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

PROTOCOL NO.: A4061038

PROTOCOL TITLE: Phase 2 Trial of AG-013736 as First-Line Treatment for Patients With Squamous Non-Small Cell Lung Cancer Receiving Treatment With Cisplatin and Gemcitabine

Study Centers: A total of 10 centers took part in the study and enrolled subjects; 1 in South Africa, 2 in Poland, 3 in Romania, and 4 in Ukraine.

Study Initiation and Final Completion Dates: 17 December 2008 and 30 November 2011

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To assess the efficacy of axitinib in combination with cisplatin/gemcitabine in subjects with advanced/metastatic, squamous non-small-cell lung cancer (NSCLC).

Secondary Objectives:

- To assess the safety of axitinib in combination with cisplatin/gemcitabine in subjects with squamous NSCLC;
- To assess population pharmacokinetics for axitinib;
- To explore vascular endothelial growth factor (VEGF) receptor signaling in circulating endothelial cells (CECs) in this subject population.

METHODS

Study Design: This was a single-stage, open-label, non-randomized, multicenter Phase 2 study in subjects with locally advanced, metastatic or recurrent squamous. All subjects were to be treated with axitinib in combination with cisplatin + gemcitabine and assessed for safety and efficacy. The study was a noncomparative, open-label study. The schedule of activities is presented in Table 1. The planned starting doses of the drug combinations are presented in Table 2.

Table 1. Schedule of Activities

		Chemotherapy Phase		Single-Agent Axitinib Phase	Final Study Visit[a]	Follow-Up for Survival
		Cycles C1-C6 (21-Day Cycles)		Cycles A1-A15 (28-Day Cycles)		
Activity	**Screen[b]**	**Day 1[c]**	**Day 8**	**Day 1**		**Bimonthly**
	≤28 Days	**±3 Days**	**±3 Days**	**±3 Days**		
Baseline Documentation						
Informed consent	X					
Medical and oncologic history	X					
Baseline signs and symptoms	X					
Physical examination[d]	X	X		X	X	
Weight, vital signs[e], ECOG status	X	X		X	X	
Laboratory assessments						
Hematology[f]	X	X	X	X	X	
Blood chemistry[g]	X	X		X	X	
Erythropoietin & thyroid function tests[h]	X	Every cycle × 3, then every other cycle				
Urinalysis[i]	X	X		X	X	
Pregnancy test (serum or urine)[j]	X					
12-lead ECG	X					
Tumor assessments						
CT or MRI scans of chest, abdomen, and other disease sites[k]	X	X (C3 & C5 only)		X (Every other cycle)	X	
Confirmatory scans[l]		(X)		(X)	(X)	
Brain CT or MRI scan[k]	X	(X)		(X)	(X)	
Chest x-ray[m]		(X)				
Study Treatment						
Chemotherapy administration		X	X			
Axitinib administration[n]		Twice daily continuously				
Drug compliance[o]		X (C2+)		X	X	
Other Assessments						
AE assessment[p]		X	X	X	X	
Concomitant medications	X	X	X	X	X	
Survival information[q]						X
Pharmacokinetics[r]		X (C2 & C3 only)				
Circulating endothelial cells[s]		X (C1, C2, & C3 only)	X (C1 only)			

Table 1. Schedule of Activities

		Chemotherapy Phase		Single-Agent Axitinib Phase	Final Study Visit[a]	Follow-Up for Survival
		Cycles C1-C6 (21-Day Cycles)		Cycles A1-A15 (28-Day Cycles)		
Activity	**Screen[b]**	**Day 1[c]**	**Day 8**	**Day 1**		**Bimonthly**
UGT1A1 and other genotyping[t]		X (C1 only)				
Exploratory research-optional blood sample[u]		(X: C1 & C2 only)	(X: C1 only)			
Exploratory research-optional archival tumor sample[v]		(X: C1)				

A = axitinib; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C = chemotherapy; CR = complete response; CT = computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PR = partial response; TSH = thyroid-stimulating hormone; UGT1A1 = uridine diphosphate-glucuronosyl transferase 1A1; WBC = white blood cell.

