PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO: A4061011

PROTOCOL TITLE: Phase 2 Study of the Anti-Angiogenesis Agent AG-013736 as Second-or Later-Line Treatment in Patients With Advanced Non-Small Cell Lung Cancer

Study Centers: A total of 8 centers took part in the study and enrolled subjects; 7 in the United States (USA) and 1 in Germany.

Study Initiation Date and Final Completion Date: 23 February 2005 to 11 July 2007

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To determine the activity of axitinib in advanced non-small cell lung cancer (NSCLC) as measured by the overall response rate (ORR), complete response (CR) and partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST).

Secondary Objectives:

- To determine the safety profile of axitinib
- To determine the progression-free survival (PFS)
- To determine the duration of response (DR)
- To determine overall survival (OS)
- To obtain blood samples for population pharmacokinetic (PK) analyses
- To explore relationships between clinical response and plasma soluble proteins
- To explore the value of dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) (DCE-MRI, for tumor blood flow and permeability) to predict response

METHODS

Study Design: This was a Simon 2-stage Minimax, Phase 2, open-label study of the investigational anti-angiogenesis agent axitinib in subjects with advanced NSCLC. If at least 1

of the first 18 subjects (ie, during Stage 1) had a confirmed objective response, then the study was to proceed to Stage 2 by enrolling 14 additional subjects. If a total of 4 confirmed responses was observed during Stages 1 and 2, then axitinib was to be considered of interest for further investigation, and an additional 28 subjects (total of 60 subjects) could be enrolled to further assess the safety and efficacy of axitinib in NSCLC.

Subjects underwent periodic safety evaluations, and dose modifications were made as appropriate for their treatment. Efficacy evaluations were performed every 8 weeks. Treatment continued until the tumor progressed, toxicity became unmanageable, or the subject withdrew consent. Subsequent therapy was provided at the discretion of the Investigator. The schedule of study procedures and evaluations is presented in Table 1.

Table 1. Schedule of Study Procedures and Evaluations

Observation	Screening Day –14 to Day 0	Day 1 (Predose)	Day 15 of Cycles 1 and 2	Every 4 Weeks[a]	Every 8 Weeks	Follow-Up Day 28 After Last Dose
Informed consent[b]	Day –28 to Day 0					
Medical history[c]	X					
Concomitant treatment[d]	X	X		X		X
Physical examination[e]	X	X[f]		X		X
Weight, height, temperature[g]	X	X		X		X
BP, pulse[h]	X	X	X	X		X
Home BP monitoring[i]		Throughout the study period				
ECOG performance status	X	X		X		X
Hematology	X	X		X		X
Chemistry	X	X[f]		X		X
Urinalysis[j]	X	X[f]		X		X
12-Lead electrocardiogram[k]	X					X
Fecal occult blood by guaiac[l]	X					
Tumor measurements	Day –28 to Day 0				X[m]	
Functional imaging (DCE-MRI)[n]	X (within 3 days prior to first dose)	Day 8 only (+/-3 days)				
Soluble protein samples		X			X	
PK plasma samples for axitinib[o]		Day 1 and Day 8 (day of DCE-MRI)		Day 29 only	Starting Day 57 (Cycle 3, Day 1)	
Adverse events[p]		Throughout the study period X				X
Blood sample for pharmacogenomics[q]	Optional					
Tumor sample for pharmacogenomics[q,r]	Optional					
Survival[s]						Every 3 months
Serum or urine pregnancy test[t]	Day –7 to 0					

Table 1. Schedule of Study Procedures and Evaluations

Tests and procedures were performed on schedule; occasional changes by ±4 days were allowable for holidays, vacations, and other administrative reasons.
BP = blood pressure; CR = complete response; CRFs = case report forms; DCE-MRI = dynamic contrast-enhanced MRI; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; PR = partial response; PK = pharmacokinetic.

