.782	(-0.80, 3.60)	0.1538	-1.3	2.5	2.7
Cycle 38/Day 1	5	1.23	1.521	(-0.70, 3.10)	0.144	-0.8	1.67	2.7
Cycle 39/Day 1	5	1.5	1.453	(-0.30, 3.30)	0.0822	-0.8	1.83	2.8
Cycle 40/Day 1	5	1.83	1.889	(-0.50, 4.20)	0.0958	-0.8	2	3.7
Cycle 41/Day 1	5	1.53	1.746	(-0.60, 3.70)	0.121	-1	1.83	3.7
Cycle 42/Day 1	5	1.67	1.637	(-0.40, 3.70)	0.0851	-0.8	2.17	3.3
Cycle 43/Day 1	5	1.31	1.267	(-0.30, 2.90)	0.0825	-0.7	1.53	2.8
Cycle 44/Day 1	5	1.34	1.345	(-0.30, 3.00)	0.0898	-0.8	1.53	2.8
Cycle 45/Day 1	4	1.5	1.694	(-1.20, 4.20)	0.1747	-0.7	1.67	3.3
Cycle 46/Day 1	4	2.17	2.113	(-1.20, 5.50)	0.1326	-1	3.17	3.3
Cycle 47/Day 1	4	1.63	1.95	(-1.50, 4.70)	0.1942	-0.8	1.92	3.5
Cycle 48/Day 1	3	2	1.041	(-0.60, 4.60)	0.0796	0.8	2.33	2.8
Cycle 49/Day 1	3	2.56	1.798	(-1.90, 7.00)	0.1328	0.5	3.33	3.8
Cycle 50/Day 1	3	2.22	1.206	(-0.80, 5.20)	0.0857	0.8	2.83	3
Cycle 51/Day 1	3	2.44	1.251	(-0.70, 5.60)	0.0773	1	3.17	3.2
Cycle 52/Day 1	1	3.33	-	-	-	3.3	3.33	3.3
Cycle 53/Day 1	1	3.33	-	-	-	3.3	3.33	3.3

Table 11. MD Anderson Symptom Inventory (MDASI): Derived Symptom Interference Change Scale by Cycle (Evaluable Population)

Variable	Axitinib (N=52)							
	N[a]	Mean	SD	Mean 95 % CI	p-Value	Min	Median	Max
Cycle 54/Day 1	1	3.33	-	-	-	3.3	3.33	3.3
Cycle 55/Day 1	1	3.5	-	-	-	3.5	3.5	3.5
Cycle 56/Day 1	1	3.5	-	-	-	3.5	3.5	3.5
Cycle 57/Day 1	1	4.5	-	-	-	4.5	4.5	4.5
Cycle 58/Day 1	1	3.67	-	-	-	3.7	3.67	3.7
Cycle 59/Day 1	1	3.33	-	-	-	3.3	3.33	3.3
Cycle 60/Day 1	1	4.83	-	-	-	4.8	4.83	4.8
Cycle 61/Day 1	1	3.33	-	-	-	3.3	3.33	3.3
Cycle 62/Day 1	1	4	-	-	-	4	4	4
Follow-up	12	0.32	2.396	(-1.20, 1.80)	0.6532	-5.2	0.58	3.8

Range of Symptom Interference Scale = -10 to 10. Symptom Interference Scale includes items #14-19 of the MDASI questionnaire.
Change from Baseline = Cycle (x) - Baseline.
Interpretation (Items and Scale Change Scores): A negative change score indicates the intensity of the symptom reduced (ie., the symptom improved).
A positive change score indicates that the symptom increased or got worse.
CI = confidence interval; min = minimum; max = maximum; N = subjects who have received at least 1 dose of study medication; SD = standard deviation.
Unplanned visits for three subjects were excluded from the summary.
a. (subjects at each cycle) = evaluable subjects included subjects who received at least 1 dose of study medication, had Baseline data, and at least 1 post-Baseline measurement.

Safety Results: A summary of non-serious AEs (all causalities) occurring in ≥5% of subjects is provided in Table 12. All 52 (100.0%) subjects had at least 1 AE during the study. The most frequently reported AEs included diarrhea, hypertension, fatigue, decreased appetite, weight decreased, pain in extremity, and nausea.