a. Final study visit assessments were only needed if the prior assessment was performed greater than 7 days previously except for scans, which were to be repeated if the prior assessment was performed greater than 4 weeks previously. Every effort was to be made to obtain a final tumor assessment.
b. Screen assessments were to be performed within 7 days of treatment, except informed consent and medical history, which were permitted to be performed within 14 days, and where noted (eg, tumor assessments).
c. Cycle 1 Day 1 assessments were not required to be repeated if performed within the previous 7 days.
d. Physical examination included height on initial examination. After the initial complete examination, targeted examinations based on signs and symptoms were performed.
e. Blood pressure (BP) was to be taken with the subject in the seated position after the subject had been sitting quietly for 5 minutes. All subjects received BP monitoring devices. Subjects were to take BP measurements at least twice daily (prior to taking a dose of axitinib) and record results in the subject diary.
f. Hematology was to be analyzed by a center-designated local laboratory. Hematology was to include WBC, hemoglobin, platelets, neutrophil count, and lymphocyte count.
g. Blood chemistry was to be analyzed by a center-designated local laboratory. Blood chemistry was to include sodium, potassium, chloride, carbon dioxide or bicarbonate, blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, and LDH.
h. Erythropoietin and thyroid function tests were to be analyzed by a center-designated local laboratory. Erythropoietin levels, TSH, and free thyroxine were to be collected during screening or on Day 1 of Cycle 1. Then erythropoietin levels and TSH tests were to be performed on Day 1 on Cycles 2 and 3, and then every other cycle thereafter (on Day 1 of Cycle 5, A1, etc). Subsequent free thyroxine levels were to be assessed as clinically indicated.
i. Urinalysis was to be analyzed by dipstick by a center-designated local laboratory. If urine protein was ≥1+ by semiquantitative method (eg, dipstick) at screening or ≥2+ on study, urine protein:creatinine ratio was to be performed.
j. Pregnancy test (serum or urine) was to be performed within 7 days of treatment for women of childbearing potential and repeated during the study if requested by the Independent Ethics Committee or if required by local regulations. To be analyzed by a center-designated local laboratory.
k. Tumor assessments at Baseline were to be performed within 28 days of study treatment and were to include brain imaging (either a CT or MRI scan) and CT or MRI scan of chest and upper abdomen, including both adrenal glands, for all subjects. The time window for scans was ±7 days. Scans of chest and abdomen, including both adrenal glands, were to be performed every other cycle (every 6 weeks during chemotherapy and every 8 weeks during axitinib maintenance). For those subjects who entered the study with controlled brain metastases, brain imaging (CT or MRI of the brain) was to be performed on the same schedule as that for the body scans. Subjects without brain metastases at randomization were to undergo repeat brain imaging only if there were signs or symptoms of brain metastases.
l. Subjects who achieved a PR or CR were to undergo confirmatory scans of 1) the brain and 2) the chest and abdomen (including both adrenal glands) 4 weeks (-0/+7 days) after the initial scan showing PR or CR. If a subsequent tumor assessment was scheduled 6 weeks after the initial documentation of response, then that scan could have been used for confirmation.
m. A chest x-ray (preferably posteroanterior and lateral views) was to be performed within the 7 days prior to the beginning of each chemotherapy cycle, starting with Cycle C2,

Table 1. Schedule of Activities

		Chemotherapy Phase		Single-Agent Axitinib Phase	Final Study Visit[a]	Follow-Up for Survival
		Cycles C1-C6 (21-Day Cycles)		Cycles A1-A15 (28-Day Cycles)		
Activity	**Screen[b]**	**Day 1[c]**	**Day 8**	**Day 1**		**Bimonthly**

to assess for tumor cavitation. If tumor cavitation was observed, axitinib was to be temporarily discontinued, and the case was to be discussed with the sponsor. If a re-staging CT or MRI scan of the chest had been performed within 7 days of Day 1, this scan was permitted to be used to assess for tumor cavitation in lieu of a chest x-ray.