a. Cycle length was 4 weeks.
b. Any time before any procedures were performed for this study.
c. Including use of nicotine products.
d. Collected from Screening to the follow-up period.
e. After the initial complete examination, targeted examinations based on signs and symptoms were performed.
f. Not repeated before first dose if Screening assessment was performed within 7 days before the first dose.
g. Height measurements were not to be collected after the first measurement.
h. BP and pulse were measured in the clinic with the subject in the seated position after the subject had been sitting quietly for 5 minutes.
i. Subjects receiving axitinib were issued BP monitoring devices. Subjects were to take their BP at least once each day and record the data in a subject diary.
j. Protein, glucose, and blood. If protein was ≥2+ by semiquantitative method (eg, dipstick) then it was quantitated by 24-hour urine collection. Dose adjustment may have been required. Screening urinalysis included microscopic examination of the sediment.
k. Additional electrocardiograms (ECGs) were performed as clinically indicated.
l. Subjects with a positive fecal occult blood test result were evaluated for active gastrointestinal bleeding. Additional tests were performed as clinically indicated.
m. Response (CR/PR) required confirmation at least 4 weeks after the response was noted. For subjects who did not progress after discontinuing study drug, additional tumor assessments were performed approximately every 8 weeks until the subjects met criteria for progression or alternate therapy was started.
n. DCE-MRI was performed at selected sites only.
o. Plasma samples (7 mL blood/sample) were obtained on the day of DCE-MRI imaging, Days 29, 57, and every 8 weeks. On the day of DCE-MRI imaging, samples were obtained 15 minutes prior to dosing (performed in the clinic) and 1, 2, and 4 hours after dosing. (± 30 minutes were allowed on sample collection to account for the imaging schedule.) Actual time samples were taken and recorded on the CRFs. On other days, samples for axitinib were obtained 15 minutes prior to the morning dose (taken in the clinic) and 1 to 2 hours after that dose.
p. Adverse events were 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.
q. Separate informed consent required.
r. Tumor samples were fresh or archived specimen.
s. Subjects were followed for survival at least every 3 months after discontinuing study treatment until at least 1 year after the initial dose for the last treated subject.
t. Subjects of childbearing potential were required to have a negative pregnancy test within 7 days prior to treatment and had to use appropriate birth control or practice abstinence.

Number of Subjects (Planned and Analyzed): A total of 60 subjects were planned to be enrolled in the study. A total of 32 subjects were enrolled and treated with axitinib (31 in the USA and 1 in Germany). All 32 subjects were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Subjects at least 18 years of age who had histologically documented advanced NSCLC (Stage IIIB with malignant pleural effusion or Stage IV); had at least 1 prior systemic therapy for metastatic disease; had no expectation of further effects of prior anticancer therapy; had at least 1 target lesion not irradiated and with a unidimensional diameter of at least 2 cm (1 cm for spiral computerized tomography scans); had Eastern Cooperative Oncology Group performance status of 0 or 1; and had no evidence of pre-existing uncontrolled hypertension.

Study Treatment: The initial dose of axitinib was 5 mg twice daily administered orally with food. Doses were to be taken as close to 12 hours apart as possible and at approximately the same times each day. Dose adjustments were based on adverse events (AEs).

Subjects who did not experience hypertension for any 2-week period during Cycles 1 and 2 could undergo dose escalation if no other AEs related to axitinib greater than Common Terminology Criteria for Adverse Events (US-NCI) Grade 2 occurred. The axitinib dose was to be escalated by 2 mg increments to a maximum of 10 mg twice daily (BID) (ie, 7 mg, 9 mg, and 10 mg BID). If a subject experienced hypertension on study or any Grade >2 axitinib-related AEs, no further dose escalation was performed.

Efficacy and Safety Endpoints:

Primary Endpoint:

- Response rate according to RECIST

Secondary Endpoints:

- Safety profile of axitinib
- Progression-free survival (PFS)
- Duration of response
- Overall survival

Safety Evaluations: Safety was assessed through laboratory test results, physical examination findings, vital signs measurements, electrocardiograms, and monitoring of AEs (serious and non-serious).

Statistical Methods: The emphasis of the statistical analyses in this study was on estimation. Due to the exploratory nature of this study, missing data were not imputed.

All subjects who received at least 1 dose of axitinib and had a baseline assessment of disease were included in the analysis of ORR and PFS. DR analysis was done for all subjects

achieving a PR or CR. All subjects who received at least 1 dose of axitinib were analyzed for OS. Primary efficacy results were based on Investigator assessment, rather than on independent third party assessment that was planned.

Primary Endpoint: The primary efficacy parameter was ORR. ORR was defined as the percentage of subjects with a confirmed CR or PR. The response rate (CR or PR) was provided with an exact 95% 2-sided confidence interval (CI) calculated using a method based on the F distribution. After discontinuing the study medication, subjects could be treated with alternative therapy. Data collected after subjects were treated with alternative therapy were used in the analysis of OS but not in any other efficacy analyses.