Table 12. Treatment Emergent Non Serious Adverse Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Axitinib n (%)
Number (%) of Subjects	
Evaluable for Adverse Events	52
with Adverse Events	52 (100.0)
Blood and lymphatic system disorders	6 (11.5)
Anaemia	3 (5.8)
Endocrine disorders	4 (7.7)
Hypothyroidism	3 (5.8)
Gastrointestinal disorders	37 (71.2)
Abdominal pain	5 (9.6)
Abdominal pain upper	8 (15.4)
Constipation	7 (13.5)
Diarrhoea	31 (59.6)
Dry mouth	4 (7.7)
Haematochezia	3 (5.8)
Nausea	14 (26.9)
Stomatitis	6 (11.5)
Vomiting	7 (13.5)
General disorders and administration site conditions	35 (67.3)
Asthenia	4 (7.7)
Chest pain	3 (5.8)
Fatigue	23 (44.2)
Mucosal inflammation	10 (19.2)
Oedema peripheral	4 (7.7)
Pain	3 (5.8)
Pyrexia	4 (7.7)
Infections and infestations	23 (44.2)
Influenza	5 (9.6)
Nasopharyngitis	4 (7.7)
Upper respiratory tract infection	4 (7.7)
Injury poisoning and procedural complications	8 (15.4)
Post procedural haemorrhage	3 (5.8)
Investigations	30 (57.7)
Blood creatinine increased	3 (5.8)
Blood pressure increased	4 (7.7)
Blood thyroid stimulating hormone increased	3 (5.8)
Haemoglobin increased	5 (9.6)
Weight decreased	18 (34.6)
Metabolism and nutrition disorders	24 (46.2)
Decreased appetite	19 (36.5)
Hypocalcaemia	4 (7.7)
Musculoskeletal and connective tissue disorders	31 (59.6)
Arthralgia	7 (13.5)
Back pain	9 (17.3)
Muscle spasm	3 (5.8)
Musculoskeletal pain	3 (5.8)
Myalgia	3 (5.8)
Pain in extremity	16 (30.8)
Nervous system disorders	30 (57.7)
Dizziness	4 (7.7)
Headache	10 (19.2)
Neuropathy peripheral	4 (7.7)
Paraesthesia	7 (13.5)
Psychiatric disorders	11 (21.2)
Depression	5 (9.6)
Insomnia	5 (9.6)

Table 12. Treatment Emergent Non Serious Adverse Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Axitinib n (%)
Renal and urinary disorders	11 (21.2)
Proteinuria	6 (11.5)
Respiratory thoracic and mediastinal disorders	35 (67.3)
Cough	11 (21.2)
Dysphonia	7 (13.5)
Dyspnoea	12 (23.1)
Haemoptysis	6 (11.5)
Oropharyngeal pain	6 (11.5)
Skin and subcutaneous tissue disorders	25 (48.1)
Alopecia	7 (13.5)
Dry skin	5 (9.6)
Eczema	3 (5.8)
Palmar-plantar erythrodysaesthesia syndrome	6 (11.5)
Pruritis	4 (7.7)
Rash	8 (15.4)
Vascular disorders	29 (55.8)
Hypertension	28 (53.8)

Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (version 15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

A summary of treatment-emergent AEs by preferred term and descending order of frequency occurring in ≥5% of subjects (treatment-related, all cycles) is provided in Table 13.

A total of 49 (94.2%) subjects had at least 1 treatment-related AE. The most frequently reported treatment-related AEs included diarrhea, hypertension, fatigue, decreased appetite, nausea and pain in extremity.

Table 13. Descending Order of Frequency Treatment-Emergent Adverse Events by MedDRA Preferred Term Occurring in ≥5% of Subjects (Treatment Related, All Cycles, All Grades)

MedDRA Preferred Term	Axitinib (N=52) n (%)
Any AE	49 (94.2)
Diarrhea	26 (50.0)
Hypertension	25 (48.1)
Fatigue	19 (36.5)
Decreased appetite	13 (25.0)
Nausea	11 (21.2)
Pain in extremity	11 (21.2)
Mucosal inflammation	10 (19.2)
Weight decreased	9 (17.3)
Dyspnea	8 (15.4)
Abdominal pain upper	7 (13.5)
Paresthesia	6 (11.5)
Abdominal pain	5 (9.6)
Alopecia	5 (9.6)
Dysphonia	5 (9.6)
Palmar-plantar erythrodysesthesia syndrome	5 (9.6)
Proteinuria	5 (9.6)
Stomatitis	5 (9.6)
Dry skin	4 (7.7)
Hemoglobin increased	4 (7.7)
Rash	4 (7.7)
Asthenia	3 (5.8)
Blood pressure increased	3 (5.8)
Cough	3 (5.8)
Myalgia	3 (5.8)
Pruritus	3 (5.8)
Vomiting	3 (5.8)

AE/SAE results are not separated out.
MedDRA (version 15.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects meeting specified criteria; SAE = serious adverse event.