n. Axitinib was to be dosed twice daily with dose titration upward or downward according to dose adjustment guidelines. Each time axitinib was dispensed, the Investigator or Designee (eg, site coordinator or pharmacist) was required to document that: 1) no cavitating tumor was observed in most recent chest x-ray or chest CT scan (performed within the 7 days prior to Day 1 dosing); and 2) no hemoptysis ≥0.5 teaspoon (2.5 mL) of blood had occurred during a 24-hour period within the past 4 weeks. If either tumor cavitation or hemoptysis ≥0.5 teaspoon (2.5 mL) of blood in 24-hour period was observed, axitinib was required to be discontinued immediately and the Sponsor notified.

o. Axitinib including any unused drug was to be returned to the clinic for drug accountability at the beginning of each cycle starting with Cycle C2.

p. The reporting period for non-serious AEs terminated 28 days after the last dose of study treatment or upon initiation of a new anticancer treatment, whichever occurred first. Ongoing treatment-related AEs were required to be followed up until resolution, return to baseline, chronicity, or initiation of subsequent anticancer treatment. The serious AE reporting period ended 28 days after the last study treatment dose, irrespective of start of any new anticancer treatment. Any serious, treatment-related AEs were required to be reported at any time.

q. Survival information was collected bimonthly after final study visit.

r. Population pharmacokinetic samples for axitinib were obtained on Cycle 2 Day 1 and Cycle 3 Day 1. On both scheduled visits, 2 samples were to be collected: 1 sample just before (15 minutes prior to) the morning axitinib dose (taken in the clinic) and another 1 to 2 hours after the morning axitinib dose.

s. Blood was collected to analyze the effects of therapy on the number, viability/apoptotic state, and/or target activity/expression in circulating endothelial cells and their progenitors on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 3 Day 1 prior to drug dosing.

t. One blood sample (2 mL) was collected on Day 1 of Cycle 1 only for genotyping of UGT1A1 and other drug metabolizing enzymes/transporters.

u. Optional blood samples for RNA transcript profiling were to be collected prior to drug dosing on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1 only for sample banking for exploratory research.

v. Optional archival tumor may have been collected on Cycle 1 Day 1 or at any time during the study for sample banking for exploratory research.

Table 2. Planned Starting Doses of Study Drug Combinations (Axitinib, Cisplatin, and Gemcitabine)

Axitinib	Cisplatin Day 1	Gemcitabine Days 1 and 8
5 mg	80 mg/m^2	1250 mg/m^2

Number of Subjects (Planned and Analyzed): Thirty-six subjects with locally advanced, metastatic or recurrent squamous NSCLC were planned to be enrolled in this study. A total of 38 subjects (1 in South Africa, 6 in Poland, 10 in Romania and 21 in Ukraine) were enrolled in the study.

Diagnosis and Main Criteria for Inclusion: The study included subjects (≥18 years of age) with histologically or cytologically confirmed diagnosis of squamous NSCLC Stage IIIB with malignant effusion (fluid cytology demonstrating malignant cells required), Stage IV, or recurrent disease after definitive local therapy. Candidates eligible for primary treatment with cisplatin and gemcitabine were diagnosed with measurable disease by response evaluation criteria in solid tumors (RECIST) and adequate organ function as defined Eastern Cooperative Oncology Group (ECOG) criteria (subjects had an ECOG performance status of 0 or 1).

Study Treatment: Axitinib was supplied as 1 mg and 5 mg film-coated tablets for oral administration. Cisplatin was supplied as a sterile 1 mg/mL solution containing sodium chloride, hydrochloric acid, and sodium hydroxide, or as a lyophilized powder. Gemcitabine was supplied as a lyophilized powder containing either 200 mg or 1 g of gemcitabine as the hydrochloride salt, mannitol, and sodium acetate. The chemotherapy was administered in 21-day cycles (up to 6 cycles while on study), and included cisplatin 80 mg/m^2 on Day 1 of each cycle and gemcitabine 1250 mg/m^2 on Days 1 and 8 of each cycle. Axitinib was administered concurrently with chemotherapy. The starting dose of axitinib was 5 mg BID at approximately 12-hour intervals, administered orally with food. Doses were taken at approximately the same times each day on a continuous schedule. Axitinib was administered in 3-week cycles during chemotherapy and 4-week cycles thereafter. The dose of axitinib was to be adjusted per tolerability and continued after completion of chemotherapy until disease progression. Cisplatin was administered according to the institution's guidelines over at least a 2-hour period. Subjects were received gemcitabine as an intravenous infusion over approximately 30 minutes on Day 1 and Day 8 of each 21-day cycle.

