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

PROTOCOL NO.: A4061010

PROTOCOL TITLE: Randomized, Placebo-Controlled, Double-Blind, Phase 2 Study of AG-013736 in Combination with Docetaxel versus Docetaxel Alone in Patients with Metastatic Breast Cancer Preceded by a Phase 1 Evaluation of the Combination

Study Centers: Forty three (43) centers took part in the study and enrolled subjects; 3 sites in Canada, 2 Czech Republic, 5 in Germany, 2 in India, 6 in Italy, 8 in Spain, 3 in United Kingdom (UK) and 14 in United States (US).

Study Initiation Date and Final Completion Date: Phase 1: 29 February 2004 to 25 March 2004; Phase 2: 21 May 2004 to 06 November 2008.

Phase of Development: Phase 2, preceded by Phase 1 evaluation

Study Objectives: The primary objective of this study was to determine whether the time to progression (TTP) of the combination of axitinib (AG-013736) and docetaxel was superior to that of docetaxel alone in subjects who had not received prior chemotherapy for metastatic breast cancer.

Secondary objectives were to:

- Determine the dose of axitinib that could be given with docetaxel administered on an every 3-week schedule.
- Determine the adverse drug event profile and dose-limiting toxicities for the combination.
- Evaluate population pharmacokinetics (PK) of axitinib in the Phase 2 and single-agent portions of the study and assess docetaxel and axitinib PK parameters in the Phase 1 portion of the study.
- Determine the response rate and duration of response for the combination.
- Assess the response rate and duration of response of single-agent axitinib in subjects who progressed on the docetaxel plus placebo arm.

METHODS

Study Design: This was a randomized, placebo-controlled, double-blind, Phase 2, multicenter study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor axitinib given in combination with docetaxel versus docetaxel plus placebo for subjects who had not received prior chemotherapy for metastatic breast cancer. A lead-in Phase 1 portion of the study was intended to identify the doses of docetaxel and axitinib in the combination arm and determined the PK of each of the drugs. Subjects were to be randomized 2:1 between the combination of docetaxel plus axitinib and docetaxel plus placebo. Assessments for tumor response was to occurr every 9 weeks (every 3 cycles). Subjects receiving docetaxel plus axitinib who experienced disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) were to be offered alternate therapy at the Investigator's discretion. There was also a provision to offer axitinib as a single agent at the Investigator's discretion to those subjects who experienced disease progression after receiving docetaxel plus placebo.

The Schedule of Activities for the different phases of the study are presented in Table 1, Table 2 and Table 3.

Table 1. Schedule of Events for Phase 1

Observation	Screening Days 14 to Day 0	Day 1 (Predose) of Each Cycle*	Day 8 and 15 of Each Cycle	Follow-Up ≥30 and ≤45 Days After Last Dose
Informed consent[a]	X			
Medical history[b]	X			
Physical exam[c]	X	X		X
Weight, temperature, BP[d], pulse	X	X		X
ECOG performance status	X	X		X
Chest x-ray[e]	X			
Electrocardiogram[f]	X	See footnote (f)		X
Stool guaiac[g]	X			
Hematology[h]	X	X	X	X
Chemistry[i]	X	X	X	X
Urinalysis[j]	X	X		X
Safety assessment (adverse events)[k]		Monitored throughout the study		
Concomitant treatment[l]	X	Monitored throughout the study		
Tumor measurements[m]	Day –28 to 0	Every 3 cycles		
Pharmacokinetic plasma samples[n]		See footnote (n)		
Pregnancy test[o]	Day –3 to 0			
Docetaxel treatment[p]		X		
Axitinib treatment[q]		Continuous daily (BID) dosing starting Cycle 1 Day 3		

∗ Cycle length was 3 weeks.
BID = twice daily; BP = blood pressure; ECOG = Eastern Cooperative Oncology Group; HR = heart rate.

