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

PROTOCOL NO.: A4061039

PROTOCOL TITLE: Randomized Phase 2 Study of Cisplatin/Pemetrexed With or Without Axitinib (AG-013736) as First-Line Treatment for Patients With Non-Squamous Non-Small Cell Lung Cancer

Study Centers: A total of 37 centers in 11 countries took part in the study and randomized subjects; 6 centers each in the United Kingdom, Spain, and the United States, 4 centers each in Taiwan and Poland, 3 centers each in Italy and the Russian Federation, 2 centers in Romania, and 1 center each in Switzerland, Japan, and Ukraine.

Study Initiation Date, Primary Completion Date, and Final Completion Date:

Study Initiation Date: 19 January 2009 (first subject first visit)

Primary Completion Date: 01 March 2011 (final data collection date for primary outcome measure)

Final Completion Date: 28 March 2012 (last subject last visit)

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To assess efficacy of axitinib given continuously in combination with pemetrexed/cisplatin in subjects with non-squamous non-small cell lung cancer (NSCLC) compared to pemetrexed/cisplatin alone.

- To assess efficacy of axitinib given in a modified schedule in combination with pemetrexed/cisplatin in subjects with non-squamous NSCLC compared to pemetrexed/cisplatin alone.

Secondary Objectives:

- To assess the safety of axitinib in combination with pemetrexed/cisplatin in subjects with non-squamous NSCLC.

- To explore the severity of symptoms and the interference on various aspects of life as noted by subjects in each treatment arm.

METHODS

Study Design: This was a randomized, open-label Phase 2 study with a non-randomized Phase 1 lead-in. The study evaluated the safety and efficacy of a combination of axitinib with pemetrexed and cisplatin administered in 3 week (21 day) cycles.

The Phase 1 lead-in safety cohort consisted of 10 subjects treated with axitinib and cisplatin/pemetrexed (open-label). The starting dose of axitinib for Phase 1 subjects was to be 5 mg twice daily (BID) taken orally with food. Cisplatin (75 mg/m^2) was to be administered intravenously (IV) according to the institution's guidelines and over a 2 hour period. Pemetrexed was also to be administered as an IV infusion. Lead-in dosing with axitinib was to begin on Day -5, -4, or -3 (3-5 days prior to Cycle 1 Day 1) and continued through to Cycle 1 Day 18. On Day 19 of Cycle 1, the axitinib dosing was to be temporarily stopped for 3 days before the second cycle (Cycle 2 Day 1) of pemetrexed/cisplatin and for 2 additional days into Cycle 2 to allow for proper pharmacokinetic (PK) sampling. The administration of axitinib beginning on Day 3 of Cycle 2 was to be continuous, without any interruptions thereafter. Pemetrexed/cisplatin was to be administered on Day 1 of each cycle. Safety and PK were to be assessed. A parallel separate Phase 1 study (A Phase 1 dose-finding study of the anti-angiogenesis agent, AG-013736, in combinations of paclitaxel/carboplatin, weekly paclitaxel, docetaxel, capecitabine, gemcitabine/cisplatin and pemetrexed/cisplatin in patients with advanced solid tumors; [NCT00454649]) also evaluated the safety and PK of axitinib and cisplatin/pemetrexed combination. If none or 1 of the first 6 evaluable subjects combined from the 2 studies (parallel separate Phase 1 study and A4061039) developed a dose-limiting toxicity (DLT) then the randomized Phase 2 portion of A4061039 was to begin.

The Phase 2 portion planned to include approximately 150 subjects with Stage IIIB, IV, or recurrent non-squamous cell NSCLC to be randomized in a 1:1:1 ratio to the 3 treatment arms**:**

- Arm I: Subjects were to receive continuous dosing of axitinib in 3 week cycles for a maximum of 6 cycles. Subjects were to receive pemetrexed/cisplatin on Day 1 of each cycle.

- Arm II: Subjects were to start axitinib on Day 2 of Cycle 1 and were to receive the drug continuously until Day 19 of Cycle 1. After a dose interruption of 3 days, they were to receive axitinib again on Day 2 of Cycle 2. The same dosing schedule (with 3 day dosing interruptions between cycles) was to continue until Cycle 5. During Cycle 6, axitinib was to be taken on Days 2 to 21. Subjects were to receive pemetrexed/cisplatin on Day 1 of each cycle for a maximum of 6 cycles.

- Arm III (control arm): Subjects were to receive pemetrexed/cisplatin on Day 1 of each cycle for a maximum of 6 cycles.

Subjects were to be stratified according to gender (male versus (vs) female) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). Subjects who completed 4-6 cycles of chemotherapy and had stable disease or better, were to continue on study until disease progression (or longer if the Investigator assessed that there was clinical benefit to continue), unacceptable toxicity, or subject refusal; subjects in axitinib-containing arms also were to continue to receive single-agent axitinib until this time. Subjects with stable disease or better who completed fewer than 4 cycles of chemotherapy and who were not candidates for continued chemotherapy or for another systemic treatment off study could continue to receive axitinib (if initially in an axitinib-containing arm) or be followed without treatment (if in Arm III of the randomized cohort) until progressive disease, unacceptable toxicity, or subject refusal. All subjects were to be followed bimonthly for survival status following discontinuation of study treatment until at least 1 year after the randomization of the last subject. The schedule of activities for the study is shown in Table 1.

Table 1. Schedule of Activities

Activity[a]	Screening[b] ≤28 Days	Chemotherapy Cycles 1-6			Single-Agent Maintenance	Final Study Visit[c]	Follow-Up for Survival[d]
		Day 1[e]	Day 8±3 Days	Day 15[f]±3 Days	Day 1 ± 3 Days (3-Week Cycles)		Bimonthly
Informed consent	X						
Medical and oncologic history	X						
ECOG performance status	X						
Physical examination[g]	X	X			X		
Weight, temperature, BP[h], pulse	X	X			X	X	
Hematology[i]	X	X	X(C1)	X(C1)	X	X	
Blood chemistry[i]	X	X			X	X	
Urine protein[j]	X	X			X	X	
Thyroid function tests[k]	X	X[k]			Every other cycle	X	
Pregnancy test (serum/urine)[l]	X						
12-lead ECG[m]	X						
CT or MRI scans of chest, abdomen[n]	X	Every 6 weeks					
CT or MRI scans of the brain[o]	X	Every 6 weeks					
Chest x-ray for tumor cavitation[p]		X					
Chemotherapy[q]		X					
Axitinib (arms I and II of Phase 2 cohorts)[r]		X (twice daily on indicated days)					
Axitinib (Phase 1 lead-in cohort) [r]	X[a, r]	X (twice daily on Cycle 1 Days 1-18 and from Cycle 2 Day 3 onward)					
Adverse events assessment[s]		X	X	X	X	X	
Concomitant medications	X	X	X	X	X		
Study drug compliance[t]		X			X		
MDASI (Phase 2 cohorts only)[u]		X	X		X	X	
Survival information[v]							X
Pop PK – Arm I, Phase 2 subjects only[w]		X(C2&C3)					
Serial PK – Phase 1 lead-in subjects only[w]	X[a, w]	X(C1 and C2) [w]					
UGT1A1 (& other drug metabolizing enzymes and transporters) genotype test[x]		X(C1)					

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Sample banking for exploratory research (optional) –blood (Phase 2 cohorts only)[y]		X (C1)		X (C1)			
Sample banking for exploratory research (optional)-archival tumor[y]		X					

AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; CR = complete response; CT = computed tomography; EC = Ethics Committee; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IRB = Institutional Review Board; MDASI = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; PA = posterior to anterior; Pop PK = population pharmacokinetics; PR = partial response; T4 = thyroxine; TSH = thyroid-stimulating hormone; UGT1A1 = uridinediphosphate-glucuronosyl transferase 1A1; PK = pharmacokinetic.

a. Schedule of activities: Schedules could vary by ±3 days to allow flexibility. Subjects in the Phase 1 lead-in cohort underwent the following visits: On Day -5 to -3(ie, 3-5 days before Cycle 1 Day 1), Phase 1 lead-in subjects underwent physical examination, weight, vital signs, hematology, and blood chemistry ≤7 days before the first dose of axitinib (assessments did not need to be repeated if performed during screening ≤7 days before the first dose of axitinib). Axitinib was to be dispensed for the 3-5 days of lead-in dosing and the 18 days of dosing in Cycle 1 (on Days 1-18). On Day -1 (ie, 1 day before Cycle 1 Day 1), Phase 1 lead-in subjects were not to take their morning dose of axitinib, but instead bring the dose to clinic, where they were to be instructed when to take their dose. Phase 1 lead-in subjects were to undergo collection of blood samples for serial PK analysis. On Cycle 1 Day 1 (ie, the day after Day -1), Phase 1 lead-in subjects were not to take their morning dose of axitinib, but instead brought the dose to clinic, where they were to be instructed when to take their dose. Phase 1 lead-in subjects were to undergo all Cycle 1 Day 1 activities except thyroid function testing. Phase 1 lead-in subjects were to undergo collection of blood samples for serial PK analysis on Cycle 1 Day 1.

b. Screening: Assessments were to be performed within 28 days of treatment except pregnancy test, which was to be performed within 72 hours of treatment in women of childbearing potential.

c. Final study visit: Assessments only needed to be performed if the prior assessment was performed greater than 7 days previously. Every effort was to be made to obtain a final tumor assessment.

d. Follow-up for survival: Started at the time of final study visit.

e. Cycle 1 Day 1 assessments were only needed to be repeated if they were not performed in the previous 7 days. Thyroid function testing was to be performed during screening and did not need to be repeated on Cycle 1 Day 1(even if performed more than 7 days previously).

f. Visits on Day 15 were required only in Cycle 1(for hematology and for optional blood sample banking for exploratory research).

g. Physical examination: Was to include height on initial examination. After the initial complete examination, targeted examinations based on signs and symptoms were to be performed.

h. 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 in the Phase 1 lead-in cohort or in Arm I or II of the Phase 2 portion of the study were to receive 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.

i. Hematology/blood chemistry: Was to be analyzed by a center-designated local laboratory. Day 8 and Day 15 hematology laboratories were only required during Cycle 1.

j. Urine protein: Urinalysis for urine protein was to be analyzed by a center-designated local laboratory. If urine protein was ≥1+ by semi-quantitative

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method (ie, dipstick) at Screening or ≥2+ on study, then urine protein:creatinine ratio was to be performed.

k. Thyroid function tests: TSH and free T4 were to be performed during screening. TSH was to be performed at the beginning of chemotherapy Cycles 2-6 and at the beginning of every other cycle of maintenance axitinib. If performed during screening, TSH did not need to be performed on Cycle 1 Day 1. Additional free T4 could have been performed as clinically indicated.

l. Pregnancy test (serum/urine): Was to be performed within 72 hours of treatment only for women of childbearing potential. Was to be repeated during the study if requested by the EC/IRB or if required by local regulations. Was to be analyzed by a center-designated local laboratory.

m. 12-lead ECG: Could have been repeated during the course of the study as medically warranted.

n. Tumor assessments (CT or MRI): During screening, CT or MRI of the chest and upper abdomen including both adrenals were required within 28 days prior to start of treatment. Subsequently, CT or MRI of the chest and upper abdomen including both adrenals were required every 6 weeks. Subjects with PR or CR had to have responses confirmed by repeat disease assessment no sooner than 4 weeks.

o. Brain scan (CT or MRI): During screening, CT or MRI of the brain was required within 28 days prior to start of treatment. Subsequently, CT or MRI of the brain was required every 6 weeks for those subjects with treated brain metastases or those subjects who developed signs or symptoms of brain metastases. Subjects with treated brain metastases who achieved a PR or CR had to have responses confirmed by repeat disease assessment, including a brain scan, no sooner than 4 weeks.

p. Assessments for tumor cavitation (chest x-ray, PA, and lateral): Required at beginning of each cycle of chemotherapy unless a CT scan had been done within 7 days prior to Day 1 of that cycle. If any tumor cavitation was observed, axitinib was to be discontinued immediately. Restarting axitinib was to be considered during maintenance phase following discussion with the Medical Monitor. If apparent tumor progression was observed by chest x-ray, CT or MRI was to be performed as soon as possible to confirm tumor progression.

q. Chemotherapy: Phase 2 subjects were to be randomized in a 1:1:1 ratio between 2 pemetrexed/cisplatin + axitinib arms and a pemetrexed/cisplatin only arm. Vitamin B12 (1000 mcg) was to be started at least 1 week prior to treatment and repeated every 9 weeks until 3 weeks after the last dose of chemotherapy, and folic acid (350 mcg to 1000 mcg) was to be taken at least 1 week before treatment and continued daily until 3 weeks after the last dose of chemotherapy. The vitamins could have been started during the screening period following informed consent.