Serious Adverse Events: A summary of all reported SAEs (all causality and treatment related) is provided in Table 14 and Table 15 respectively. A total of 22 (42.3%) subjects had an SAE during the study. The most frequently reported SAEs during the study were fatigue and dyspnea (3 [5.8%] subjects each) and disease progression and weight decreased (2 [3.8%] subjects each).

A total of 11 (21.2%) subjects had a treatment-related SAE during the study. The most frequently reported treatment-related SAEs during the study were dyspnea and weight decreased (2 [3.8%] subjects each). Treatment-related SAE reported in 1 subject each included cardiac failure congestive, cerebral ischemia, fatigue, jugular vein thrombosis, myocardial infarction, neuropathy peripheral, oral pain, pancreatitis, respiratory failure, and skin ulcer.

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and MedDRA Preferred Term (All Cycles) (All Causalities)

System Organ Class and MedDRA Preferred Term	Axitinib (N=52)
	All Causalities
Evaluable for AEs	52
With AEs	22 (42.3)
Discontinued due to AEs	10 (19.2)
Number (%) of subjects with SAEs	
Cardiac disorders	3 (5.8)
Cardiac failure congestive	1 (1.9)
Hypertensive heart disease	1 (1.9)
Myocardial infarction	1 (1.9)
Myocardial ischemia	1 (1.9)
Gastrointestinal disorders	3 (5.8)
Hematemesis	1 (1.9)
Oral pain	1 (1.9)
Pancreatitis	1 (1.9)
General disorders and administration site conditions	5 (9.6)
Chest pain	1 (1.9)
Disease progression	2 (3.8)
Fatigue	3 (5.8)
Immune system disorders	1 (1.9)
Hypersensitivity	1 (1.9)
Infections and infestations	2 (3.8)
Appendicitis	1 (1.9)
Upper respiratory tract infection	1 (1.9)
Injury, poisoning and procedural complications	1 (1.9)
Fracture	1 (1.9)
Investigations	2 (3.8)
Weight decreased	2 (3.8)
Musculoskeletal and connective tissue disorders	1 (1.9)
Flank pain	1 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.9)
Prostate cancer	1 (1.9)
Nervous system disorders	3 (5.8)
Cerebral ischemia	1 (1.9)
Monoplegia	1 (1.9)
Neuropathy peripheral	1 (1.9)
Respiratory, thoracic and mediastinal disorders	6 (11.5)
Dyspnea	3 (5.8)
Hydrothorax	1 (1.9)
Laryngeal obstruction	1 (1.9)
Respiratory failure	1 (1.9)
Skin and subcutaneous tissue disorders	1 (1.9)
Skin ulcer	1 (1.9)
Vascular disorders	2 (3.8)
Arteriosclerosis	1 (1.9)
Jugular vein thrombosis	1 (1.9)

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (version 15.1) coding dictionary applied.
AE = adverse event; incl = including; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; SAE = serious adverse event.

Table 15. Treatment-Emergent Serious Adverse Events by System Organ Class and MedDRA Preferred Term (All Cycles) (Treatment Related)

System Organ Class and MedDRA Preferred Term	Axitinib (N=52)
	Treatment Related
Evaluable for AEs	52
With AEs	11 (21.2)
Discontinued due to AEs	7 (13.5)
Number (%) of subjects with SAEs	
Cardiac failure congestive	1 (1.9)
Hypertensive heart disease	0
Myocardial infarction	1 (1.9)
Myocardial ischemia	0
Hematemesis	0
Oral pain	1 (1.9)
Pancreatitis	1 (1.9)
Chest pain	0
Disease progression	0
Fatigue	1 (1.9)
Hypersensitivity	0
Appendicitis	0
Upper respiratory tract infection	0
Fracture	0
Weight decreased	2 (3.8)
Flank pain	0
Prostate cancer	0
Cerebral ischemia	1 (1.9)
Monoplegia	0
Neuropathy peripheral	1 (1.9)
Dyspnea	2 (3.8)
Hydrothorax	0
Laryngeal obstruction	0
Respiratory failure	1 (1.9)
Skin ulcer	1 (1.9)
Arteriosclerosis	0
Jugular vein thrombosis	1 (1.9)

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (version 15.1) coding dictionary applied.
AE = adverse event; incl = including; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; SAE = serious adverse event.

Permanent Discontinuations Due to Adverse Events: A total of 13 (25.0%) subjects permanently discontinued study drug due to an AE, 7 (13.5%) subjects permanently discontinued study drug due to at least 1 treatment-related AE (peripheral neuropathy; dyspnea [2 subjects]; proteinuria; skin ulcer; myocardial infarction; cerebral ischemia and respiratory failure). Subjects who discontinued the study drug due to an AE is provided in Table 16.