Table 1. Schedule of Events for Phase 1

Observation	Screening Days 14 to Day 0	Day 1 (Predose) of Each Cycle*	Day 8 and 15 of Each Cycle	Follow-Up ≥30 and ≤45 Days After Last Dose

a. Informed consent was to be obtained before any study-specific procedures.
b. Including history of prior treatments for breast cancer and use of nicotine products.
c. Including height on initial examination. After the initial complete examination, targeted examinations based on signs and symptoms were to be performed.
d. Blood pressure was to be taken with the subject in the seated position after the subject had been sitting quietly for 5 minutes. The subject was to take blood pressure measurements at least once daily and record results in the subject diary.
e. Additional chest x-rays were to be taken if clinically necessary.
f. Electrocardiograms (ECGs) were to be obtained at Screening Day 1, Day 22, and Follow-up Visits. All the ECGs were to be performed according to recent FDA recommendations involving triplicate measurements, 5 minutes apart, at the same time of day for each occasion. Machine-read QT, HR, and QTc were acceptable. ECGs were to be performed on Day 1 at predose and 0.5 to 1.5 hours after the docetaxel infusion and on Day 22 at predose and 1 to 2 hours after axitinib dosing. In addition, the time of day selected to perform ECGs at screening, Day 1 (post-docetaxel dose), and follow-up coincided with a time frame of 1 to 2 hours after treatment with axitinib on Day 22. ECGs were to be performed before any scheduled pharmacokinetic blood draws.
g. If positive, follow-up measures were to be taken to rule out active gastrointestinal bleeding.
h. Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets. Prothrombin time and partial thromboplastin time were to be obtained at screening and followed as clinically indicated.
i. Sodium, potassium, chloride, bicarbonate or carbon dioxide, lactate dehydrogenase, aspartate transaminase, alanine transaminase, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen, creatinine, and glucose.
j. Protein, glucose, and blood. If protein was ≥1+ by semi-quantitative method (eg, dipstick) then it was to be quantified by 24-hour urine collection. Dose adjustment was to be done as required. Baseline urinalysis was to include microscopic examination of the sediment.
k. Adverse events were to be collected throughout the study period. Adverse events that were serious, suspected to be related to study drug, or considered significant by the Investigator or Pfizer medical monitor were to be followed up after therapy discontinuation until the event or its sequelae resolved or stabilized at a level acceptable to the Investigator and the Pfizer medical monitor or his/her designated representative.
l. Was to be collected from screening to the follow-up visit.
m. Tumor assessments were to be done every 9 weeks. Response (complete [CR] or partial response [PR]) required confirmation at least 4 weeks after the response was noted.
n. Plasma pharmacokinetic samples were to be collected over a 49-hour period after the first and second doses of docetaxel. Also plasma samples were to be collected over a 13.5-hour period following the morning dose on Days 21 and 22.
o. Subjects of childbearing potential were to have had a negative serum or urine pregnancy test within 3 days before treatment and practiced appropriate birth control.
p. Infusion length was 1 hour.
q. After 8 cycles, subjects benefiting from treatment were to be permitted to continue docetaxel plus axitinib treatment on a follow-on protocol.

Table 2. Schedule of Events for Phase 2

Observation	Screening Days 14 to Day 0	Day 1 (Predose) of Each Cycle*	Day 8 and 15 of Each Cycle	Follow-Up 28 Days After Last Dose
Informed consent[a]	X			
Medical history[b]	X			
Physical exam[c]	X	X		X
Weight, temperature, BP[d], pulse	X	X		X
ECOG performance status	X	X		X
Chest x-ray[e]	X			
Electrocardiogram[f]	X			X
Stool guaiac[g]	X			
Hematology[h]	X	X	X	X
Chemistry[i]	X	X	X	X
Urinalysis[J]	X	X		X
Safety assessment (adverse events)[k]	X	Monitored throughout the study		
Concomitant treatment[l]	X	Monitored throughout the study		
Tumor measurements[m]	Day –28 to 0	Every 3 cycles		
Pharmacokinetic plasma samples[n]		See footnote ([n])		
Pregnancy test[o]	Day –3 to 0			
Docetaxel treatment[p]		X		
Axitinib treatment		Continuous daily (BID) dosing		