r. Axitinib was to be administered according to the assigned treatment. On the indicated days, axitinib was to be taken twice daily with dose titration upward or downward according to dose adjustment guidelines. Treatment Arm I: Axitinib was to be taken twice daily starting on Cycle 1 Day 1. Subjects were to be instructed not to take the morning dose of axitinib on Cycle 2 Day 1 and on Cycle 3 Day 1, but to bring the dose to clinic and take it when instructed, after the collection of the first blood sample for PK analysis. During the maintenance phase, axitinib was to be taken twice daily continuously, starting on the first day of the maintenance phase.
Treatment Arm II Axitinib was to be taken twice daily on Days 2-19 during chemotherapy cycles (except the last cycle, where axitinib was to be taken on Days 2-21). During the maintenance phase, axitinib was to be taken twice daily continuously, starting on the first day of the maintenance phase.
Treatment Arm III: Axitinib was not to be dispensed or taken. Phase 1 Lead-in Cohort: Axitinib dosing was to start before Cycle 1 Day 1 to facilitate PK sample collection. Axitinib was to be started 3-5 days before Cycle 1 (ie, on Day -5, Day -4, or Day -3) and continued through Cycle 1 Days 1 through 18. Axitinib was not to be taken on Cycle 1 Days 19-21 or on Cycle 2 Days 1-2. Axitinib was to be restarted on Cycle 2 Day 3. Subjects were instructed not to take the morning dose of axitinib at home on Day -1 (the day before Cycle 1 Day 1), on Cycle 1 Day 1, and on Cycle 2 Day 1. On these 3 days, the subject was to bring the dose to clinic and take it when instructed, after the collection of the first blood sample for PK analysis. Each time axitinib was dispensed, the Investigator or designee (eg, site coordinator or pharmacist) was to document that: a) no cavitating tumor was

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observed in most recent chest x-ray or chest CT scan (performed within the prior 4 weeks during chemotherapy or within the prior 8 weeks during maintenance); and b) no hemoptysis ≥0.5 teaspoon (2.5 mL) of blood had occurred during any 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 discontinued immediately and Sponsor notified.

s. Adverse events assessments: 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 to be followed-up until resolution, returned to baseline, chronicity, or initiation of subsequent anticancer treatment. The serious adverse events (SAEs) reporting period ended 28 days after the last study treatment dose, irrespective of start of any new anticancer treatment. Serious, treatment-related AEs were to be reported at any time.

t. Study drug compliance: Axitinib containers including any unused drug were to be returned to the clinic for drug accountability at the beginning of each cycle starting with the second cycle of chemotherapy.

u. MDASI: Only subjects in each arm of the Phase 2 cohort (not those in the Phase 1 lead-in cohort) were to complete the MDASI questionnaire. The MDASI was to be collected on Day 1 and Day 8 of each chemotherapy cycle (starting with Cycle 1 Day 1), and on Day 1 of every cycle of the single-agent maintenance. It was also to be completed at the final study visit only if the prior MDASI assessment was completed greater than 7 days previously. It was recommended to have questionnaires completed prior to any other scheduled activities, including prior to having any tests or receiving any chemotherapy, and prior to any discussion with their physician of the subject's progress.

v. Survival information: Collected bimonthly following discontinuation of study treatment until at least 1 year after randomization of the last subject.

w. Pharmacokinetics: For Phase 1 subjects, serial PK samples were to be obtained on the following visits: Cycle 1 Day -1 (ie, on the day before the Cycle 1 Day 1 visit, in order to assess PK for axitinib alone), Cycle 1 Day 1 (PK for axitinib in combination with pemetrexed/cisplatin), and Cycle 2 Day 1 (PK for pemetrexed/cisplatin alone). For Phase 2 subjects in Treatment Arm I only: Only subjects in Treatment Arm I (not those in the Phase 1 lead-in cohort or those in Arms II, and III of the Phase 2 cohort) were to undergo collection of blood samples for Pop PK analysis.
Pop PK samples for axitinib were to be 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.

x. One (2 mL) blood sample was to be collected for genotyping of drug metabolizing enzymes and transporters only, including *UGT1A1*.

y. Sample banking for exploratory research (optional): A blood sample for ribonucleic acid (RNA) transcript profiling was to be requested for subjects in the Phase 2 cohorts only on Cycle 1 Day 1 and Cycle 1 Day 15. An archival tumor sample on Cycle 1 Day 1(or at any other time) was to be requested for both Phase 1 and Phase 2 cohorts.

Number of Subjects (Planned and Analyzed): A total of 10 subjects were planned, screened, and treated in the Phase 1 portion of the study. Approximately 150 subjects with non-squamous cell NSCLC were planned to be randomized in a 1:1:1 ratio to the three treatment arms in the Phase 2 portion of the study. Overall, 176 subjects were screened, 170 subjects were assigned to treatment and 168 subjects received treatment. A total of 55 subjects received axitinib (continuous) + pemetrexed/cisplatin, 58 subjects received axitinib (modified) + pemetrexed/cisplatin, and 55 subjects received pemetrexed/cisplatin.

Diagnosis and Main Criteria for Inclusion: Inclusion Criteria – Male or female with age ≥18 (20 in Japan), histologically or cytologically confirmed diagnosis of adeno-, large cell or bronchioalveolar NSCLC, with cytologic specimens for diagnosis or for cell type classification obtained from bronchial brushings or washings or from needle aspiration of a defined lesion (sputum cytology alone was not acceptable for diagnosis or for cell type classification), Stage IIIB with malignant effusion (with cytologic confirmation of malignant pleural or pericardial effusion), Stage IV, or recurrent disease after definitive loco-regional therapy, and candidate for primary treatment with cisplatin and pemetrexed. Subjects with mixed NSCLC with predominantly squamous cell carcinoma should be classified as squamous and thus did not qualify for this study.

Exclusion Criteria - Any histological/cytological evidence of predominantly squamous NSCLC, small cell or carcinoid lung cancer, NSCLC that could not be classified as one of the eligible histologies (adenocarcinoma, large cell or bronchioalveolar), prior systemic therapy for Stage IIIB (with malignant effusion), Stage IV, or recurrent NSCLC (prior treatment with systemic therapy as adjuvant chemotherapy or in conjunction with radiotherapy for Stage II or III NSCLC was permitted if the last dose of chemotherapy was completed 12 months or more prior to randomization), and prior treatment with a vascular endothelial growth factor (VEGF) or VEGF receptor inhibitor.

Study Treatment: All subjects in the Phase 1 and Phase 2 parts of the study received axitinib (except Phase 2 treatment arm III), cisplatin, and pemetrexed.

Phase 1: The starting dose of axitinib for Phase 1 subjects was 5 mg BID taken orally (at approximately 12-hour intervals) with food. Lead-in dosing with axitinib was to begin on Day -5, -4, or -3 and was to continue through to Cycle 1 Day 18. On Day 19 of Cycle 1, the axitinib dosing was to be temporarily stopped for 3 days before the second cycle of pemetrexed/cisplatin and for 2 additional days into Cycle 2. The administration of axitinib beginning on Day 3 of Cycle 2 was to be continuous, without any interruptions thereafter. Pemetrexed/cisplatin was administered on Day 1 of each cycle. Dosing interruptions were purely for PK sampling purposes. Subjects were to be instructed not to take the morning dose of axitinib at home on Day -1 (the day before Cycle 1 Day 1), on Cycle 1 Day 1, and on Cycle 2 Day 1. On these 3 days, the subjects were to bring the dose to clinic and take it when instructed, after the collection of the first blood sample for PK analysis.

Phase 2: Axitinib: The starting dose of axitinib was 5 mg BID administered orally with food. Doses were to be taken as close to 12 hours apart as possible and at approximately the same times each day. Cisplatin: 75 mg/m^2, 2-hour IV infusion on Day 1 of each cycle.

Pemetrexed: 500 mg/m^2 was to be administered IV on Day 1 of each cycle. Vitamin B12 (1000 μg) was to be administered at least 1 week prior to treatment and repeated every 9 weeks until 3 weeks after the last dose of chemotherapy. Folic acid (350 μg to 1000 μg) was to be taken at least 1 week before treatment and continued daily until 3 weeks after the last dose of chemotherapy.

Dose Modification: Available axitinib dose levels are presented in Table 2.

Table 2. Axitinib Dose Levels

Dose Level	Dose, BID
+2	10 mg
+1	7 mg
0 (starting dose)	5 mg
-1	3 mg
-2	2 mg

BID = twice daily

If any subject required a dose reduction below 2 mg BID axitinib, axitinib was to be discontinued.

Subjects experiencing a drug-related DLT were to have axitinib, pemetrexed, or cisplatin, or all 3 agents held until the toxicity reduced to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or lower. Treatment could have been restarted at approximately 75% of the previous dose of pemetrexed or cisplatin or the dose of axitinib could have been lowered by 1 level. The choice of agent to be dose reduced depended upon the toxicity observed. The dose of axitinib was to be adjusted for toxicities such as hypertension or proteinuria. Axitinib dose reductions or interruptions by themselves were not considered to be DLT. The dose of pemetrexed was to be adjusted for toxicities such as myelosuppression or liver toxicity. In cases where it was not obvious as to which drug was the major contributor to the AE(s), 1 or more drugs were to be held and/or reduced. Decisions on individual subject dose reductions were decided jointly by the Phase 1 Investigators and the Sponsor.

Efficacy Endpoints:

Primary Endpoint - Progression free survival (PFS), defined as the time from the date of randomization to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurs first.

Secondary Endpoints:

- Overall survival (OS), defined as the time from the date of randomization to the date of death due to any cause

- 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 Response

Evaluation Criteria in Solid Tumors [RECIST] criteria). Confirmed responses were those that persisted on a follow-up imaging assessment ≥4 weeks after the initial objective documentation of response

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

- Patient Reported Outcomes (PRO) exploration of the symptom severity and interference of subjects in each treatment arm according to the MD Anderson Symptom Inventory (MDASI)

Safety Evaluations: Assessment of the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory abnormalities (severity graded by the National Cancer Institute CTCAE [version 3.0]).

Statistical Methods: Analysis Sets: The full analysis population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. The full analysis population was the primary population for evaluating all efficacy endpoints as well as subject characteristics in the randomized Phase 2 portion of the study. The safety analysis population included all subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The safety analysis population was the primary population for evaluating treatment administration/compliance and safety in both the Phase 1 and Phase 2 portions. The pharmacokinetic concentration set included all subjects who were treated and had at least 1 concentration on at least 1 day of pharmacokinetic assessment day.

Primary Efficacy Analyses: PFS was summarized in the full analysis population using Kaplan-Meier methods. The median event time for each treatment arm and corresponding 2-sided 95% confidence interval (CI) for the median was provided for PFS. The hazard ratio and its 95% CI were estimated. A stratified log-rank test (1-sided, α=0.20) was used to compare PFS between the randomized treatment arms. The purpose of this study was to assess the efficacy and safety of axitinib in combination with pemetrexed/cisplatin rather than hypothesis testing. Therefore, multiple comparison adjustment was not considered in this study. An unstratified log-rank test (1-sided, α=0.20) was also calculated. Cox regression models were used to explore the potential influences of the stratification factors (ECOG performance status: 0 vs 1 and gender: male vs female) on the primary PFS endpoint.

Secondary Efficacy Analysis: The number and percent of subjects who achieved objective response (CR or PR) was summarized along with the corresponding exact 2-sided 95% CI calculated using a method based on the F distribution. A Pearson χ^2 test (unstratified) and Cochran-Mantel-Haenszel (CMH) test stratified by baseline stratification factors (ECOG performance status: 0 vs 1; gender: male vs female) was used to compare objective response rate between the randomized treatment arms. Time-to-event endpoints, including OS and DR

were summarized using Kaplan-Meier methods. DR was calculated for the subgroup of subjects with objective disease response. The median event time and 2-sided 95% CI for the median was provided for each endpoint. The hazard ratio and its 95% CI were estimated for OS. The survival probability at 1 year was estimated for each treatment arm using the Kaplan-Meier method and the 2-sided 95% CI for the log [-log (1-year survival probability)] was calculated using a normal approximation and then back transformed to give the CI for the 1-year survival rate itself.