Efficacy Endpoints:

Primary Endpoint: Overall confirmed objective response rate (ORR), defined as the proportion of subjects with a confirmed best response characterized as either a complete response (CR) or partial response (PR) (target lesions and tumor response defined according to RECIST guidelines). Confirmed responses are those that persist on a follow-up imaging assessment ≥4 weeks after the initial objective documentation of response.

Secondary Endpoints:

- Overall Survival (OS) defined as the difference in time between the date of death due to any cause and the date of the first dose of axitinib;
- Progression-Free Survival (PFS) defined as the difference in time between the first date that either criteria for progression are met or the subject died due to any cause, and the date of the first dose of axitinib;
- Duration of Response (DR) defined as the time from first documentation of response to the date of progression or death due to any cause, whichever occurs first;
- Overall safety profile, characterized by type, frequency, severity (as graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) of adverse events (AEs) and laboratory abnormalities.

Safety Evaluations: The safety of axitinib was assessed by AE and serious AE (SAE) monitoring, physical examinations, clinical laboratory assessments, electrocardiogram (ECG), vital signs, and ECOG performance status assessments.

Statistical Methods: The primary endpoint, ORR, was calculated for the intent-to-treat (ITT) population (ie, subjects receiving at least 1 dose of study drug) and a 2-sided 95% confidence interval (CI) for ORR was provided using an exact 2-sided 95% CI using a method based on the F distribution. The secondary endpoints, PFS, DR and OS were calculated for the ITT population and were analyzed using Kaplan-Meier methods, with median values and 95% CI presented. DR was only calculated for the subgroup of subjects with objective response.

RESULTS

Subject Disposition and Demography: A total of 38 subjects with advanced/metastatic, squamous NSCLC were screened and assigned to treatment. All 38 subjects received at least 1 dose of study medication. As of the completion date for this study, 100% of subjects had discontinued from the study. The most common reason for discontinuation from the study was death (20 subjects [52.6%]) (Table 3).

Table 3. Subject Disposition

Number (%) of Subjects	Axitinib + Gemcitabine + Cisplatin (N=38)
Screened	38
Assigned to study treatment	38
Treated	38
Completed	0
Discontinued	38
Primary reason for discontinuation from study	
AE	3 (7.9)
Subject died	20 (52.6)
Protocol violation	1 (2.6)
Other	8 (21.1)
Study terminated by Sponsor	5 (13.2)
Subject refused continued treatment for reason other than AE	1 (2.6)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
AE = adverse event.

Thirty-seven (97.4%) subjects were white, and 34 (89.5%) subjects were male. Subjects ranged in age from 47 to 73 years; 28 (73.7%) subjects were <65 years old and 10 (26.3%) subjects were ≥65 years old (Table 4).

Table 4. Subject Demographics

	Axitinib + Gemcitabine + Cisplatin (N=38)
Age (years)	
Mean (standard deviation)	60.5 (7.1)
Median	59.50
Min, max	47, 73
N	38
Age (years), n (%)	
<65	28 (73.7)
≥65	10 (26.3)
Sex, n (%)	
Male	34 (89.5)
Female	4 (10.5)
Race, n (%)	
White	37 (97.4)
Black	1 (2.6)
Weight (kg)	
Mean (standard deviation)	75.1 (18.1)
Median	69.5
Min, Max	53.0, 125.0
N	38
Height (cm)	
Mean (standard deviation)	171.8 (7.5)
Median	174.0
Min, Max	151.0, 183.0
N	38
Smoking Status	
Never smoked	5 (13.2)
Smoker	33 (86.8)
Time since histopathological diagnosis (weeks)	
Mean (standard deviation)	4.8 (13.2)
Median	2.21
Min, max	0.7, 83.4
Histological classification, n (%)	
Squamous cell carcinoma	38 (100.0)
Current stage, n (%)	
Stage IIIB	5 (13.2)
Stage IV	33 (86.8)
ECOG performance status, n (%)	
0	12 (31.6)
1	26 (68.4)

% = (n/N)*100; ECOG = Eastern Cooperative Oncology Group; max = maximum; min = minimum; N = total number of subjects; n = number of subjects in specified category.