Secondary Endpoints: Estimates of the PFS curve, DR and survival time from the Kaplan-Meier method were presented. Median event time and a 2-sided 95% CI for the median were provided.

Safety data were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: Thirty-two subjects were treated with axitinib in this study. Table 2 is an overall summary of subject disposition. All 32 subjects were known to have discontinued the study. One subject with disease progression was classified as having discontinued due to an AE ("non-fatal AE" of disease progression).

Table 2. Subject Disposition

Number (%) of Subjects	Axitinib (N=32)
Number of subjects treated	32
Number of subjects discontinued	32 (100%)
Primary reason for discontinuation	
Death	2 (6.3%)
Non-fatal adverse event	7 (21.9%)
Lack of efficacy	23 (71.9%)

N = number of subjects.

A summary of demographic characteristics is provided in Table 3. The population for this study was primarily White (87.5%) and there were slightly more males (59.4%) than females; median age was 66.5 years.

Table 3. Summary of Demographic and Baseline Characteristics

Variable	Axitinib (N=32)
Age (years)	
Mean (standard deviation)	64.1 (12.3)
Median (range)	66.5 (39-80)
Gender [n (%)]	
Male	19 (59.4)
Female	13 (40.6)
Ethnicity (n [%])	
Caucasian	28 (87.5)
Black	3 (9.4)
Asian	1 (3.1)
Screening ECOG Performance Status (n [%])	
0[a]	13 (40.6)
1[b]	16 (50.0)
Missing	3 (9.4)

ECOG = Eastern Cooperative Oncology Group; N = total number of subjects; n = number of subjects.
a. Fully active, was able to carry on all pre-disease performance without restriction.
b. Restricted in physically strenuous activity but ambulatory and was able to carry out work of a light or sedentary nature.

Efficacy Results: This study was designed initially using a Simon's 2-stage Minimax design to determine if the true ORR with axitinib was ≥20% in subjects with advanced NSCLC, in which case it would be of interest for further study in this population. In Stage 1, 18 subjects were to be treated, and if at least 1 confirmed response was observed among these first 18 subjects, then the study was to proceed to Stage 2, and an additional 14 subjects were to be enrolled. Thereafter, an additional 28 subjects (total of 60 subjects) could be enrolled to further assess the safety and efficacy of axitinib in NSCLC. Based on safety and efficacy observed in Stage 1 and the early portions of Stage 2 (before complete ORR data were available), a decision was made to limit enrollment to 32 subjects, as further development of axitinib both as a single agent and in combination with chemotherapy was already on-going in other Phase 2 and 3 studies.

Two of the first 18 subjects (11.1%) had confirmed PR, enrollment proceeded to Stage 2, and a total of 32 subjects were enrolled and treated. The ORR was 9.4% (3 of 32 subjects) with a 95% CI of 2.0% to 25.0%.

Primary Endpoint Results: ORR was 9.4% (95% CI: 2.0% to 25.0%). Three subjects (9.4%) had PR; no subjects had CR (Table 4).

Table 4. Tumor Response From Investigator Assessment (All Treated Subjects)

	Axitinib	
Best Tumor Response During Study	**(N=32)**	**95% CI[a]**
Complete response	0	0
Partial response	3 (9.4%)	0
Stable disease	10 (31.3%	0
Progressive disease	9 (28.1%)	0
Indeterminate	6 (18.8%)	0
Missing	4 (12.5%)	0
Overall response rate[b]	3 (9.4%)	(2.0, 25.0)

All subjects who had received at least 1 dose of axitinib, had a baseline assessment of disease, and had the correct histological cancer type were included in the analysis.
CI = confidence interval; N = total number of subjects; RECIST = Response Evaluation Criteria in Solid Tumors.

a. The 95% CI for the proportion of responders was a 2-sided exact confidence interval based on the F-distribution.
b. Overall response rate according to RECIST = Complete Responders (CR) + Partial Responders (PR), based on the subject's best documented response during the study.

Secondary Endpoint Results:

PFS, based on Investigator assessment, is summarized in Table 5. At the time of database closure, 26 subjects (81.3%) were known to have progressed or died. Median PFS was 148 days (approximately 4.9 months; 95% CI: 109 to 213 days).