∗ Cycle length was 3 weeks. Tests and procedures were done on schedule, but occasional changes by +/- 4 days were allowed for holidays, vacations, and other administrative reasons.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BP = blood pressure; BUN = blood urea nitrogen; CO_2 = carbon di oxide; CR = complete response; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; LDH = lactate dehydrogenase; PR = partial response.

Table 2. Schedule of Events for Phase 2

Observation	Screening Days 14 to Day 0	Day 1 (Predose) of Each Cycle*	Day 8 and 15 of Each Cycle	Follow-Up 28 Days After Last Dose

a. Informed consent was obtained earlier and prior to any study-specific procedures.
b. Including history of prior treatments for breast cancer and use of nicotine products.
c. Including height on initial examination. After the initial complete examination, targeted examinations based on signs and symptoms were to be performed.
d. Blood pressure was to be taken with the subject in the seated position after the subject had been sitting quietly for 5 minutes. The subject was to take blood pressure measurements at least once daily and record results in the subject diary.
e. Additional chest x-rays were to be taken if clinically necessary. If a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the chest was performed as part of tumor assessment at baseline, a chest X-ray was not required.
f. Additional ECGs were to be taken if clinically indicated.
g. If positive, follow-up measures were to be taken to rule out active gastrointestinal bleeding.
h. Hgb, Hct, RBC, WBC with differential, and platelets. Prothrombin time and partial thromboplastin time should be obtained at screening and followed as clinically indicated. Starting with Cycle 4, the frequency of hematology assessments may have decreased at the discretion of the Investigator. At a minimum, assessments were required before the first infusion on Day 1 of each cycle.
i. Sodium, potassium, chloride, bicarbonate or CO_2, LDH, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, BUN, creatinine, and glucose. Starting with Cycle 4, the frequency of biochemistry assessments may have decreased at the discretion of the Investigator. At a minimum, assessments are required before the first infusion on Day 1 of each cycle.
j. Protein, glucose, and blood. If protein ≥1+ by semiquantitative method (eg, dipstick) then quantitate by 24-hour urine collection. Dose adjustment required for some subjects. Baseline urinalysis included microscopic examination of the sediment.
k. Adverse events were to be collected throughout the study period starting at the time written Consent was to be given through at least 28 days after the last dose of study medications. Adverse events that were serious, suspected to be related to study drug or considered significant by the Investigator or Pfizer medical monitor were to be followed after therapy discontinuation until the event or its sequelae resolved or stabilized at a level acceptable to the Investigator and the Pfizer medical monitor or his/her designated representative.
l. To be collected from screening to the follow-up visit.
m. Tumor assessments was done every 9 weeks. Response (CR/PR) requires confirmation at least 4 weeks after the response was noted. For subjects who had not progressed after discontinuing study drug, additional tumor assessments was performed approximately every 9 weeks until subject meets metcriteria for progression or alternate therapy started.
n. Plasma samples for axitinib obtained on Day 1 (1 to 2 hours after the first dose), Day 22 (just before and 1 to 2 hours after the morning dose axitinib /placebo), Day 43 (just before and 1 to 2 hours after the morning dose) and then every 9 weeks thereafter (just before and 1 to 2 hours after the morning dose). If radiographic scans (performed to assess disease) and pharmacokinetic collections were scheduled on the same day, the pharmacokinetic sample collection was completed before administration of oral contrast media for scanning. If scheduling was problematic, the pharmacokinetic collection was delayed by 1 cycle. If only intravenous contrast media was used, timing of scans and pharmacokinetic collections is not an issue.
o. Subjects of childbearing potential had a negative serum or urine pregnancy test within 3 days before treatment and practiced appropriate birth control.
p. Infusion length was 1 hour.