Efficacy Results:

Primary Endpoint:

Primary Efficacy Endpoint: ORR, a summary of the best overall tumor response as determined by the Investigator is provided in Table 5.

Table 5. Best Overall Tumor Response by Treatment, Investigator's Assessment (Full Analysis Set)

Variable	Axitinib + Gemcitabine + Cisplatin (N=38)
Subjects with baseline assessment, n (%)	37 (97.4)
Subjects with measurable disease at Baseline, n (%)	37 (97.4)
Best overall response, n (%)	
Complete response	1 (2.6)
Partial response	14 (36.8)
Stable disease	9 (23.7)
Progressive disease	3 (7.9)
Early death[a]	2 (5.3)
Indeterminate	8 (21.1)
Overall confirmed objective response rate (CR + PR)	15 (39.5)
95% exact CI[b]	(24.0%, 56.6%)

CI = confidence interval; CR = complete response; N = total number of subjects; n = number of subjects in specified category; PR = partial response.
a. Early death is defined as a death occurring before the first planned tumor assessment.
b. Using exact method based on F-distribution.

Secondary Efficacy Endpoints: PFS is summarized for the full analysis set in Table 6.

Table 6. Summary of Progression-Free Survival by Treatment (Full Analysis Set)

	Axitinib + Gemcitabine + Cisplatin (N=38)
Progression status, n (%)	
Subjects observed to have progressed or died due to any cause while on study[a]	20 (52.6)
Type of event	
Objective progression	17 (85.0)
Death without objective progression	3 (15.0)
Subjects did not progress or die due to any cause while on study[a]	18 (47.4)
Reason for censorship	
No Baseline or on-study assessment	8 (44.4)
Alive, on-study, and progression-free at the time of the analysis	0
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on study	1 (5.6)
PD occurred after ≥2 consecutive, missed assessments	0
PD occurred after given new anti-tumor treatment	0
Withdrew consent for follow-up	0
Lost to follow-up	0
Subject took new anti-tumor therapy	0
Other	9 (50.0)
Progression-free survival (months)	
Quartiles (95% CI)	
25%	3.4 (2.7, 6.0)
50%	6.2 (4.5, 9.3)
75%	9.7 (6.8, 23.9)

CI = confidence interval; N = total number of subjects in treatment group; n = number of subjects; PD = progressive disease.
a. On study included treatment plus 28-day follow-up period.

OS is summarized for the full analysis set in Table 7.

Table 7. Summary of Overall Survival by Treatment (Full Analysis Set)

	Axitinib + Gemcitabine + Cisplatin (N=38)
Subject status, n (%)	
Dead	21[a] (55.3)
Cause of death	
Disease under study	20 (95.2)
Study treatment toxicity	0
Unknown	0
Other	1 (4.8)
Alive[b]	17 (44.7)
Reason for censorship	
Alive	12 (70.6)
Subject not willing to participate	4 (23.5)
Lost to follow-up	1 (5.9)
Survival time (months)	
Quartile (95% CI)	
25%	10.2 (6.6, 12.9)
50%	14.2 (11.8, 23.1)
75%	NA[c]
1-year survival probability (95% CI)[d]	63.16 (44.73, 76.91)

CI = confidence interval; N = total number of subjects; n = number of subjects in specified category.

a. The death of 1 subject was reported after the subject discontinued from study. This report was not required, but is included in the total number of deaths.
b. Subjects who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
c. Not available
d. Calculated from the log [-log (1-year survival probability)] using a normal approximation and back transformation.

DR is summarized for the safety analysis set in Table 8.