The determination of antitumor activity was based on objective tumor assessments made according to the RECIST system of unidimensional evaluation. A minor modification was adopted in the use of spiral CT scans, where the minimum lesion size qualifying as measurable was twice the reconstruction interval used and at least 10 mm in the longest dimension. Radiological tumor assessments were performed at screening, every 6 weeks during the study, and whenever disease progression was suspected. Bone scans could have been performed if indicated. Measurable lesions that had been previously irradiated were not considered target lesions unless an increase in size had been observed following completion of radiation therapy. Following the final study visit, all subjects were followed bimonthly for survival status. Information on subsequent anticancer therapy was also collected.

The primary analysis was based on data obtained as of the cutoff date of 01 March 2011. The last subject completed the study on 28 March 2012. Results for the primary analysis at the data cutoff point are reported below unless otherwise stated.

RESULTS

Subject Disposition and Demography: A summary of subject evaluation groups and data sets analyzed in Phase 1 for the primary analysis is provided in Table 3. A total of 10 subjects were screened and treated in Phase 1 of the study. The maximum tolerated dose (MTD) of axitinib in combination with pemetrexed (500 mg/m^2 administered every 3 weeks) and cisplatin (75 mg/m^2 administered every 3 weeks) was determined to be 5 mg BID given continuously in the Phase 1 study.

Table 3. Phase 1 - Subject Evaluation Groups and Data Set Analyzed

Category	Phase 1 Axitinib + Pem/Cis
Number of subjects screened, n	10
Assigned to study treatment, n	10
Treated, n	10
Completed, n (%)	1 (10.0)
Discontinued[a], n (%)	7 (70.0)
Subject died	6 (60.0)
Other	1 (10.0)
Ongoing at date of cutoff, n (%)	2 (20.0)
Analyzed for safety[b]	
Adverse events, n (%)	10 (100.0)
Laboratory data, n (%)	10 (100.0)
Full analysis population, n (%)[c]	10 (100.0)
Safety analysis population, n (%)[d]	10 (100.0)

Cis = cisplatin; n = number of subjects; Pem = pemetrexed.

a. Discontinuations occurring outside the lag period were attributed to the last study treatment received.

b. Subjects were analyzed for safety if they had at least 1 active adverse event or laboratory measurement in the database.

c. The full analysis population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.

d. The safety analysis population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to the actual study treatment received.

A summary of subject evaluation groups and data sets analyzed in Phase 2 is provided in Table 4. A total of 170 subjects were assigned treatment in Phase 2 of the study, and 168 subjects received treatment. Two subjects were randomized, but did not receive study treatment (2 subjects in the pemetrexed/cisplatin arm). A total of 55 subjects received axitinib (continuous) + pemetrexed/cisplatin, 58 subjects received axitinib (modified) + pemetrexed/cisplatin, and 55 subjects received pemetrexed/cisplatin.

Table 4. Phase 2 - Subject Evaluation Groups and Data Sets Analyzed

Category		Phase 2		
		Axitinib (Cont) + Pem/Cis	Axitinib (Mod) + Pem/Cis	Pem/Cis
Assigned to study treatment, n	170	55	58	57
Treated, n		55	58	55
Discontinued, n (%)		55	58	55
Subject died		37 (67.3)	48 (82.8)	31 (54.4)
Protocol deviation		2 (3.6)	0	1 (1.8)
Lost to follow-up		1 (1.8)	1 (1.7)	4 (7.0)
Other		1 (1.8)	2 (3.4)	4 (7.0)
Subject refused continued treatment for reason other than AEs		1 (1.8)	0	1 (1.8)
Study termination by Sponsor		13 (23.6)	7 (12.1)	14 (24.6)
Analyzed for safety				
Adverse events, n (%)		55 (100.0)	58 (100.0)	55 (96.5)
Laboratory data, n (%)		54 (98.2)	58 (100.0)	55 (96.5)
Full analysis population, n (%)		55 (100.0)	58 (100.0)	57 (100.0)
Safety analysis population, n (%)		55 (100.0)	58 (100.0)	55 (96.5)

A subject was considered to have started a cycle if the subject took at least 1 dose of axitinib or cisplatin or pemetrexed. Otherwise subjects that were randomized but not treated are assigned to Cycle 0.
AEs = adverse events; Cis = cisplatin; Cont = continuous dosing; Mod = modified dosing; n = number of subjects; Pem = pemetrexed.

There were 9 males and 1 female included in Phase 1 of the study (Table 5). The mean age of subjects was 60.7 years (range, 46 to 69 years). All 10 Phase 1 subjects were White. Nine Phase 1 subjects were previous smokers and 1 subject never smoked. Phase 1 subjects had baseline ECOG performance status of 0 (4 subjects) and 1 (6 subjects).

There were more males (range, 61.8% to 64.9%) than females included in Phase 2 of the study (Table 5). The mean age of subjects ranged from 58.5 to 61.4 years. Most subjects were White (range, 70.9% to 84.5%). Most subjects were previous smokers (range, 72.7% to 84.5%). Most subjects had baseline ECOG performance status of 1 (range, 49.1% to 56.9%).

Table 5. Demographic and Baseline Characteristics (Full Analysis Population)

Category	Phase 1	Phase 2		
	Axitinib + Pem/Cis (N=10)	Axitinib (Cont) + Pem/Cis (N=55)	Axitinib (Mod) + Pem/Cis (N=58)	Pem/Cis (N=57)
Age (years)				
Mean (±SD)	60.7 (8.1)	61.1 (8.5)	61.4 (9.7)	58.5 (8.3)
Median	63.5	62.0	62.0	59.0
Range	46, 69	30, 77	35, 83	42, 76
<65, n (%)	5 (50.0)	35 (63.6)	34 (58.6)	43 (75.4)
≥65, n (%)	5 (50.0)	20 (36.4)	24 (41.4)	14 (24.6)
Sex, n (%)				
Male	9 (90.0)	34 (61.8)	37 (63.8)	37 (64.9)
Female	1 (10.0)	21 (38.2)	21 (36.2)	20 (35.1)
Race, n (%)				
White	10 (100.0)	39 (70.9)	49 (84.5)	45 (78.9)
Black	0	0	1 (1.7)	0
Asian	0	15 (27.3)	8 (13.8)	12 (21.1)
Other	0	1 (1.8)	0	0
Weight (kg)				
Mean (±SD)	78.6 (24.0)	71.5 (15.6)	69.0 (16.4)	69.0 (13.8)
Median	68.2	71.7	65.7	69.0
Range	48.0, 125.0	43.3, 122.0	40.0, 128.0	39.0, 124.0
Height (cm)				
Mean (±SD)	173.6 (9.2)	169.3 (10.3)	167.2 (8.7)	166.8 (8.1)
Median	174.5	170.0	168.0	167.0
Range	154.0, 186.0	144.0, 190.0	147.0, 189.5	151.0, 190.0
Smoking status, n (%)				
Never smoked	1 (10.0)	15 (27.3)	9 (15.5)	12 (21.1)
Smoker	9 (90.0)	40 (72.7)	49 (84.5)	45 (78.9)
ECOG performance status, n (%)				
0	4 (40.0)	25 (45.5)	25 (43.1)	27 (47.4)
1	6 (60.0)	30 (54.6)	33 (56.9)	28 (49.1)
Not reported	0	0	0	2 (3.5)

Cis = cisplatin; Cont = continuous dosing; Mod = modified dosing; N = total number of subjects; n = number of subjects meeting predefined criteria; Pem = pemetrexed; SD = standard deviation; ECOG = Eastern Cooperative Oncology Group.

Efficacy Results:

Progression Free Survival: A summary of PFS for the full analysis population for Phase 1 is provided in Table 6. A total of 6 (60.0%) Phase 1 subjects progressed or died due to any cause while on study and 4 (40.0%) Phase 1 subjects did not progress or die due to any cause while on study.

Table 6. Phase 1 - Summary of Progression-Free Survival (Full Analysis Population)

Progression Status	Phase 1
	Axitinib + Pem/Cis (N=10)
Overall analysis	
Subject observed to have progressed or died due to any cause while on study[a], n (%)	6 (60.0)
Type of event	
Objective progression	5 (83.3)
Death without objective progression	1 (16.7)
Subject did not progress or die due to any cause while on study[a], n (%)	4 (40.0)
Reason for censorship	
No baseline or on-study assessments	0
Alive, on study, and progression free at the time of the analysis	2 (50.0)
PD or death occurred after ≥2 consecutive, missed assessments	0
PD occurred after given new antitumor treatment	0
Withdrew consent for follow-up	0
Lost to follow-up	0
Subject taking new antitumor therapy	0
Other	2 (50.0)

PFS algorithm included all measurements, even those completed after 28 days of last dose.
Reason for censorship=other: Subject was alive but discontinued treatment for objective progression or relapse, or discontinued the study, or died after missed ≥2 consecutive assessments.
Cis = cisplatin; N = total number of subjects; n = number of subjects meeting predefined criteria; Pem = pemetrexed; PD = progressive disease; PFS = progression-free survival.
a. On study includes treatment + follow-up periods.

A summary of PFS by treatment (stratified analysis) for the full analysis population in the Phase 2 portion of the study is provided in Table 7.

The median PFS was 8.0 months with a 95% CI of (6.7, 10.0), 8.1 months with a 95% CI of (6.8, 9.9), and 7.1 months with a 95% CI of (5.8, 9.4 months), respectively, for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms.

Controlling for ECOG performance status and gender, the hazard ratios (axitinib [continuous] + pemetrexed/cisplatin vs pemetrexed/cisplatin and axitinib [modified] + pemetrexed/cisplatin vs pemetrexed/cisplatin) were 0.831 with a 95% CI of (0.508, 1.360) and 0.947 with a 95% CI of (0.580, 1.546), respectively, favoring the axitinib groups.

A total of 35 (63.6%), 36 (62.1%), and 31 (54.4%) subjects progressed or died while on study, respectively, for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms.

Table 7. Phase 2 - Summary of Progression-Free Survival by Treatment, Stratified Analysis (Full Analysis Population)

Progression Status	Axitinib (Cont) + Pem/Cis (N=55)	Axitinib (Mod) + Pem/Cis (N=58)	Pem/Cis (N=57)
Overall stratified analysis			
Subject observed to have progressed or died due to any cause while on study[a], n (%)	35 (63.6)	36 (62.1)	31 (54.4)
Type of event			
Objective progression	34 (97.1)	33 (91.7)	29 (93.5)
Death without objective progression	1 (2.9)	3 (8.3)	2 (6.5)
Subject did not progress or die due to any cause while on study[a], n (%)	20 (36.4)	22 (37.9)	26 (45.6)
Reason for censorship			
No baseline or on-study assessments	3 (15.0)	5 (22.7)	8 (30.8)
Alive, on study, and progression free at the time of the analysis	7 (35.0)	8 (36.4)	10 (38.5)
PD or death occurred after ≥2 consecutive, missed assessments	2 (10.0)	2 (9.1)	0
PD occurred after given new antitumor treatment	0	1 (4.5)	0
Withdrew consent for follow-up	0	0	0
Lost to follow-up	0	0	0
Subject taking new antitumor therapy	1 (5.0)	0	1 (3.8)
Other	7 (35.0)	6 (27.3)	7 (26.9)
Kaplan-Meier estimates of time to event (months)			
Quartiles (95% CI)			
25%	5.3 (4.3, 6.7)	5.3 (3.5, 6.9)	4.3 (2.6, 6.3)
50%	8.0 (6.7, 10.0)	8.1 (6.8, 9.9)	7.1 (5.8, 9.4)
75%	13.9 (9.7, 19.5)	10.7 (9.4, 13.3)	10.6 (8.4)
Hazard ratio (axitinib [cont] vs pem/cis[b])	0.831	-	-
95% CI for hazard ratio	0.508-1.360	-	-
p-value[c]	0.3037	-	-
Hazard ratio (axitinib [mod] vs pem/cis[d])	-	0.947	-
95% CI for hazard ratio	-	0.580-1.546	-
p-value[c]	-	0.3565	-

Cont = continuous dosing; Mod = modified dosing; N = total number of subjects; n = number of subjects meeting predefined criteria; Pem = pemetrexed; Cis = cisplatin; CI = confidence interval; PD = progressive disease: ECOG = Eastern Cooperative Oncology Group; vs = versus.

a. On study includes treatment + follow-up period.
b. Assuming proportional hazards, a hazard ratio <1 indicates reduction in hazard rate to favor axitinib (cont): hazard ratio >1 indicates reduction to favor pem/cis.
c. For the overall stratified analysis, the p-value is from a 1-sided log-rank test of treatment stratified by ECOG performance status and gender.
d. Assuming proportional hazards, a hazard ratio <1 indicates reduction in hazard rate to favor axitinib (mod): hazard ratio >1 indicates reduction to favor pem/cis. .