Table 5. Progression-Free Survival (PFS) From Investigator Assessment (All Treated Subjects)

Progression-Free Survival Time[a]	**Axitinib (N=32)**	**95% CI[b]**
Progression status		
Subject progressed or died	26 (81.3%)	
Subject did not progress or die	6 (18.8%)	
Progression-free survival time (days)		
Quartile (95% confidence interval)[c]		
25 percentile	95.0	(57.0, 125.0)
Median	148.0	(109.0, 213.0)
75 percentile	280.0	(176.0, 367.0)

All subjects who had received at least 1 dose of axitinib, had a baseline assessment of disease, and had the correct histological cancer type were included in the analysis.
CI = confidence interval; N = total number of subjects.

a. PFS was defined as 1 plus the number of days between the date of first dose and the date of documented objective progression or the date of death, whichever was first.
b. The 2-sided 95% CIs were estimated based on the Brookmeyer and Crowley method.
c. Median, 25 and 75 percentile for PFS were estimated by Kaplan-Meier method. Subjects lacking an evaluation of tumor response after their first dose had their event time censored at Day 1. Subjects not experiencing disease progression during the treatment and follow-up periods 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.

DR, based on Investigator assessment, is summarized in Table 6. All 3 responders progressed or died; subjects progressed with DR of 252, 322, and 179 days (approximately 8.3, 10.6, and 5.9 months).

Table 6. Duration of Response Among Responders From Investigator Assessment

	Axitinib (N=3)[a]
Subject status	
Subject progressed or died	3 (100%)
Subject did not progress or die	0
Mean duration of response (days)[b]	252.0
95% CI of median duration of response (days)[c]	(179.0, 322.0)

Response included both CR and PR. Duration of response = first date criteria for progression occurred or the date at which subject died due to any cause or the date of last lesion assessment verifying lack of disease progression for subjects who died during follow-up-first date criteria for PR or CR met +1.
CI = confidence interval; CR = complete response; N = total number of subjects; PR = partial response.
a. N was the total number of subjects in the treatment group with a confirmed response.
b. Median duration of response comes from the Kaplan-Meier curve.
c. 95% CI was based on Brookmeyer and Crowley method.

OS is summarized in Table 7. At the time of database closure, 19 subjects (59.4%) were known to have died. Median survival time was 450 days (approximately 14.8 months; 95% CI: 326 to not determined).

Table 7. Survival Analysis (All Treated Subjects)

Survival[a]	Axitinib (N=32)	95% CI[b]
Subject status		
Died	19 (59.4%)	
Alive	13 (40.6%)	
Survival time (days)		
Quartile (95% CI)[c]		
25 percentile	262.0	(110.0, 390.0)
Median	450.0	(326.0, ND)
75 percentile		(481.0, ND)

CI = confidence interval; N = total number of subjects; ND = not determined.
a. Survival time was 1 plus the difference in days between the date of death and the date of first dose.
b. The 2-sided 95% CIs for median, 25 and 75 percentile for survival time were estimated based on the Brookmeyer and Crowley method.
c. Kaplan-Meier estimates of median, 25 and 75 percentile for survival. Subjects not expiring had their survival times censored on the last date of known contact that the subject was documented to be alive. Subjects lacking data beyond first dose had their survival times censored at 1 day.

Safety Results: Table 8 is an overall summary of AEs. All subjects experienced at least 1 AE, and 30 subjects (93.8%) experienced AEs that were considered to be related to the study drug. Eleven subjects (34.4%) discontinued the study because of AEs, and 17 subjects (53.1%) had a dose reduction because of an AE. Nineteen subjects (59.4%) died including 4 who died on treatment or within 28 days of their last dose of study medication and 15 (46.9%) who died during follow-up.

Table 8. Overall Summary of Treatment-Emergent Adverse Events (All Treated Subjects)

Number (%) of Subjects	Axitinib (N=32)
At least 1 adverse event	32 (100%)
At least 1 serious adverse event	16 (50.0%)
Discontinued due to adverse event	11 (34.4%)
Dose reduction due to adverse event	17 (53.1%)
Death	19 (59.4%)
On treatment or within 28 days after last dose	4 (12.5%)
>28 days after last dose if related to study treatment	0

AEs and SAEs are not separated out.
AEs = adverse events; N = number of subjects; SAEs = serious adverse events.