Table 8. Duration of Tumor Response by Treatment, Investigator's Assessment

	Axitinib + Gemcitabine + Cisplatin[a] (N=15)
Response status, n (%)	
Subjects with a response and subsequent progression or death due to any cause while on study[b]	11 (73.3)
Type of event	
Objective progression	11 (100.0)
Death without objective progression	0 (0.0)
Subjects with a response who had not progressed or died due to any cause while on study[b]	4 (26.7)
Reason for censorship	
No Baseline or on-study assessment	0 (0.0)
Alive, on-study, and progression free at the time of the analysis	0 (0.0)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on study	1 (25.0)
PD occurred after ≥2 consecutive, missed assessments	0 (0.0)
PD occurred after given new anti-tumor treatment	0 (0.0)
Withdrew consent for follow-up	0 (0.0)
Lost to follow-up	0 (0.0)
Subject took new anti-tumor therapy	0 (0.0)
Other	3 (75.0)
Response duration (months)	
Quartiles (95% CI)	
25%	4.66 (3.5, 5.8)
50%	5.78 (4.7, 7.2)
75%	7.19 (5.8, 22.2)

CI = confidence interval; CR = complete response; N = total number of subjects in treatment group; n = number of subjects; PD = progressive disease; PR = partial response.

a. Duration of response was calculated for the subgroup of subjects with a confirmed objective tumor response (PR + CR).

b. On study included treatment plus 28-day follow-up period.

Safety Results: Overall, 36 (94.7%) subjects reported at least 1 all-causality AEs and 34 (89.5%) subjects reported at least 1 treatment-related AEs. A total of 15 (39.5%) subjects reported at least 1 all-causality SAEs and 7 (18.4%) subjects reported at least 1 treatment-related SAEs. There were 13 (34.2%) subjects who had temporary discontinuations due to treatment-emergent AEs and 5 (13.2%) subjects who experienced dose reductions due to treatment-emergent AEs (Table 9).

Table 9. Overall Summary of Treatment-Emergent Adverse Events (All-Causality and Treatment-Related)

Number (%) of Subjects	Axitinib + Gemcitabine + Cisplatin (N=38)	
	All Causality	Treatment-Related
Subjects with ≥1 AE	36 (94.7)	34 (89.5)
Subjects with ≥1 SAE	15 (39.5)	7 (18.4)
Subjects with ≥1 AE related to axitinib	22 (57.9)	22 (57.9)
Subjects with ≥1 AE related to gemcitabine/cisplatin	30 (78.9)	30 (78.9)
Subjects with ≥1 AE related to axitinib + gemcitabine/cisplatin	14 (36.8)	14 (36.8)
Subjects with ≥1 SAE related to axitinib	3 (7.9)	3 (7.9)
Subjects with ≥1 SAE related to gemcitabine/cisplatin	5 (13.2)	5 (13.2)
Subjects with ≥1 SAE related to axitinib + gemcitabine/cisplatin	1 (2.6)	1 (2.6)
Subjects with action taken permanently discontinued related to axitinib	8 (21.1)	4 (10.5)
Subjects with action taken permanently discontinued related to gemcitabine	6 (15.8)	4 (10.5)
Subjects with action taken permanently discontinued related to cisplatin	5 (13.2)	4 (10.5)
Subjects who died	4 (10.5)	0

The AE/SAE results are not separated out.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SAE = serious adverse event.

Treatment-emergent AEs (all causality and treatment related) occurring in ≥5% of subjects are presented in in Table 10.

Table 10. Treatment-Emergent Adverse Events by Preferred Terms for ≥5% of Subjects (All-Causality and Treatment-Related)