Overall Survival: A summary of OS for the full analysis population in the Phase 1 portion of the study is provided in Table 8. A total of 6 (60.0%) Phase 1 subjects died and 4 (40.0%) Phase 1 subjects were alive at the time the database was closed for analyses.

Table 8. Phase 1 - Summary of Overall Survival (Full Analysis Population)

	Phase 1
	Axitinib + Pem/Cis (N=10)
Subject status, n (%)	
Died, n (%)	6 (60.0)
Cause of death	
Disease under study	5 (83.3)
Study treatment toxicity	0
Unknown	0
Other	1 (16.7)
Alive, n (%)[a]	4 (40.0)
Reason for censorship	
Alive	4 (100.0)
Subject no longer willing to participate	0
Lost to follow-up	0

Cis = cisplatin; N = total number of subjects; n = number of subjects meeting predefined criteria; Pem = pemetrexed.
a. 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.

For the Phase 2 portion of the study, the median OS at the date of cutoff was 17.1 months, 14.6 months, and 15.3 months for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms, respectively.

An OS update was performed after all subjects completed the follow-up period and the study closed; the updated median OS for the axitinib(continuous) + pemetrexed/cisplatin, axitinib(modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms was 17.0 months, 14.7 months, and 15.9 months, respectively (Table 9). The updated hazard ratios for axitinib (continuous) + pemetrexed/cisplatin vs pemetrexed/cisplatin and axitinib (modified) + pemetrexed/cisplatin vs pemetrexed/cisplatin were 1.05 and 1.45, respectively (p-values >0.5, controlling for the ECOG performance status and gender).

Table 9. Phase 2 - Updated Summary of Overall Survival by Treatment, Stratified Analysis (Full Analysis Population)

Parameter	Phase 2		
	Axitinib (Cont) + Pem/Cis (N=55)	Axitinib (Mod) + Pem/Cis (N=58)	Pem/Cis (N=57)
Died	37 (67.3)	48 (82.8)	31 (54.4)
Cause of death			
Disease under study	35 (94.6)	46 (95.8)	29 (93.5)
Unknown	1 (2.7)	2 (4.2)	1 (3.2)
Other	1 (2.7)	0	1 (3.2)
Alive[a]	18 (32.7)	10 (17.2)	26 (45.6)
Reason for censorship			
Alive	16 (88.9)	9 (90.0)	21 (80.8)
Subject no longer willing to participate	1 (5.6)	0	1 (3.8)
Lost to follow-up	1 (5.6)	1 (10.0)	4 (15.4)
Kaplan-Meier estimates of time to event (months)			
Quartiles [95% CI]			
25%	11.1 [9.7, 12.6]	8.7 [6.2, 11.5]	7.2 [5.4, 11.4]
50%	17.0 [12.6, 22.5]	14.7 [11.5, 18.1]	15.9 [11.1, NC]
75%	NC [22.5, NC]	22.9 [18.1, 28.3]	NC [24.6, NC]
1-Year survival probability (95% CI)[b]	65.6 [51.1, 76.7]	60.3 [46.6, 71.6]	58.1 [43.6, 70.1]
Hazard ratio (axitinib [cont] vs pem/cis)[c]	1.05	-	-
95% CI for hazard ratio	0.65-1.69	-	-
p-value[d]	0.58	-	-
Hazard ratio (axitinib [mod] vs pem/cis)[e]	-	1.45	-
95% CI for hazard ratio	-	0.92-2.29	-
p-value[d]	-	0.94	-

Cis = cisplatin; CI = confidence interval; Cont = continuous dosing; ECOG = Eastern Cooperative Oncology Group; Mod = modified dosing; N = number of subjects; NC = not calculated; Pem = pemetrexed; vs = versus.

a. 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.
b. Calculated from the log (-log [12-month survival probability]) using a normal approximation and back transformation.
c. Assuming proportional hazards, a hazard ratio <1 indicated reduction in hazard rate to favor axitinib (cont); hazard ratio >1 indicated reduction to favor pem/cis.
d. For the overall stratified analysis, the p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status and gender.
e. Assuming proportional hazards, a hazard ratio <1 indicated reduction in hazard rate to favor axitinib (mod); hazard ratio >1 indicated reduction to favor pem/cis.

Objective Response Rate: A summary of best overall tumor response based on the derived Investigator's assessment for the full analysis population in the Phase 1 portion of the study is provided in Table 10. All 10 Phase 1 subjects had a baseline assessment and had measurable disease at Baseline. There were 4 (40.0%) Phase 1 subjects with a confirmed PR. The overall confirmed ORR was 40% for Phase 1 of the study.

Table 10. Phase 1 - Best Overall Tumor Response – Derived Investigator's Assessment (Full Analysis Population)

	Phase 1
	Axitinib + Pem/Cis (N=10)
Subjects with baseline assessment, n (%)	10 (100.0)
Subjects with measurable disease at baseline, n (%)	10 (100.0)
Best overall response, n (%)	
Complete response	0
Partial response	4 (40.0)
Stable disease	5 (50.0)
Progressive disease	1 (10.0)
Not assessed	0
Indeterminate	0
Overall confirmed objective response rate (CR+PR), n (%)	4 (40.0)

Cis = cisplatin; CR = complete response; N = total number of subjects; n = number of subjects meeting prespecified criteria; Pem = pemetrexed; PR=partial response.

For Phase 2 of the study, 54 (98.2%), 58 (100.0%), and 55 (96.5%) subjects had measurable disease at Baseline for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms, respectively (Table 11). There were no CRs. A total of 25 (45.5%), 23 (39.7%), and 15 (26.3%) for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms, respectively, experienced PR. The overall confirmed objective response rates were 45.5%, 39.7%, and 26.3% for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms, respectively. The difference in objective response rate between axitinib (continuous) + pemetrexed/cisplatin vs pemetrexed/cisplatin was statistically significant (p=0.0143).

Table 11. Phase 2 - Best Overall Tumor Response – Stratified Analysis – Derived Investigator's Assessment (Full Analysis Population)

Overall Stratified Analysis	Phase 2		
	Axitinib (Cont) + Pem/Cis (N=55)	Axitinib (Mod) + Pem/Cis (N=58)	Pem/Cis (N=57)
Subjects with baseline assessment, n (%)	55 (100.0)	58 (100.0)	56 (98.2)
Subjects with measurable disease at baseline, n (%)	54 (98.2)	58 (100.0)	55 (96.5)
Best overall response, n (%)			
Complete response	0	0	0
Partial response	25 (45.5)	23 (39.7)	15 (26.3)
Stable disease	18 (32.7)	19 (32.8)	22 (38.6)
Progressive disease	4 (7.3)	7 (12.1)	8 (14.0)
Not assessed	0	1 (1.7)	1 (1.8)
Indeterminate	7 (12.7)	8 (13.8)	9 (15.8)
Overall confirmed objective response rate (CR+PR), n (%)	25 (45.5)	23 (39.7)	15 (26.3)
95% CI[a]	32.0-59.4	27.0-53.4	15.5-39.7
Treatment comparison (axitinib [cont] vs pem/cis)			
Risk ratio[b]	1.753	-	-
95% CI of risk ratio[b]	1.047-2.935	-	-
p-value[c]	0.0143	-	-
Treatment comparison (axitinib [mod] vs pem/cis)			
Risk ratio[b]	-	1.512	-
95% CI of risk ratio[b]	-	0.870-2.626	-
p-value[c]	-	0.0665	-

Cis = cisplatin; CI = confidence interval; CR = complete response; Cont = continuous dosing; ECOG = Eastern Cooperative Oncology Group; Mod = modified dosing; N = total number of subjects; n = number of subjects meeting predefined criteria; Pem = pemetrexed; PR=partial response; vs = versus.

a. Using exact method based on F-distribution.
b. Calculated based on a normal distribution.
c. For the overall stratified analysis, the p-value is from a 1-sided Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and gender.

Duration of Response: A summary of the DR among responders in the Phase 2 portion of the study, derived from the Investigator's assessment, can be found in Table 12. This summary is based on the DR update which was performed after all subjects completed the follow up period and the study closed. The updated median DR was 7.8, 6.7, and 7.1 months for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms, respectively.

Table 12. Phase 2 - Updated Duration of Tumor Response Among Responders, Derived Investigator's Assessments

Overall Unstratified Analysis	Axitinib (Cont) + Pem/Cis (N=25)	Axitinib (Mod) + Pem/Cis (N=23)	Pem/Cis (N=15)
Subject with a response and subsequent progression or death due to any cause while on study[a], n (%)	20 (80.0)	21 (91.3)	11 (73.3)
Type of event			
Objective progression	20 (100)	21 (100)	11 (100)
Death without objective progression	0	0	0
Subject with a response who had not progressed or died due to any cause while on study[a], n (%)	5 (20.0)	2 (8.7)	4 (26.7)
Reason for censorship			
PD occurred after ≥2 consecutive, missed assessments	2 (40.0)	1 (50.0)	1 (25.0)
Other	3 (60.0)	1 (50.0)	3 (75.0)
Response duration (months)			
Quartiles [95% CI]			
25%	5.3 [4.2, 7.0]	4.9 [4.1, 6.7]	4.2 [3.0, 7.3]
50%	7.8 [5.6, 11.4]	6.7 [5.0, 7.8]	7.1 [4.2, 24.7]
75%	15.4 [7.8, 17.5]	8.2 [6.7, 12.6]	24.7 [6.9, NC]

The duration of tumor response algorithm included all measurements even those completed after 28 days of last dose. Measurements were derived from the tumor measurement page.
Cis = cisplatin; CI = confidence interval; Cont = continuous dosing; Mod = modified dosing; n = number of subjects meeting prespecified criteria; N = total number of subjects; NC = not calculated; Pem = pemetrexed; PD = progressive disease.
a. On-study included treatment plus follow-up period.

Patient Reported Outcomes (Phase 2):

MDASI questionnaire completion rates for the axitinib treatment arms and control arm were generally lower on Day 8 compared to Day 1 during the chemotherapy treatment portion of this study (ie, Cycles 1-6). Clinically meaningful and statistical worsening of symptoms for the axitinib treatment arms and control arm primarily occurred on Day 8 of the respective cycles which may have impacted completion rates.

The mean MDASI symptom severity scores at Baseline (Cycle 1 Day 1) were 1.75, 2.09, and 1.80 for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin treatment arms, respectively. The mean MDASI symptom interference scores at Baseline (Cycle 1 Day 1) were 2.36, 2.97, and 2.64 for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin treatment arms, respectively.

The axitinib (modified) + pemetrexed/cisplatin arm had a higher (worse) mean score at Baseline (Cycle 1 Day 1) than the pemetrexed/cisplatin arm for pain. The axitinib (modified) + pemetrexed/cisplatin and pemetrexed/cisplatin arms had higher (worse) mean scores at Baseline (Cycle 1 Day 1) than the axitinib (continuous) + pemetrexed/cisplatin arm for shortness of breath. The axitinib (modified) + pemetrexed/cisplatin arm had higher (worse)

mean scores for work at Baseline (Cycle 1 Day 1) than the axitinib (continuous) + pemetrexed/cisplatin arm. These differences may have affected the results.

The symptom severity and interference for all 3 treatment arms was low overall with absolute scores less than 3 on a scale of 0-10 for the majority of time points during this study. Overall, all 3 treatment arms caused some clinically meaningful and significant worsening of symptom severity and interference with subject feeling and function as measured by the MDASI.

Changes from Baseline in MDSAI symptom severity scores are presented in Table 13. Changes from Baseline in MDSAI symptom interference scores are presented in Table 14.