Treatment-emergent AEs (TEAEs) occurring in ≥5% of subjects are summarized in Table 9. The most common AEs were constitutional events (fatigue, anorexia, arthralgia, hypertension not otherwise specified [NOS], weight decreased, and headache NOS), gastrointestinal events (diarrhea NOS, nausea, vomiting NOS, and dyspepsia), and respiratory events (dyspnea NOS, cough, hoarseness, and upper respiratory tract infection NOS).

Table 9. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate Greater Than or Equal to 5 (All Treated Subjects)

	Axitinib (N=32)
Number of subjects with adverse events	31
Number of subjects with adverse events by System Organ Class	
MedDRA (v13.1) and preferred term:	
Blood and lymphatic system disorders	6
Anaemia	3
Cardiac disorders	5
Tachycardia	4
Endocrine disorders	2
Hypothyroidism	2
Gastrointestinal disorders	27
Abdominal pain	4
Abdominal pain upper	3
Constipation	6
Diarrhoea	15
Dyspepsia	7
Dysphagia	4
Flatulence	2
Glossodynia	3
Nausea	15
Oral discomfort	2
Oral pain	4
Stomatitis	2
Vomiting	10
General disorders and administration site conditions	28
Chest pain	4
Fatigue	27
Gait disturbance	2
Mucosal inflammation	5
Oedema peripheral	5
Pain	2
Infections and infestations	12
Bronchitis	2
Rhinitis	2
Upper respiratory tract infection	7
Injury, poisoning and procedural complications	6
Traumatic haematoma	2
Investigations	14
Alanine aminotransferase increased	2
Blood creatinine increased	2
Weight decreased	11
Metabolism and nutrition disorders	24
Decreased appetite	19
Dehydration	3
Hyperglycaemia	2
Hypoglycaemia	2
Hypokalaemia	4
Hypomagnesaemia	3

Table 9. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate Greater Than or Equal to 5 (All Treated Subjects)

	Axitinib (N=32)
Hyponatraemia	4
Musculoskeletal and connective tissue disorders	20
Arthralgia	8
Back pain	3
Bone pain	2
Muscular weakness	5
Musculoskeletal pain	4
Myalgia	3
Pain in extremity	4
Nervous system disorders	19
Ataxia	2
Dizziness	3
Headache	8
Neuropathy peripheral	3
Somnolence	2
Psychiatric disorders	10
Anxiety	2
Confusional state	2
Depression	2
Insomnia	4
Renal and urinary disorders	9
Proteinuria	6
Urinary retention	2
Respiratory, thoracic and mediastinal disorders	25
Cough	11
Dysphonia	12
Dyspnoea	10
Epistaxis	4
Haemoptysis	3
Hypoxia	2
Oropharyngeal pain	2
Skin and subcutaneous tissue disorders	13
Alopecia	3
Dry skin	3
Rash	5
Rash erythematous	2
Vascular disorders	13
Hypertension	10
Hypotension	2

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; v = version.

Treatment-related AEs are summarized by SOC, preferred term in Table 10. The most common treatment-related AEs included constitutional (fatigue, anorexia, hypertension NOS, and arthralgia), gastrointestinal (diarrhea NOS, nausea, and vomiting NOS), and respiratory (hoarseness) events.

Table 10. Treatment-Emergent Adverse Events Related to Study Treatment by System Organ Class and Preferred Term (All Treated Subjects)

System Organ Class[a] Preferred Term	Axitinib (N=32)	
	Subjects n (%)	No. of Events
Any treatment-related adverse events	30 (93.8%)	391
Blood and lymphatic system disorders	4 (12.5%)	6
Anaemia NOS	2 (6.3%)	2
Gastrointestinal disorders	22 (68.8%)	99
Abdominal pain NOS	3 (9.4%)	4
Abdominal pain upper	3 (9.4%)	3
Constipation	2 (6.3%)	2
Diarrhoea NOS	14 (43.8%)	29
Dyspepsia	6 (18.8%)	9
Dysphagia	2 (6.3%)	2
Flatulence	2 (6.3%)	3
Gastrooesophageal reflux disease	2 (6.3%)	3
Glossodynia	3 (9.4%)	5
Nausea	11 (34.4%)	15
Oral discomfort	2 (6.3%)	3
Oral pain	4 (12.5%)	6
Stomatitis	2 (6.3%)	2
Vomiting NOS	7 (21.9%)	8
General disorders and administration site conditions	23 (71.9%)	69
Fatigue	23 (71.9%)	55
Mucosal inflammation NOS	5 (15.6%)	6
Investigations	8 (25.0%)	17
Weight decreased	5 (15.6%)	8
Metabolism and nutrition disorders	20 (62.5%)	62
Anorexia	16 (50.0%)	40
Appetite decreased NOS	2 (6.3%)	2
Dehydration	2 (6.3%)	2
Hyperkalaemia	2 (6.3%)	2
Hypokalaemia	3 (9.4%)	3
Hypomagnesaemia	3 (9.4%)	5
Hyponatraemia	3 (9.4%)	4
Musculoskeletal and connective tissue disorders	12 (37.5%)	22
Arthralgia	7 (21.9%)	10
Muscle weakness NOS	3 (9.4%)	5
Myalgia	2 (6.3%)	3
Pain in limb	2 (6.3%)	2
Nervous system disorders	15 (46.9%)	30
Ataxia	2 (6.3%)	2
Dizziness	2 (6.3%)	2
Dysphonia	3 (9.4%)	7
Headache NOS	4 (12.5%)	8
Peripheral neuropathy NOS	3 (9.4%)	3
Psychiatric disorders	3 (9.4%)	3