Preferred Term	Axitinib + Gemcitabine + Cisplatin (N=38)	
	n (%)	
	All Causality	Treatment-Related
Any AEs	36 (94.7)	34 (89.5)
Anaemia	12 (31.6)	11 (28.9)
Leukopenia	5 (13.2)	5 (13.2)
Neutropenia	9 (23.7)	9 (23.7)
Thrombocytopenia	4 (10.5)	4 (10.5)
Diarrhoea	5 (13.2)	3 (7.9)
Nausea	16 (42.1)	16 (42.1)
Vomiting	11 (28.9)	11 (28.9)
Asthenia	6 (15.8)	4 (10.5)
Chest pain	4 (10.5)	0
Fatigue	7 (18.4)	6 (15.8)
Hyperthermia	2 (5.3)	0
Pyrexia	2 (5.3)	2 (5.3)
Disease progression	2 (5.3)	0
Influenza	2 (5.3)	0
Pneumonia	2 (5.3)	0
Alanine aminotransferase increased	2 (5.3)	2 (5.3)
Blood creatinine increased	2 (5.3)	1 (2.6)
Creatinine renal clearance decreased	5 (13.2)	5 (13.2)
Weight decreased	9 (23.7)	4 (10.5)
Dehydration	2 (5.3)	2 (5.3)
Decreased appetite	8 (21.1)	7 (18.4)
Hemiparesis	2 (5.3)	0
Peripheral sensory neuropathy	2 (5.3)	2 (5.3)
Nephropathy toxic	4 (10.5)	3 (7.9)
Cough	4 (10.5)	2 (5.3)
Dyspnoea	4 (10.5)	2 (5.3)
Haemoptysis	3 (7.9)	2 (5.3)
Pulmonary cavitation	3 (7.9)	3 (7.9)
Alopecia	5 (13.2)	5 (13.2)
Rash	4 (10.5)	4 (10.5)
Hypertension	10 (26.3)	10 (26.3)

The AE/SAE results are not separated out.
Subjects were only counted once per treatment for each AEs subcategory row.
MedDRA (version 14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in treatment group; n = number of subjects with AEs.

A total of 8 (21.1%) subjects permanently discontinued from treatment due to AEs during the study (Table 11). Axitinib, gemcitabine, and cisplatin were considered a reason for permanent discontinuation in 4 (50.0%) subjects.

Table 11. Permanent Discontinuations From Axitinib Due to Adverse Events

Serial Number	MedDRA Preferred Term	Maximum CTCAE Grade	SAE (Yes/No)	Outcome	Causality
1	Creatinine renal clearance decreased	2	No	Still present	Axitinib
2	Pulmonary cavitation	1	No	Still present	Axitinib/gemcitabine/cisplatin
3	Lung abscess	3	Yes	Resolved	Other-intercurrent illness
4	Cerebrovascular accident	5	Yes	Resolved	Other illness-essential hypertension
5	Hemiplegia	4	Yes	Still present	Other illness-acute ischemic cerebral stroke (left sylvian theritory) probably due to atherothrombotic disease
6	Hemiparesis	4	No	Still present	Disease under study
7	Pulmonary embolism	4	Yes	Resolved	Axitinib
8	Hypertension	3	Yes	Resolved	Axitinib

NCI CTCAE Version 3.0 applied.
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; SAE = serious adverse event.

Overall, 13 (34.2%) subjects temporarily discontinued from treatment due to AEs. The most frequently reported reasons for temporary discontinuations from treatment were vomiting and anemia (3 [7.9%] subjects each), and nausea, fatigue, dyspnea, and hypertension (2 [5.3%] subjects each).

Dose reductions due to AEs were observed in 5 (13.2%) subjects. The most frequently reported AEs resulting in dose reductions was hypertension (2 [5.3%] subjects); the remaining AEs resulting in dose reductions were reported in only 1 (2.6%) subject each.

Overall, 21 (55.3%) subjects died during the study: 4 (10.5%) subjects died on-study and 17 (44.7%) subjects died during follow-up. The majority of subjects died due to the disease under study. There were no toxic deaths and none of the Grade 5 AEs resulting in death were considered related to study treatment. A summary of deaths is presented in Table 12.

Table 12. Summary of Deaths

Variable	Axitinib + Gemcitabine + Cisplatin (N=38)
	n (%)
Subjects who died	21[a] (55.3)
Subjects who died on-study[b]	4 (10.5)
Disease under study	3 (7.9)
Study treatment toxicity	0
Unknown	0
Other	1 (2.6)
Stroke, multiple organ failure	1 (2.6)
Subjects who died during follow-up[c]	17 (44.7)
Disease under study	17 (44.7)
Study treatment toxicity	0
Unknown	0
Other	0

N = total number of subjects in treatment group; n = number of subjects with specified criteria.

a. The death of subject was reported after the subject discontinued from study. This report was not required, but is included in the total number of deaths.
b. 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.
c. Follow-up deaths were those that occurred more than 28 days after the last dose of study drug.