Table 13. MDASI Questionnaire Change Scores by Cycle: Symptom Intensity Scale (Full Analysis Population)

Time Point	Axitinib (Cont) +Pem/Cis (N=55)			Axitinib (Mod) + Pem/Cis (N=58)			Pem/Cis (N=57)		
	N[a]	Mean	Mean 95% CI	N[a]	Mean	Mean 95% CI	N[a]	Mean	Mean 95% CI
Cycle C1/Day 8	49	1.55	(1.09, 2.02)	49	0.36	(0.00, 0.72)	50	0.95	(0.56, 1.34)
Cycle C2/Day 1	51	0.12	(-0.26, 0.49)	51	-0.05	(-0.46, 0.35)	41	0.39	(0.01, 0.77)
Cycle C2/Day 8	39	1.52	(0.98, 2.06)	38	0.39	(-0.14, 0.92)	34	0.69	(0.24, 1.13)
Cycle C3/Day 1	45	0.57	(0.16, 0.97)	47	0.29	(-0.13, 0.71)	39	0.32	(-0.15, 0.79)
Cycle C3/Day 8	38	1.33	(0.75, 1.92)	35	0.87	(0.18, 1.56)	32	1.15	(0.61, 1.68)
Cycle C4/Day 1	43	0.85	(0.28, 1.42)	43	0.48	(-0.06, 1.02)	38	0.37	(-0.05, 0.79)
Cycle C4/Day 8	33	1.37	(0.64, 2.09)	33	0.9	(0.30, 1.51)	27	1.48	(0.77, 2.19)
Cycle C5/Day 1	35	0.59	(0.05, 1.12)	34	0.48	(-0.17, 1.12)	29	0.72	(0.25, 1.18)
Cycle C5/Day 8	29	1.19	(0.38, 2.00)	26	0.82	(0.10, 1.55)	25	1.16	(0.46, 1.87)
Cycle C6/Day 1	27	0.67	(0.04, 1.30)	28	0.42	(-0.22, 1.06)	28	0.67	(0.11, 1.23)
Cycle C6/Day 8	25	1.44	(0.71, 2.17)	25	0.85	(0.23, 1.47)	21	1.28	(0.48, 2.08)
Cycle A1/Day 1	35	0.63	(0.27, 0.99)	33	0.24	(-0.32, 0.79)	21	0.68	(-0.09, 1.45)
Cycle A2/Day 1	32	0.36	(-0.11, 0.83)	30	-0.01	(-0.55, 0.54)	14	0.14	(-0.49, 0.77)
Cycle A3/Day 1	27	0.25	(-0.30, 0.79)	26	0.01	(-0.63, 0.65)	10	0.12	(-0.38, 0.63)
Cycle A4/Day 1	22	0.03	(-0.65, 0.70)	25	0.07	(-0.56, 0.70)	-	-	
Cycle A5/Day 1	17	0.19	(-0.78, 1.16)	23	-0.12	(-0.73, 0.48)	12	0.30	(-0.37, 0.96)
Cycle A6/Day 1	17	0.10	(-0.56, 0.77)	16	-0.23	(-1.21, 0.76)	10	0.14	(-0.83, 1.11)
Cycle A7/Day 1	15	-0.26	(-0.99, 0.47)	15	-0.33	(-1.37, 0.70)	-	-	-
Cycle A8/Day 1	15	-0.28	(-0.91, 0.35)	14	0.3	(-0.76, 1.36)	10	0.02	(-1.15, 1.20)
Cycle A9/Day 1	13	-0.46	(-1.29, 0.38)	11	0.34	(-0.51, 1.19)	-	-	-
Cycle A10/Day 1	-	-	-	10	0.61	(-0.38, 1.59)	-	-	-
EOT	40	0.66	(0.12, 1.20)	35	1.02	(0.40, 1.63)	31	0.99	(0.33, 1.64)

Cis = cisplatin; CI = confidence interval; Cont = continuous dosing; EOT = end of treatment; MDASI = MD Anderson Symptom Inventory;
Mod = modified dosing; N = number of subjects; NC = not calculated; Pem = pemetrexed.
Formula: change score = cycle (x) - baseline.
Interpretation: 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.
Range: Symptom Intensity Scale = -10 to 10.
a. Includes evaluable subjects who had received at least 1 dose of study medication, had baseline data, and at least 1 postbaseline measurement.

Table 14. MDASI Questionnaire Change Scores by Cycle: Symptom Interference Scale (Full Analysis Population)

Time Point	Axitinib (Cont) +Pem/Cis (N=55)			Axitinib (Mod) + Pem/Cis (N=58)			Pem/Cis (N=57)		
	N[a]	Mean	Mean 95% CI	N[a]	Mean	Mean 95% CI	N[a]	Mean	Mean 95% CI
Cycle C1/Day 8	49	1.48	(0.80, 2.16)	49	-0.03	(-0.75, 0.68)	50	0.81	(0.27, 1.36)
Cycle C2/Day 1	51	0.27	(-0.21, 0.75)	51	-0.24	(-0.76, 0.29)	41	0.3	(-0.25, 0.84)
Cycle C2/Day 8	39	2	(1.07, 2.93)	38	0.03	(-0.61, 0.66)	34	0.52	(0.05, 0.99)
Cycle C3/Day 1	45	0.64	(0.07, 1.21)	47	-0.21	(-0.81, 0.40)	39	0.03	(-0.41, 0.46)
Cycle C3/Day 8	38	1.54	(0.57, 2.50)	35	0.28	(-0.46, 1.03)	32	0.41	(-0.00, 0.82)
Cycle C4/Day 1	43	0.72	(-0.18, 1.62)	43	0.11	(-0.50, 0.73)	38	0.28	(-0.16, 0.71)
Cycle C4/Day 8	33	1.39	(0.20, 2.58)	33	1.08	(0.23, 1.92)	27	1.2	(0.48, 1.93)
Cycle C5/Day 1	35	0.14	(-0.67, 0.95)	34	-0.05	(-0.88, 0.78)	29	0.49	(-0.10, 1.09)
Cycle C5/Day 8	29	0.78	(-0.42, 1.97)	26	0.88	(-0.19, 1.94)	25	0.76	(-0.03, 1.55)
Cycle C6/Day 1	27	0.18	(-0.76, 1.12)	28	0.17	(-0.68, 1.01)	28	0.66	(-0.04, 1.36)
Cycle C6/Day 8	25	1	(-0.16, 2.16)	25	1.04	(0.17, 1.91)	21	1.2	(0.32, 2.08)
Cycle A1/Day 1	35	0.49	(-0.20, 1.18)	33	0.39	(-0.34, 1.13)	21	0.96	(0.28, 1.64)
Cycle A2/Day 1	32	0.25	(-0.52, 1.02)	30	0.16	(-0.67, 0.98)	14	0.1	(-0.82, 1.01)
Cycle A3/Day 1	27	0.02	(-0.82, 0.87)	26	-0.20	(-1.15, 0.76)	10	0.27	(-0.43, 0.96)
Cycle A4/Day 1	22	0.33	(-0.43, 1.10)	25	0.23	(-0.58, 1.05)	-	-	-
Cycle A5/Day 1	17	0.36	(-0.54, 1.27)	23	0.12	(-1.02, 1.27)	12	0.4	(-0.56, 1.37)
Cycle A6/Day 1	17	0.16	(-0.47, 0.79)	16	0.28	(-0.82, 1.39)	10	0.12	(-0.92, 1.15)
Cycle A7/Day 1	15	0.12	(-0.68, 0.92)	15	0.00	(-1.14, 1.15)	-	-	-
Cycle A8/Day 1	15	-0.07	(-0.96, 0.82)	14	0.30	(-0.70, 1.29)	10	0.42	(-0.39, 1.23)
Cycle A9/Day 1	13	-0.13	(-1.03, 0.77)	11	1.05	(0.09, 2.00)	-	-	-
Cycle A10/Day	-	-	-	10	1.03	(0.06, 2.01)	-	-	-
EOT	40	0.69	(-0.26, 1.64)	35	0.69	(-0.22, 1.59)	31	0.91	(0.06, 1.77)

Cis = cisplatin; CI = confidence interval; Cont = continuous dosing; EOT = end of treatment; MDASI = MD Anderson Symptom Inventory;
Mod = modified dosing; N = number of subjects; NC = not calculated; Pem = pemetrexed.
Formula: change score = cycle (x) - baseline.
Interpretation: A negative change score indicates the interference from the symptoms the symptom reduced (ie, improved function).
A positive change score indicates that the symptom increased or got worse.
Range of Symptom Interference Scores = -10 to 10.
a. Includes evaluable subjects who had received at least 1 dose of study medication, had baseline data, and at least 1 postbaseline measurement.

Safety Results:

A summary of the incidence of treatment-emergent AEs in the Phase 1 part of the study is provided in Table 15.

Table 15. Phase 1 - Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA Preferred Term	Axitinib + Pem/Cis n (%)
Number (%) of subjects:	
Evaluable for AEs	10
With AEs	10 (100.0)
Blood and lymphatic system disorders	8 (80.0)
Anaemia	5 (50.0)
Leukopenia	1 (10.0)
Lymphopenia	1 (10.0)
Neutropenia	5 (50.0)
Thrombocytopenia	2 (20.0)
Ear and labyrinth disorders	1 (10.0)
Deafness	1 (10.0)
Eye disorders	2 (20.0)
Lacrimation increased	2 (20.0)
Gastrointestinal disorders	9 (90.0)
Abdominal distension	1 (10.0)
Abdominal pain	1 (10.0)
Abdominal pain upper	1 (10.0)
Aerophagia	1 (10.0)
Constipation	4 (40.0)
Diarrhoea	5 (50.0)
Dry mouth	1 (10.0)
Dyspepsia	3 (30.0)
Dysphagia	1 (10.0)
Gastrooesophageal reflux disease	1 (10.0)
Gingival bleeding	1 (10.0)
Glossodynia	1 (10.0)
Nausea	6 (60.0)
Oesophageal pain	1 (10.0)
Perianal erythema	1 (10.0)
Proctalgia	1 (10.0)
Rectal fissure	1 (10.0)
Rectal haemorrhage	1 (10.0)
Rectal tenesmus	1 (10.0)
Vomiting	4 (40.0)
General disorders and administration site conditions	10 (100.0)
Asthenia	5 (50.0)
Chest pain	1 (10.0)
Cyst	1 (10.0)
Fatigue	8 (80.0)
Influenza like illness	1 (10.0)
Mucosal inflammation	1 (10.0)
Mucous membrane disorder	1 (10.0)
Xerosis	1 (10.0)
Infections and infestations	3 (30.0)
Oral candidiasis	1 (10.0)
Oral fungal infection	1 (10.0)
Subcutaneous abscess	1 (10.0)
Injury, poisoning and procedural complications	1 (10.0)
Rib fracture	1 (10.0)

Table 15. Phase 1 - Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA Preferred Term	Axitinib + Pem/Cis n (%)
Investigations	5 (50.0)
Aspartate aminotransferase	1 (10.0)
Blood creatinine	1 (10.0)
Blood creatinine increased	2 (20.0)
Haemoglobin	1 (10.0)
Hypophonesis	1 (10.0)
Neutrophil count	1 (10.0)
Transaminases	1 (10.0)
Weight decreased	1 (10.0)
White blood cell count	1 (10.0)
Metabolism and nutrition disorders	9 (90.0)
Decreased appetite	7 (70.0)
Dehydration	1 (10.0)
Hyperglycaemia	4 (40.0)
Hypomagnesaemia	1 (10.0)
Hyponatraemia	3 (30.0)
Hypophosphataemia	1 (10.0)
Musculoskeletal and connective tissue disorders	5 (50.0)
Arthralgia	2 (20.0)
Back pain	1 (10.0)
Musculoskeletal pain	1 (10.0)
Pain in extremity	1 (10.0)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	1 (10.0)
Metastases to central nervous system	1 (10.0)
Nervous system disorders	7 (70.0)
Dysgeusia	2 (20.0)
Dyskinesia	1 (10.0)
Headache	2 (20.0)
Neuropathy peripheral	1 (10.0)
Paraesthesia	2 (20.0)
Sinus headache	1 (10.0)
Psychiatric disorders	4 (40.0)
Agitation	2 (20.0)
Depression	2 (20.0)
Expressive language disorder	1 (10.0)
Renal and urinary disorders	5 (50.0)
Proteinuria	3 (30.0)
Renal impairment	1 (10.0)
Renal pain	1 (10.0)
Respiratory, thoracic and mediastinal disorders	8 (80.0)
Cough	1 (10.0)
Dysphonia	1 (10.0)
Dyspnoea	4 (40.0)
Epistaxis	3 (30.0)
Hiccups	1 (10.0)
Lung disorder	1 (10.0)
Pulmonary embolism	1 (10.0)
Skin and subcutaneous tissue disorders	3 (30.0)

Table 15. Phase 1 - Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA Preferred Term	Axitinib + Pem/Cis n (%)
Alopecia	1 (10.0)
Dry skin	1 (10.0)
Pruritus	2 (20.0)
Rash	3 (30.0)
Skin ulcer	1 (10.0)
Vascular disorders	7 (70.0)
Hypertension	7 (70.0)
Phlebitis	1 (10.0)

Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
Data cutoff date: 17 May 2012
AE = adverse events; Cis = cisplatin; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects reported AE; Pem = pemetrexed.