Table 10. Treatment-Emergent Adverse Events Related to Study Treatment by System Organ Class and Preferred Term (All Treated Subjects)

System Organ Class[a] Preferred Term	Axitinib (N=32)	
	Subjects n (%)	No. of Events
Insomnia	2 (6.3%)	2
Renal and urinary disorders	5 (15.6%)	5
Proteinuria	4 (12.5%)	4
Respiratory, thoracic and mediastinal disorders	15 (46.9%)	28
Cough	2 (6.3%)	2
Epistaxis	2 (6.3%)	2
Haemoptysis	2 (6.3%)	2
Hoarseness	9 (28.1%)	16
Skin and subcutaneous tissue disorders	9 (28.1%)	19
Alopecia	3 (9.4%)	3
Rash NOS	5 (15.6%)	8
Vascular disorders	15 (46.9%)	22
Hypertension NOS	10 (31.3%)	16
Hypertension aggravated	2 (6.3%)	2

AEs and SAEs are not separated out.
AEs = adverse events; n = number of subjects; N = total number of subjects; NOS = not otherwise specified; SAEs = serious adverse events.

a. The denominator for percent was the number of subjects who received treatment. For number of subjects, each subject was counted once within each category (each System Organ Class or each preferred term within System Organ Class).

Serious Adverse Events (SAEs): All SAEs, are summarized in Table 11, and all treatment related SAEs are summarized in Table 12. Sixteen subjects (50.0%) experienced a total of 36 SAEs, including 6 subjects (18.8%) who experienced 7 treatment-related SAEs. The only SAEs experienced by more than 1 subject were disease progression NOS (5 subjects [15.6%], 5 events), confusion (3 subjects [9.4%], 3 events), and dehydration and dyspnea NOS (each 2 subjects [6.3%], 2 events); only 1 of these events (disease progression NOS) was considered treatment-related. Most SAEs resolved, with the exception of 1 event each of disease progression, confusion, and dyspnea NOS; and also a large intestinal ulcer.

Table 11. Treatment-Emergent Serious Adverse Events (All Causalities) by System Organ Class and Preferred Term (All Treated Subjects)

System Organ Class Preferred Term	Axitinib (N=32)	
	Subjects n (%)	No. of Events
Any serious adverse events	16 (50.0%)	36
Cardiac disorders	2 (6.3%)	2
Acute coronary syndrome	1 (3.1%)	1
Bradycardia NOS	1 (3.1%)	1
Gastrointestinal disorders	5 (15.6%)	7
Appendicitis	1 (3.1%)	1
Colitis NOS	1 (3.1%)	1
Diarrhoea haemorrhagic	1 (3.1%)	1
Dysphagia	1 (3.1%)	1
Large intestinal ulcer	1 (3.1%)	1
Oesophageal stenosis acquired	1 (3.1%)	1
Rectal haemorrhage	1 (3.1%)	1
General disorders and administration site conditions	5 (15.6%)	6
Disease progression NOS	5 (15.6%)	5
General physical health deterioration	1 (3.1%)	1
Infections and infestations	3 (9.4%)	3
Bronchitis acute NOS	1 (3.1%)	1
Infection NOS	1 (3.1%)	1
Pneumonia NOS	1 (3.1%)	1
Metabolism and nutrition disorders	3 (9.4%)	3
Dehydration	2 (6.3%)	2
Hyperkalaemia	1 (3.1%)	1
Nervous system disorders	3 (9.4%)	4
Ataxia	1 (3.1%)	1
Cerebrovascular accident	1 (3.1%)	1
Convulsions NOS	1 (3.1%)	1
Transient ischaemic attack	1 (3.1%)	1
Psychiatric disorders	3 (9.4%)	3
Confusion	3 (9.4%)	3
Renal and urinary disorders	1 (3.1%)	1
Renal failure acute	1 (3.1%)	1
Respiratory, thoracic and mediastinal disorders	3 (9.4%)	5
Chronic obstructive airways disease exacerbated	1 (3.1%)	1
Cough	1 (3.1%)	1
Dyspnoea NOS	2 (6.3%)	2
Dyspnoea exacerbated	1 (3.1%)	1
Vascular disorders	1 (3.1%)	2
Hypotension NOS	1 (3.1%)	1
Inferior vena caval obstruction	1 (3.1%)	1