Serious adverse events (all causality and treatment-related) occurring on-treatment are summarized in Table 13.

Table 13. Treatment-Emergent Serious Adverse Events by Preferred Terms (All-Causality and Treatment-Related)

Preferred Term	Axitinib + Gemcitabine + Cisplatin (N=38)	
	n (%)	
	All-Causality	Treatment-Related
Any SAEs	15 (39.5)	7 (18.4)
Anaemia	2 (5.3)	2 (5.3)
Neutropenia	1 (2.6)	1 (2.6)
Haematemesis	1 (2.6)	1 (2.6)
Fatigue	1 (2.6)	1 (2.6)
Multi-organ failure	1 (2.6)	0
Disease progression	2 (5.3)	0
Lung abscess	1 (2.6)	0
Pneumonia	2 (5.3)	0
Femoral neck fracture	1 (2.6)	0
Dehydration	2 (5.3)	2 (5.3)
Cerebrovascular accident	1 (2.6)	0
Hemiplegia	1 (2.6)	0
Ischaemic stroke	1 (2.6)	0
Dyspnoea	1 (2.6)	1 (2.6)
Haemoptysis	1 (2.6)	0
Pulmonary artery thrombosis	1 (2.6)	0
Pulmonary embolism	1 (2.6)	1 (2.6)
Hypertension	1 (2.6)	1 (2.6)

MedDRA (version 14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in treatment group; n = number of subjects with SAEs; SAE = serious adverse event.

A single (6.3%) 3-grade increase (Grade 0 to Grade 3) was observed for white blood cells and three (18.8%) 3-grade increases (Grade 0 to Grade 3) were observed for absolute neutrophils. There were no 4-grade changes observed for any laboratory parameter. A 3-grade increase (Grade 0 to Grade 3) and a 3-grade decrease (Grade 3 to Grade 0) were observed for hyponatremia. Overall, no subjects had an increase in urine protein values of >1 grade.

Overall, 3 (7.9%) subjects had an elevated systolic blood pressure (BP) ≥160 mmHg at any time during the study: an elevated systolic BP ≥160 mmHg was recorded for 1 subject at Cycles 1, 2, 3, 5, and 6. No subjects had an elevated diastolic BP ≥105 mmHg at any time during the study. Three (7.9%) subjects had a baseline to postbaseline systolic BP shift from <160 mmHg to ≥160 mmHg; no subjects had a diastolic BP shift from Baseline to postbaseline.

There were no ECGs results considered abnormal and clinically significant. There were no increases from Baseline in thyroid-stimulating hormone.

CONCLUSIONS:

- The ORR (95% CI) was 39.5% (24.0% to 56.6%). The null hypothesis that the true response rate is ≤40% was not rejected (with a target α error rate of 0.10), and the alternative hypothesis that the true response rate is ≥60% was rejected (with a target β-error rate of 0.15).

- The median PFS (95% CI) was 6.2 months (4.5 to 9.3 months). The median OS (95% CI) was 14.2 months (11.8 to 23.1 months). The median DR (95% CI) was 5.78 months (4.7 to 7.2 months).

- For CD105 + vascular endothelial growth factor + CEC, subjects in the less than median group showed a trend towards higher median weeks PFS compared to subjects in the greater than or equal to median group at Baseline, C1D8 and C2D1. For percentage Platelet-derived growth factor receptor beta (PDGFRβ) + Circulating endothelial progenitor (CEP) at C1D8 only, mean values were significantly higher in responders than in nonresponders. For PDGFRβ + CEP cells/mL at C3D1 only, mean values were significantly lower in responders compared to nonresponders.

- Treatment with axitinib + gemcitabine + cisplatin was generally tolerable and manageable in subjects with squamous NSCLC. The most common Grade ≥3 all-causality AEs were neutropenia (13.2%), hypertension (13.2%), anemia (7.9%), and fatigue (7.9%).