An overview of treatment-emergent treatment-related AEs for the safety analysis population for Phase 1 is provided in Table 16.

Table 16. Phase 1 - Summary of Treatment-Related Adverse Events by Treatment, MedDRA System Organ Class, Preferred Term (Safety Analysis Population)

System Organ Class Preferred Term	Axitinib+Pem/Cis (N=10) n (%)
Any AEs	10 (100.0)
Blood and lymphatic system disorders	7 (70.0)
Anaemia	3 (30.0)
Leukopenia	1 (10.0)
Lymphopenia	1 (10.0)
Neutropenia	5 (50.0)
Thrombocytopenia	1 (10.0)
Ear and labyrinth disorders	1 (10.0)
Deafness	1 (10.0)
Eye disorders	1 (10.0)
Lacrimation increased	1 (10.0)
Gastrointestinal disorders	9 (90.0)
Abdominal distension	1 (10.0)
Abdominal pain upper	1 (10.0)
Constipation	3 (30.0)
Diarrhoea	5 (50.0)
Dry mouth	1 (10.0)
Dyspepsia	3 (30.0)
Gastrooesophageal reflux disease	1 (10.0)
Glossodynia	1 (10.0)
Nausea	5 (50.0)
Vomiting	3 (30.0)
General disorders and administration site conditions	10 (100.0)
Asthenia	5 (50.0)
Fatigue	7 (70.0)
Mucosal inflammation	1 (10.0)
Xerosis	1 (10.0)
Investigations	3 (30.0)
Aspartate aminotransferase	1 (10.0)
Blood creatinine	1 (10.0)
Blood creatinine increased	1 (10.0)
Haemoglobin	1 (10.0)
Neutrophil count	1 (10.0)
White blood cell count	1 (10.0)
Metabolism and nutrition disorders	8 (80.0)
Dehydration	1 (10.0)
Hypomagnesaemia	1 (10.0)
Hyponatraemia	2 (20.0)
Decreased appetite	7 (70.0)
Musculoskeletal and connective tissue disorders	1 (10.0)
Pain in extremity	1 (10.0)
Nervous system disorders	4 (40.0)
Dysgeusia	2 (20.0)
Neuropathy peripheral	1 (10.0)
Paraesthesia	1 (10.0)
Psychiatric disorders	1 (10.0)
Depression	1 (10.0)

Table 16. Phase 1 - Summary of Treatment-Related Adverse Events by Treatment, MedDRA System Organ Class, Preferred Term (Safety Analysis Population)

System Organ Class Preferred Term	Axitinib+Pem/Cis (N=10) n (%)
Renal and urinary disorders	3 (30.0)
Proteinuria	3 (30.0)
Respiratory, thoracic and mediastinal disorders	2 (20.0)
Epistaxis	2 (20.0)
Skin and subcutaneous tissue disorders	3 (30.0)
Alopecia	1 (10.0)
Dry skin	1 (10.0)
Pruritus	1 (10.0)
Rash	3 (30.0)
Vascular disorders	6 (60.0)
Hypertension	6 (60.0)
Phlebitis	1 (10.0)

MedDRA (version 14.0) coding dictionary applied.
Data cutoff date: 01 Mar 2011.
AEs and SAEs are not separated out in this table.
AEs = adverse events; Cis = cisplatin; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects reported AE; Pem = pemetrexed; SAEs = serious adverse events.

There was 1 Phase 1 subject with 1 serious adverse event (SAE) (respiratory tract infection) during the study (Table 17). The SAE was not considered to be treatment related.

Table 17. Phase 1 - Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA Preferred Term	Axitinib + Pem/Cis n (%)
Number (%) of Subjects: evaluable for AEs	10
With AEs	1 (10.0)
Infections and infestations	1 (10.0)
Respiratory tract infection	1 (10.0)

Subjects are only counted once per treatment for each row.
MedDRA (version 15.0) coding dictionary applied.
AE = adverse events; Cis = cisplatin; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects reported AE; Pem = pemetrexed.

A summary of the incidence of treatment-emergent AEs occurring in ≥5% of subjects in any treatment group in the Phase 2 part of the study is provided in Table 18.

Table 18. Phase 2 - Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis n (%)	Axitinib (Mod) + Pem/Cis n (%)	Pem/Cis n (%)
Number (%) of subjects:			
Evaluable for AEs	55	58	55
With AEs	54 (98.2)	56 (96.6)	54 (98.2)
Blood and lymphatic system disorders	23 (41.8)	28 (48.3)	28 (50.9)
Anaemia	7 (12.7)	19 (32.8)	23 (41.8)
Leukopenia	6 (10.9)	8 (13.8)	3 (5.5)
Neutropenia	17 (30.9)	12 (20.7)	15 (27.3)
Thrombocytopenia	8 (14.5)	4 (6.9)	4 (7.3)
Cardiac disorders	1 (1.8)	2 (3.4)	4 (7.3)
Tachycardia	1 (1.8)	2 (3.4)	4 (7.3)
Ear and labyrinth disorders	5 (9.1)	3 (5.2)	2 (3.6)
Hypoacusis	3 (5.5)	1 (1.7)	0
Tinnitus	2 (3.6)	3 (5.2)	2 (3.6)
Endocrine disorders	3 (5.5)	3 (5.2)	0
Hypothyroidism	3 (5.5)	3 (5.2)	0
Eye disorders	3 (5.5)	5 (8.6)	6 (10.9)
Conjunctivitis	2 (3.6)	0	3 (5.5)
Dry eye	0	3 (5.2)	0
Vision blurred	2 (3.6)	2 (3.4)	3 (5.5)
Gastrointestinal disorders	46 (83.6)	41 (70.7)	44 (80.0)
Abdominal distension	1 (1.8)	3 (5.2)	2 (3.6)
Abdominal pain	9 (16.4)	4 (6.9)	5 (9.1)
Abdominal pain upper	5 (9.1)	8 (13.8)	7 (12.7)
Cheilitis	4 (7.3)	1 (1.7)	0
Constipation	20 (36.4)	15 (25.9)	23 (41.8)
Diarrhoea	22 (40.0)	20 (34.5)	9 (16.4)
Dyspepsia	2 (3.6)	4 (6.9)	2 (3.6)
Dysphagia	3 (5.5)	1 (1.7)	1 (1.8)
Flatulence	4 (7.3)	1 (1.7)	1 (1.8)
Gastrooesophageal reflux disease	2 (3.6)	5 (8.6)	4 (7.3)
Haemorrhoids	3 (5.5)	2 (3.4)	0
Mouth ulceration	4 (7.3)	3 (5.2)	3 (5.5)
Nausea	37 (67.3)	30 (51.7)	32 (58.2)
Odynophagia	1 (1.8)	3 (5.2)	0
Stomatitis	10 (18.2)	7 (12.1)	3 (5.5)
Vomiting	26 (47.3)	19 (32.8)	14 (25.5)
General disorders and administration site conditions	42 (76.4)	42 (72.4)	39 (70.9)
Asthenia	9 (16.4)	11 (19.0)	7 (12.7)
Chest pain	6 (10.9)	6 (10.3)	5 (9.1)
Face oedema	1 (1.8)	1 (1.7)	3 (5.5)
Fatigue	27 (49.1)	25 (43.1)	25 (45.5)
Mucosal inflammation	2 (3.6)	4 (6.9)	3 (5.5)
Oedema	4 (7.3)	2 (3.4)	4 (7.3)
Oedema peripheral	3 (5.5)	6 (10.3)	3 (5.5)
Pain	3 (5.5)	6 (10.3)	2 (3.6)

Table 18. Phase 2 - Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis n (%)	Axitinib (Mod) + Pem/Cis n (%)	Pem/Cis n (%)
Pyrexia	5 (9.1)	10 (17.2)	3 (5.5)
Infections and infestations	13 (23.6)	9 (15.5)	4 (7.3)
Nasopharyngitis	9 (16.4)	2 (3.4)	0
Pneumonia	2 (3.6)	3 (5.2)	3 (5.5)
Sinusitis	1 (1.8)	3 (5.2)	1 (1.8)
Urinary tract infection	3 (5.5)	3 (5.2)	1 (1.8)
Injury, poisoning and procedural complications	0	4 (6.9)	1 (1.8)
Fall	0	4 (6.9)	1 (1.8)
Investigations	19 (34.5)	18 (31.0)	12 (21.8)
Alanine aminotransferase increased	0	3 (5.2)	2 (3.6)
Aspartate aminotransferase increased	0	4 (6.9)	2 (3.6)
Blood creatinine increased	5 (9.1)	2 (3.4)	3 (5.5)
Blood thyroid stimulating hormone increased	4 (7.3)	2 (3.4)	0
Creatinine renal clearance decreased	4 (7.3)	3 (5.2)	3 (5.5)
Neutrophil count decreased	5 (9.1)	2 (3.4)	1 (1.8)
Weight decreased	4 (7.3)	6 (10.3)	4 (7.3)
Metabolism and nutrition disorders	33 (60.0)	32 (55.2)	30 (54.5)
Decreased appetite	29 (52.7)	28 (48.3)	23 (41.8)
Dehydration	0	3 (5.2)	2 (3.6)
Hyperglycaemia	2 (3.6)	2 (3.4)	5 (9.1)
Hypoalbuminaemia	0	4 (6.9)	0
Hypokalaemia	1 (1.8)	3 (5.2)	1 (1.8)
Hyponatraemia	1 (1.8)	4 (6.9)	0
Musculoskeletal and connective tissue disorders	13 (23.6)	15 (25.9)	6 (10.9)
Arthralgia	7 (12.7)	3 (5.2)	1 (1.8)
Back pain	5 (9.1)	7 (12.1)	5 (9.1)
Musculoskeletal pain	2 (3.6)	4 (6.9)	1 (1.8)
Pain in extremity	4 (7.3)	4 (6.9)	0
Nervous system disorders	23 (41.8)	24 (41.4)	15 (27.3)
Dizziness	4 (7.3)	6 (10.3)	3 (5.5)
Dysgeusia	9 (16.4)	6 (10.3)	1 (1.8)
Headache	12 (21.8)	17 (29.3)	9 (16.4)
Neuropathy peripheral	5 (9.1)	2 (3.4)	1 (1.8)
Neurotoxicity	0	3 (5.2)	0
Paraesthesia	2 (3.6)	5 (8.6)	3 (5.5)
Peripheral sensory neuropathy	2 (3.6)	5 (8.6)	0
Psychiatric disorders	16 (29.1)	11 (19.0)	11 (20.0)
Anxiety	1 (1.8)	1 (1.7)	3 (5.5)
Depression	4 (7.3)	4 (6.9)	0
Insomnia	13 (23.6)	8 (13.8)	10 (18.2)

Table 18. Phase 2 - Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis n (%)	Axitinib (Mod) + Pem/Cis n (%)	Pem/Cis n (%)
Renal and urinary disorders	2 (3.6)	12 (20.7)	2 (3.6)
Proteinuria	1 (1.8)	7 (12.1)	0
Renal failure	2 (3.6)	3 (5.2)	1 (1.8)
Urinary retention	0	3 (5.2)	1 (1.8)
Respiratory, thoracic and mediastinal disorders	38 (69.1)	26 (44.8)	23 (41.8)
Cough	12 (21.8)	7 (12.1)	9 (16.4)
Dysphonia	13 (23.6)	8 (13.8)	0
Dyspnoea	13 (23.6)	13 (22.4)	11 (20.0)
Epistaxis	8 (14.5)	2 (3.4)	0
Haemoptysis	4 (7.3)	1 (1.7)	3 (5.5)
Hiccups	8 (14.5)	5 (8.6)	3 (5.5)
Oropharyngeal pain	6 (10.9)	4 (6.9)	1 (1.8)
Rhinorrhoea	1 (1.8)	4 (6.9)	2 (3.6)
Skin and subcutaneous tissue disorders	19 (34.5)	20 (34.5)	13 (23.6)
Alopecia	9 (16.4)	6 (10.3)	6 (10.9)
Dry skin	5 (9.1)	3 (5.2)	1 (1.8)
Palmar-plantar erythrodysaesthesia syndrome	10 (18.2)	5 (8.6)	0
Pruritus	4 (7.3)	2 (3.4)	2 (3.6)
Rash	7 (12.7)	10 (17.2)	5 (9.1)
Vascular disorders	40 (72.7)	32 (55.2)	8 (14.5)
Hypertension	37 (67.3)	28 (48.3)	6 (10.9)
Hypotension	6 (10.9)	4 (6.9)	3 (5.5)

Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
Data cutoff date: 17 May 2012.
AE = adverse events; Cis = cisplatin; Cont = continuous dosing; MedDRA = Medical Dictionary for Regulatory Activities; Mod = modified dosing; n = number of subjects reported AE; Pem = pemetrexed.