N = total number of subjects; n = number of subjects; NOS = not otherwise specified.

Table 12. Treatment-Emergent Serious Adverse Events Related to Study Treatment by System Organ Class and Preferred Term (All Treated Subjects)

System Organ Class[a] Preferred Term	Axitinib (N=32)	
	Subjects n (%)	Events
Any serious treatment-related adverse events	6 (18.8%)	7
Cardiac disorders	1 (3.1%)	1
Acute coronary syndrome	1 (3.1%)	1
Gastrointestinal disorders	1 (3.1%)	1
Diarrhoea haemorrhagic	1 (3.1%)	1
General disorders and administration site conditions	1 (3.1%)	1
Disease progression NOS	1 (3.1%)	1
Metabolism and nutrition disorders	1 (3.1%)	1
Hyperkalaemia	1 (3.1%)	1
Nervous system disorders	1 (3.1%)	1
Cerebrovascular accident	1 (3.1%)	1
Renal and urinary disorders	1 (3.1%)	1
Renal failure acute	1 (3.1%)	1
Vascular disorders	1 (3.1%)	1
Inferior vena caval obstruction	1 (3.1%)	1

N = total number of subjects; n = number of subjects; NOS = not otherwise specified.

a. The denominator for percent was the number of subjects who received treatment. For number of subjects, each subject was counted once within each category (each System Organ Class or each preferred term within System Organ Class).

Permanent Discontinuations Due to AEs: Eleven subjects (34.4%) had a total of 13 AEs for which their study treatment was permanently discontinued. Disease progression NOS led to the discontinuation of 4 subjects (12.5%), fatigue led to the discontinuation of 3 subjects (9.4%); and anorexia, confusion, acute coronary syndrome, pulmonary embolism, inferior vena caval obstruction, and diarrhea NOS each led to the discontinuation of 1 subject (3.1%).

Temporary Discontinuations: Seventeen subjects (53.1%) had dose reductions or temporary discontinuations due to an AE.

Deaths: Five subjects (15.6%) died due to disease progression NOS (4 subjects died on treatment or within 28 days of their last dose of study treatment). Four of these events were considered disease-related; and 1 event was assessed as treatment-related.

There was no evidence of a clinically significant mean change in any laboratory parameter, and there were few marked laboratory changes. One subject had Grade 4 hyperkalemia that was reported as a SAE. Three subjects (9.4%) experienced maximum urinary protein results of 3+, and 3 subjects (9.4%) experienced maximum urinary protein results of 2+ after taking study treatment.

Four subjects (14.8%) had a shift in systolic BP from <160 mmHg at baseline to ≥160 mmHg at ≥1 time point on study, and 1 subject (3.7%) had a shift in diastolic BP from <105 mmHg at baseline to ≥105 mmHg at ≥1 time point. Subjects developing hypertension on-study were easily managed with antihypertensives. BP elevations resolved by the next assessment.

CONCLUSION: The ORR was 9.4% (95% CI: 2.0% to 25.0%) in subjects with advanced NSCLC; and 31.3% of the non-responders had SD at 4 months. The median OS was approximately 14.8 months. Taken together, axitinib appears to have activity in NSCLC and warrants further testing. Phase 1-3 studies of axitinib as a single agent or in combination with chemotherapy have been planned or are underway. The AE profile of axitinib was clinically manageable with no unexpected toxicities.