Table 16. Permanent Study Drug Discontinuations Due to Adverse Events

Serial No.	Sex/Age[a]/ Race	MedDRA (version 15.1) Preferred Term	Grade/Outcome	Causality
1	M/73/W	Neuropathy peripheral	3/resolved	Study drug
2	M/64/W	Dyspnea	3/resolved	Study drug
3	M/71/W	Proteinuria	3/still present	Study drug
4	F/60/W	Skin ulcer	3/unknown	Study drug
5	M/64/W	Arteriosclerosis	5/resolved	Other-underlying cardiac disease
		Hypertensive heart disease	5/resolved	Other-underlying cardiac disease
6	F/68/W	Upper respiratory tract infection	4/resolved	Other-not study drug related
7	M/61/W	Disease progression	5/resolved	Disease under study
8	M/64/W	Myocardial infarction	4/resolved	Study drug
9	F/64/W	Cerebral ischemia	4/resolved	Study drug
		Respiratory failure	3/resolved	Study drug
10	F/70/W	Dyspnea	5/resolved	Study drug
11	M/61/W	Chest pain	4/resolved	Other illness-unknown
12	F/35/W	Hematemesis	4/resolved	Disease under study
13	M/49/A	Laryngeal obstruction	5/resolved	Disease under study

MedDRA (version 15.1) coding dictionary applied.
M = male; F = female; W = white; MedDRA=Medical Dictionary for Regulatory Activities.
a. Age at screening.

Dose Reductions or Temporary Discontinuations Due to Adverse Events: A total of 22 (42.3%) subjects had a dose reduction due to an AE, 18 (34.6%) subjects had a treatment-related dose reduction due to an AE. A total of 41 (78.8%) subjects had a temporary discontinuation due to an AE.

Deaths: A summary of subjects who died on-study and during follow-up is provided in Table 17. A total of 6 (18.2%) subjects died on-study. Reasons for deaths on-study were disease under study (3 subjects) and other (4 subjects); 1 subject had disease under study and other listed as a reason for death. A total of 27 (81.8%) subjects died during follow-up. Reasons for deaths during follow-up were disease under study (24 subjects) and unknown (3 subjects).

Table 17. Summary of Deaths

	Axitinib (N=52) n (%)
Subjects who died	33 (63.5)
Subjects who died on-study[a]	6 (18.2)
Cause of death	
Disease under study	3 (50.0)
Study treatment toxicity	0
Unknown	0
Other	4 (66.7)
Acute dyspnea	1 (25.0)
Hematemesis	1 (25.0)
Hypertensive arteriosclerotic cardiovascular disease	1 (25.0)
Laryngemphraxis	1 (25.0)
Subjects who died during follow-up[b]	27 (81.8)
Cause of death	
Disease under study	24 (88.9)
Study treatment toxicity	0
Unknown	3 (11.1)
Other	0

Subjects could have more than 1 cause of death.
a. On-study deaths were those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
b. Follow-up deaths were those that occurred more than 28 days after the last dose of study drug.

Laboratory Evaluations: No subject had a hematology laboratory parameter with maximum CTC Grade of 4. A total of 5 (9.8%) subjects had hematology laboratory parameter with a maximum CTC Grade of 3 (absolute lymphocytes). Of 51 subjects with at least 1 blood pressure measurement, 7 (13.7%) had a maximum sitting diastolic blood pressure on treatment >105 mm Hg, 13 (25.5%) had a maximum sitting systolic blood pressure on treatment >160 mm Hg. All on-treatment ECGs collected at Week 4 (Day 29) were considered by the Investigator as normal or abnormal, not clinically significant.

CONCLUSIONS:

- The primary efficacy endpoint, ORR, was 34.6% (95% CI: 22.0%, 49.1%); all responses were PR. Therefore, the null hypothesis that the true ORR is ≤5% was rejected in favor of the alternative hypothesis that the true ORR is >20%.

- Secondary efficacy objectives included assessment of DR, PFS, and OS. The median DR was 74.71 weeks (95% CI: 59.14 weeks, 112.29 weeks), the median PFS was 70.14 weeks (95% CI: 64.14 weeks, 93.71 weeks), the median OS was 118.43 weeks (95% CI: 63.57 weeks, 174.57 weeks), and the 1-year survival probability was 67.87% (95% CI: 53.19%, 78.83%).

- Axitinib administered orally at a starting dose of 5 mg BID was generally tolerable and manageable in this study population.

- Results from POPPK modeling using data from the Phase 2 subjects in this study (pooled with data from other axitinib clinical studies) are intended to be reported in a separate POPPK report, and are not included in this report.

- Since changes from baseline in MDASI items scores were minor, subjects were not considered to have any significant deterioration in their quality of life during axitinib therapy.