A total of 55 (100.0%) subjects in the axitinib (continuous) + pemetrexed/cisplatin group; 55 (94.8%) subjects in the axitinib (modified) + pemetrexed/cisplatin group and 52 (94.5%) subjects in the pemetrexed/cisplatin group experienced a treatment-related AE during the study (Table 19).

Table 19. Phase 2 - Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term, for Events Occurring in ≥5% of Subjects in Any Treatment Group (Safety Analysis Population)

System Organ Class Preferred Term	Axitinib (Cont) + Pem/Cis (N=55)		Axitinib (Mod) + Pem/Cis (N=58)		Pem/Cis (N=55)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any AEs	55 (100)	952	55 (94.8)	691	52 (94.5)	413
Blood and lymphatic system disorders	22 (40.0)	74	24 (41.4)	91	26 (47.3)	67
Anaemia	7 (12.7)	15	15 (25.9)	34	19 (34.5)	32
Leukopenia	5 (9.1)	13	8 (13.8)	19	3 (5.5)	3
Neutropenia	16 (29.1)	32	12 (20.7)	23	15 (27.3)	24
Thrombocytopenia	8 (14.5)	13	4 (6.9)	12	3 (5.5)	7
Ear and labyrinth disorders	4 (7.3)	7	5 (8.6)	8	2 (3.6)	5
Tinnitus	2 (3.6)	2	3 (5.2)	3	2 (3.6)	5
Eye disorders	8 (14.5)	9	6 (10.3)	7	7 (12.7)	8
Vision blurred	2 (3.6)	2	2 (3.4)	2	3 (5.5)	3
Gastrointestinal disorders	47 (85.5)	330	40 (69.0)	200	39 (70.9)	140
Abdominal pain	6 (10.9)	6	1 (1.7)	1	2 (3.6)	2
Abdominal pain upper	4 (7.3)	6	2 (3.4)	2	4 (7.3)	4
Cheilitis	4 (7.3)	10	1 (1.7)	2	0 (0.0)	0
Constipation	15 (27.3)	35	11 (19.0)	17	16 (29.1)	23
Diarrhoea	19 (34.5)	58	17 (29.3)	35	5 (9.1)	6
Mouth ulceration	3 (5.5)	5	3 (5.2)	5	1 (1.8)	2
Nausea	38 (69.1)	109	29 (50.0)	69	33 (60.0)	70
Stomatitis	10 (18.2)	17	6 (10.3)	14	2 (3.6)	2
Vomiting	27 (49.1)	64	17 (29.3)	36	14 (25.5)	24
General disorders and administration site conditions	33 (60.0)	90	33 (56.9)	86	28 (50.9)	76
Asthenia	7 (12.7)	17	8 (13.8)	18	3 (5.5)	9
Fatigue	22 (40.0)	56	22 (37.9)	51	21 (38.2)	48
Mucosal inflammation	2 (3.6)	4	4 (6.9)	5	4 (7.3)	6
Oedema peripheral	3 (5.5)	3	2 (3.4)	2	2 (3.6)	3
Pyrexia	3 (5.5)	4	0 (0.0)	0	0 (0.0)	0
Infections and infestations	6 (10.9)	9	8 (13.8)	8	4 (7.3)	4
Pneumonia	3 (5.5)	5	2 (3.4)	2	0 (0.0)	0
Investigations	21 (38.2)	36	17 (29.3)	38	12 (21.8)	15
Blood creatinine increased	4 (7.3)	5	3 (5.2)	4	3 (5.5)	3
Blood thyroid stimulating hormone increased	4 (7.3)	4	2 (3.4)	3	0 (0.0)	0
Creatinine renal clearance decreased	4 (7.3)	4	3 (5.2)	5	3 (5.5)	3
Neutrophil count decreased	5 (9.1)	8	2 (3.4)	3	1 (1.8)	1
Weight decreased	3 (5.5)	3	3 (5.2)	4	2 (3.6)	2

Table 19. Phase 2 - Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term, for Events Occurring in ≥5% of Subjects in Any Treatment Group (Safety Analysis Population)

System Organ Class Preferred Term	Axitinib (Cont) + Pem/Cis (N=55)		Axitinib (Mod) + Pem/Cis (N=58)		Pem/Cis (N=55)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Metabolism and nutrition disorders	28 (50.9)	75	23 (39.7)	59	23 (41.8)	43
Dehydration	3 (5.5)	3	3 (5.2)	4	2 (3.6)	2
Hyponatraemia	1 (1.8)	1	3 (5.2)	3	0 (0.0)	0
Decreased appetite	25 (45.5)	68	22 (37.9)	37	21 (38.2)	39
Musculoskeletal and connective tissue disorders	4 (7.3)	5	5 (8.6)	5	2 (3.6)	5
Arthralgia	3 (5.5)	3	2 (3.4)	2	1 (1.8)	1
Nervous system disorders	20 (36.4)	52	23 (39.7)	38	5 (9.1)	8
Dysgeusia	9 (16.4)	14	6 (10.3)	6	1 (1.8)	2
Headache	9 (16.4)	19	6 (10.3)	8	2 (3.6)	3
Neuropathy peripheral	5 (9.1)	5	2 (3.4)	3	0 (0.0)	0
Neurotoxicity	0 (0.0)	0	3 (5.2)	3	0 (0.0)	0
Peripheral sensory neuropathy	2 (3.6)	3	4 (6.9)	5	0 (0.0)	0
Psychiatric disorders	6 (10.9)	9	0 (0.0)	0	1 (1.8)	2
Insomnia	4 (7.3)	6	0 (0.0)	0	1 (1.8)	2
Renal and urinary disorder	3 (5.5)	6	13 (22.4)	22	3 (5.5)	3
Proteinuria	1 (1.8)	2	5 (8.6)	7	0 (0.0)	0
Renal failure	1 (1.8)	1	3 (5.2)	9	1 (1.8)	1
Respiratory, thoracic and mediastinal disorders	20 (36.4)	61	13 (22.4)	27	6 (10.9)	8
Dysphonia	10 (18.2)	14	6 (10.3)	9	0 (0.0)	0
Dyspnoea	3 (5.5)	5	3 (5.2)	4	2 (3.6)	2
Epistaxis	7 (12.7)	11	1 (1.7)	2	0 (0.0)	0
Hiccups	7 (12.7)	21	5 (8.6)	8	3 (5.5)	5
Oropharyngeal pain	3 (5.5)	4	1 (1.7)	1	0 (0.0)	0
Skin and subcutaneous tissue disorders	23 (41.8)	70	22 (37.9)	33	15 (27.3)	15
Alopecia	8 (14.5)	8	6 (10.3)	6	6 (10.9)	6
Dry skin	4 (7.3)	5	2 (3.4)	2	1 (1.8)	1
Palmar-plantar erythrodysaesthesia syndrome	10 (18.2)	19	5 (8.6)	8	0 (0.0)	0
Pruritus	3 (5.5)	5	2 (3.4)	2	1 (1.8)	1
Rash	8 (14.5)	17	9 (15.5)	9	4 (7.3)	4
Vascular disorders	40 (72.7)	109	29 (50.0)	65	6 (10.9)	7
Hypertension	36 (65.5)	96	28 (48.3)	58	2 (3.6)	2
Hypotension	4 (7.3)	8	0 (0.0)	0	1 (1.8)	1

Adverse events and serious adverse events are not separated out in this table.
Subjects were only counted once per treatment for each AE subcategory row.
% = (n/N)*100.
MedDRA (version 14.0) coding dictionary applied.

Table 19. Phase 2 - Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term, for Events Occurring in ≥5% of Subjects in Any Treatment Group (Safety Analysis Population)

System Organ Class Preferred Term	Axitinib (Cont) + Pem/Cis (N=55)		Axitinib (Mod) + Pem/Cis (N=58)		Pem/Cis (N=55)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events

Data cutoff date: 01 Mar 2011.
AE = adverse events; Cis = cisplatin; Cont = continuous dosing; MedDRA = Medical Dictionary for Regulatory Activities; Mod = modified dosing; N = total number of subjects; Pem = pemetrexed.

Treatment-emergent SAEs due to all causalities which occurred during Phase 2 of the study are summarized in Table 20.

Table 20. Phase 2 - Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis n (%)	Axitinib (Mod) + Pem/Cis n (%)	Pem/Cis n (%)
Number (%) of subjects:			
Evaluable for AEs	55	58	55
With AEs	19 (34.5)	20 (34.5)	13 (23.6)
Blood and lymphatic system disorders	1 (1.8)	3 (5.2)	3 (5.5)
Anaemia	0	2 (3.4)	1 (1.8)
Febrile neutropenia	0	1 (1.7)	0
Pancytopenia	0	0	1 (1.8)
Thrombocytopenia	1 (1.8)	0	1 (1.8)
Cardiac disorders	1 (1.8)	2 (3.4)	1 (1.8)
Angina unstable	0	1 (1.7)	0
Atrial fibrillation	1 (1.8)	0	1 (1.8)
Bradycardia	0	1 (1.7)	0
Left ventricular dysfunction	1 (1.8)	0	0
Pericarditis	1 (1.8)	0	0
Gastrointestinal disorders	9 (16.4)	4 (6.9)	3 (5.5)
Abdominal pain	0	0	1 (1.8)
Colitis	0	1 (1.7)	0
Diarrhoea	1 (1.8)	0	0
Gastritis	1 (1.8)	1 (1.7)	0
Gastrointestinal toxicity	1 (1.8)	0	0
Nausea	4 (7.3)	1 (1.7)	1 (1.8)
Oesophagitis	0	1 (1.7)	0
Small intestine ulcer	1 (1.8)	0	0
Vomiting	5 (9.1)	2 (3.4)	2 (3.6)
General disorders and administration site conditions	3 (5.5)	3 (5.2)	3 (5.5)
Asthenia	1 (1.8)	0	0
Chest pain	0	1 (1.7)	2 (3.6)
Disease progression	0	1 (1.7)	1 (1.8)
Fatigue	1 (1.8)	0	0
Mucosal inflammation	1 (1.8)	0	0
Sudden death	0	1 (1.7)	0
Hepatobiliary disorders	0	1 (1.7)	1 (1.8)
Cholangitis	0	0	1 (1.8)
Cholecystitis	0	0	1 (1.8)
Cholecystitis acute	0	1 (1.7)	0
Infections and infestations	3 (5.5)	3 (5.2)	2 (3.6)
Device related infection	0	0	1 (1.8)
Lower respiratory tract infection	0	1 (1.7)	1 (1.8)
Oesophageal candidiasis	0	1 (1.7)	0
Pneumonia	2 (3.6)	0	0
Postoperative wound infection	1 (1.8)	0	0
Sepsis	0	1 (1.7)	0
Injury, poisoning and procedural complications	3 (5.5)	0	0
Ankle fracture	1 (1.8)	0	0

Table 20. Phase 2 - Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis n (%)	Axitinib (Mod) + Pem/Cis n (%)	Pem/Cis n (%)
Hip fracture	1 (1.8)	0	0
Toxicity to various agents	1 (1.8)	0	0
Investigations	0	1 (1.7)	0
Blood creatinine increased	0	1 (1.7)	0
Metabolism and nutrition disorders	3 (5.5)	3 (5.2)	0
Dehydration	3 (5.5)	3 (5.2)	0
Musculoskeletal and connective tissue disorders	1 (1.8)	0	0
Musculoskeletal chest pain	1 (1.8)	0	0
Nervous system disorders	4 (7.3)	2 (3.4)	0
Basal ganglia infarction	1 (1.8)	0	0
Depressed level of consciousness	1 (1.8)	0	0
Epilepsy	0	1 (1.7)	0
Presyncope	2 (3.6)	0	0
Somnolence	0	1 (1.7)	0
Psychiatric disorders	1 (1.8)	0	0
Depression	1 (1.8)	0	0
Renal and urinary disorders	0	1 (1.7)	1 (1.8)
Renal failure acute	0	0	1 (1.8)
Renal tubular necrosis	0	1 (1.7)	0
Respiratory, thoracic and mediastinal disorders	1 (1.8)	4 (6.9)	1 (1.8)
Dyspnoea	0	1 (1.7)	0
Pleural effusion	0	0	1 (1.8)
Pneumothorax	1 (1.8)	0	0
Pulmonary embolism	0	2 (3.4)	0
Respiratory failure	0	1 (1.7)	0
Skin and subcutaneous tissue disorders	1 (1.8)	1 (1.7)	0
Rash	1 (1.8)	1 (1.7)	0
Vascular disorders	2 (3.6)	3 (5.2)	2 (3.6)
Deep vein thrombosis	0	0	1 (1.8)
Femoral artery occlusion	0	1 (1.7)	0
Hypertension	2 (3.6)	0	0
Hypotension	0	1 (1.7)	0
Hypovolaemic shock	0	0	1 (1.8)
Post thrombotic syndrome	0	1 (1.7)	0

Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
Data cutoff date: 17 May 2012.
AE = adverse events; Cis = cisplatin; MedDRA = Medical Dictionary for Regulatory Activities; Mod = modified dosing; n = number of subjects reported AE; Pem = pemetrexed.

A summary of treatment-related SAEs for Phase 2 is provided in Table 21. There were 18 (32.7%), 13 (22.4%), and 6 (10.9%) subjects who experienced a treatment-related SAEs

during Phase 2 of the study (axitinib [continuous] + pemetrexed/cisplatin, axitinib [modified] + pemetrexed/cisplatin, and pemetrexed/cisplatin, respectively).

The most commonly reported treatment-related SAEs were vomiting (9 subjects), nausea (6 subjects), and dehydration (5 subjects).

Table 21. Phase 2 - Summary of Treatment-Related Serious Adverse Events by Treatment (Safety Analysis Population)

MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis (N=55) n (%)	Axitinib (Mod) + Pem/Cis (N=58) n (%)	Pem/Cis (N=55) n (%)
Any SAE	18 (32.7)	13 (22.4)	6 (10.9)
Vomiting	5 (9.1)	2 (3.4)	2 (3.6)
Nausea	4 (7.3)	1 (1.7)	1 (1.8)
Dehydration	3 (5.5)	2 (3.4)	0
Pneumonia	2 (3.6)	0	0
Hypertension	2 (3.6)	0	0
Rash	1 (1.8)	1 (1.7)	0
Thrombocytopenia	1 (1.8)	0	1 (1.8)
Atrial fibrillation	1 (1.8)	0	0
Left ventricular dysfunction	1 (1.8)	0	0
Diarrhea	1 (1.8)	0	0
Small intestine ulcer	1 (1.8)	0	0
Gastrointestinal toxicity	1 (1.8)	0	0
Asthenia	1 (1.8)	0	0
Fatigue	1 (1.8)	0	0
Mucosal inflammation	1 (1.8)	0	0
Toxicity to various agents	1 (1.8)	0	0
Depressed level of consciousness	1 (1.8)	0	0
Presyncope	1 (1.8)	0	0
Depression	1 (1.8)	0	0
Anemia	0	1 (1.7)	0
Febrile neutropenia	0	1 (1.7)	0
Bradycardia	0	1 (1.7)	0
Chest pain	0	1 (1.7)	0
Sepsis	0	1 (1.7)	0
Blood creatinine increased	0	1 (1.7)	0
Epilepsy	0	1 (1.7)	0
Renal tubular necrosis	0	1 (1.7)	0
Dyspnea	0	1 (1.7)	0
Pulmonary embolism	0	1 (1.7)	0
Post thrombotic syndrome	0	1 (1.7)	0
Femoral artery occlusion	0	1 (1.7)	0
Pancytopenia	0	0	1 (1.8)
Cholangitis	0	0	1 (1.8)
Cholecystitis	0	0	1 (1.8)
Lower respiratory tract infection	0	0	1 (1.8)
Renal failure acute	0	0	1 (1.8)
Hypovolemic shock	0	0	1 (1.8)

MedDRA (version 14.0) coding dictionary applied.
Cis=cisplatin; Cont = continuous dosing; MedDRA = Medical Dictionary for Regulatory Activities; Mod = modified dosing; n = number of subjects reported AE; N = total number of subjects; Pem = pemetrexed; SAE = serious adverse event.

A summary of AEs that led to axitinib and chemotherapy treatment discontinuation for Phase 1 subjects is provided in Table 22. One subject experienced an AE (blood creatinine increased) that led to axitinib treatment discontinuation.

Table 22. Phase 1 - Summary of Adverse Events That Led to Axitinib and Chemotherapy Treatment Discontinuation (Safety Analysis Population)

MedDRA Preferred Term	Phase 1
	Axitinib + Pem/Cis (N=10) n (%)
Blood creatinine increased	1 (10.0)

MedDRA (version 14.0) coding dictionary applied.
Subjects were only counted once per treatment for each adverse event subcategory row.
Cis = cisplatin; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects reported AE; N = total number of subjects; Pem = pemetrexed.

A summary of AEs that led to axitinib treatment discontinuation for Phase 2 subjects is provided in Table 23.

Table 23. Phase 2 - Summary of Adverse Events That Led to Axitinib Treatment Discontinuation (Safety Analysis Population)

MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis (N=55) n (%)	Axitinib (Mod) + Pem/Cis (N=58) n (%)	Pem/Cis (N=55) n (%)
Any AE	11 (20.0)	20 (34.5)	0
Hypertension	2 (3.6)	4 (6.9)	0
Atrial fibrillation	1 (1.8)	0	0
Left ventricular dysfunction	1 (1.8)	0	0
Nausea	1 (1.8)	0	0
Small intestine ulcer	1 (1.8)	0	0
Vomiting	1 (1.8)	0	0
Lacunar infarction	1 (1.8)	0	0
Depression	1 (1.8)	0	0
Dermatitis	1 (1.8)	0	0
Rash	1 (1.8)	0	0
Peripheral arterial occlusive disease	1 (1.8)	0	0
Anemia	0	1 (1.7)	0
Bradycardia	0	1 (1.7)	0
Ocular toxicity	0	1 (1.7)	0
Therapeutic response unexpected	0	1 (1.7)	0
Disease progression	0	1 (1.7)	0
Blood creatinine increased	0	1 (1.7)	0
Creatinine renal clearance decreased	0	1 (1.7)	0
Decreased appetite	0	1 (1.7)	0
Lung neoplasm	0	1 (1.7)	0
Somnolence	0	1 (1.7)	0
Ischemic stroke	0	1 (1.7)	0
Renal tubular necrosis	0	1 (1.7)	0
Pulmonary embolism	0	1 (1.7)	0
Respiratory failure	0	1 (1.7)	0
Pulmonary cavitation	0	1 (1.7)	0
Femoral artery occlusion	0	1 (1.7)	0

Subjects were only counted once per treatment for each adverse event subcategory row.
MedDRA (version 14.0) coding dictionary applied.
AE = adverse event; Cis = cisplatin; Cont = continuous dosing; MedDRA = Medical Dictionary for Regulatory Activities; Mod = modified dosing; n = number of subjects reported AE; N = total number of subjects; Pem = pemetrexed.

A summary of AEs that led to axitinib and chemotherapy treatment discontinuation for Phase 2 is provided in Table 24.

Table 24. Phase 2 - Summary of Adverse Events That Led to Axitinib and Chemotherapy Treatment Discontinuation (Safety Analysis Population)

MedDRA Preferred Term	Axitinib (Cont) + Pem/Cis (N=55) n (%)	Axitinib (Mod) + Pem/Cis (N=58) n (%)	Pem/Cis (N=55) n (%)
Any AE	6 (10.9)	10 (17.2)	0
Hypertension	1 (1.8)	1 (1.7)	0
Nausea	1 (1.8)	0	0
Vomiting	1 (1.8)	0	0
Depression	1 (1.8)	0	0
Rash	1 (1.8)	0	0
Peripheral arterial occlusive disease	1 (1.8)	0	0
Blood creatinine increased	0	1 (1.7)	0
Anemia	0	1 (1.7)	0
Therapeutic response unexpected	0	1 (1.7)	0
Creatinine renal clearance decreased	0	1 (1.7)	0
Decreased appetite	0	1 (1.7)	0
Somnolence	0	1 (1.7)	0
Renal tubular necrosis	0	1 (1.7)	0
Respiratory failure	0	1 (1.7)	0
Femoral artery occlusion	0	1 (1.7)	0

Subjects were only counted once per treatment for each adverse event subcategory row.
MedDRA (version 14.0) coding dictionary applied.
AE = adverse event; Cis = cisplatin; Cont = continuous dosing; MedDRA = Medical Dictionary for Regulatory Activities; Mod = modified dosing; n = number of subjects reported AE; N = total number of subjects; Pem = pemetrexed.

A summary of all deaths for Phase 1 subjects is provided in Table 25.

Table 25. Phase 1 - Summary of All Deaths (Full Analysis Population)

Variable	Phase 1
	Axitinib + Pem/Cis (N=10) n (%)
Subjects who died	6 (60.0)
Subjects who died on study[a]	0
Subjects who died during follow-up[b]	6 (60.0)
Disease under study	5 (50.0)
Study treatment toxicity	0
Unknown	0
Other	1 (10.0)
Stroke	1 (10.0)

Cis = cisplatin; n = number of subjects meeting prespecified criteria; N = total number of subjects; Pem = pemetrexed.

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.

A total of 116 subjects died during Phase 2, including 37 (67.3%), 48 (82.8%), and 31 (54.4%) axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin subjects, respectively (full analysis population updated when all subjects completed the follow up period and the study closed) (Table 26). The most common reason for death during Phase 2 was the disease under study.

Table 26. Phase 2 - Updated Summary of All Deaths (Full Analysis Population)

Parameter	Axitinib (Cont) + Pem/Cis (N=55) n (%)	Axitinib (Mod) + Pem/Cis (N=58) n (%)	Pem/Cis (N=57) n (%)
Subjects who died	37 (67.3)	48 (82.8)	31 (54.4)
Subjects who died on-study[a]	0	2 (3.4)	1 (1.8)
Disease under study	0	1 (1.7)	1 (1.8)
Unknown	0	1 (1.7)	0
Subjects who died during follow-up[b]	37 (67.3)	46 (79.3)	30 (52.6)
Disease under study	35 (63.6)	45 (77.6)	28 (49.1)
Unknown	1 (1.8)	1 (1.7)	1 (1.8)
Other	1 (1.8)	0	1 (1.8)
Respiratory failure	0	0	1 (1.8)
Respiratory failure caused by pneumonia	1 (1.8)	0	0

Cis = cisplatin; Cont = continuous dosing; Mod = modified dosing; n = number of subjects meeting prespecified criteria; N = number of subjects; Pem = pemetrexed.

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.

CONCLUSIONS:

- Axitinib administered on a continuous schedule + pemetrexed/cisplatin was not more effective than pemetrexed/cisplatin, with a median PFS of 8.0 months vs 7.1 months and median OS of 17.1 vs 15.3 months, respectively, in subjects with non-squamous NSCLC.

- Axitinib administered on a modified schedule + pemetrexed/cisplatin was not more effective than pemetrexed/cisplatin, with a median PFS of 8.1 months vs 7.1 months and median OS of 14.6 vs 15.3 months, respectively, in subjects with non-squamous NSCLC.

- The MTD of axitinib in combination with pemetrexed (500 mg/m^2 administered every 3 weeks) and cisplatin (75 mg/m^2 administered every 3 weeks) was determined to be 5 mg BID given continuously. Based on PK analysis, axitinib and pemetrexed can be administered in combination without the expectation of changes in plasma concentrations of either drug.

- Axitinib administered both continuously and on a modified schedule + pemetrexed/cisplatin was generally tolerable and manageable in subjects with non-squamous NSCLC.

- The symptom severity and interference for all 3 treatment arms was low overall with absolute scores less than 3 on a scale of 0-10 for the majority of time points during this study. Overall, all 3 treatment arms caused some clinically meaningful and significant worsening of symptom severity and interference with subject feeling and function as measured by the MDASI.

- Addition of axitinib using a continuous schedule + pemetrexed/cisplatin did not extend OS compared to pemetrexed/cisplatin alone, with an updated (when all subjects completed the follow-up period) median OS of 17.0 vs 15.9 months, respectively, and a hazard ratio of 1.05 in subjects with non-squamous NSCLC.

- Addition of axitinib using a modified schedule + pemetrexed/cisplatin did not extend OS compared to pemetrexed/cisplatin alone, with an updated (when all subjects completed the follow-up period) median OS of 14.7 vs 15.9 months, respectively, and a hazard ratio of 1.45 in subjects with non-squamous NSCLC.

- The updated (when all subjects completed the follow-up period) median DR was 7.8, 6.7, and 7.1 months for the axitinib (continuous) + pemetrexed/cisplatin, axitinib (modified) + pemetrexed/cisplatin, and pemetrexed/cisplatin arms, respectively.