Table 3. Schedule of Tests and Procedures for Patients on Single-Agent Axitinib After Progressing on Docetaxel Plus Placebo

Observation	Day 1 (Predose)*	Every 2 Weeks for the First 8 Weeks	Every 4 Weeks After the First 8 Weeks	Follow-Up 28 Days After Last Dose
Physical exam[a]	X	X	X	X
Weight, temperature, BP[b], pulse	X	X	X	X
ECOG performance status	X	X	X	X
Hematology[c]	X	X	X	X
Chemistry[d]	X	X	X	X
Urinalysis[e]	X	X	X	X
Safety assessment (adverse events[f])	Monitored throughout the study			
Concomitant treatment				
Tumor measurements[g]		Every 8 Weeks		
Pharmacokinetic plasma samples[h]	See footnote ([h])			
Axitinib treatment[i]	Continuous daily (BID) dosing			

∗ Visit Day was reset to Day 1 on the first day of dosing with single-agent axitinib. Cycle length was 4 weeks. Tests and procedures were done on schedule, but occasional changes by +/- 4 days were allowable for holidays, vacations, and other administrative reasons.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BP = blood pressure; BUN = blood urea nitrogen; CO_2 = carbon di oxide; CR = complete response; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; LDH = lactate dehydrogenase; PR = partial response.

Table 3. Schedule of Tests and Procedures for Patients on Single-Agent Axitinib After Progressing on Docetaxel Plus Placebo

Observation	Day 1 (Predose)*	Every 2 Weeks for the First 8 Weeks	Every 4 Weeks After the First 8 Weeks	Follow-Up 28 Days After Last Dose

a. Targeted examinations based on signs and symptoms were performed.

b. Blood pressure was taken with the subject in the seated position after the subject sat quietly for 5 minutes. The subject had taken blood pressure measurements at least once daily and recorded results in the Subject Diary.

c. Hgb, Hct, RBC, WBC with differential, and platelets. Prothrombin time and partial thromboplastin time was obtained at screening and followed as clinically indicated.

d. Sodium, potassium, chloride, bicarbonate or CO_2, LDH, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, BUN, creatinine, and glucose.

e. Protein, glucose, and blood. If protein ≥1+ by semiquantitative method (eg, dipstick) then quantitate by 24-hour urine collection. Dose adjustment was performed if required.

f. Adverse events were collected throughout the study period starting at the time written consent was given through at least 28 days after the last dose of study medications. Adverse events that were serious, suspected to be related to study drug or considered significant by the Investigator or Pfizer medical monitor must have been followed after therapy discontinuation until the event or its sequelae resolved or stabilized at a level acceptable to the Investigator and the Pfizer medical monitor or his/her designated representative.

g. Tumor assessments were done every 8 weeks. Response (CR/PR) requires confirmation at least 4 weeks after the response is noted. Baseline should be reset based on last assessment done during randomized Phase 2 portion of the study. For subjects with CR or PR who had not progressed after discontinuing study drug, additional tumor assessments were performed approximately every 8 weeks until patient meets criteria for progression or alternate therapy started

h. Plasma samples obtained on Day 1 (1-2 hours after the first dose), Day 29 (just before and 1-2 hours after the morning dose), Day 57 (just before and 1-2 hours after the morning dose) and then every 8 weeks thereafter (just before and 1 to 2 hours after the morning dose). If radiographic scans (performed to assess disease) and pharmacokinetic collections were scheduled on the same day, the pharmacokinetic sample collection should have been completed before administration of oral contrast media for scanning. If scheduling was problematic, the pharmacokinetic collection were delayed by 1 cycle. If only intravenous contrast media is used, timing of scans and pharmacokinetic collections is not an issue.

i. After 8 cycles, subjects benefiting from treatment may have continued axitinib treatment on a follow-on protocol.

Number of Subjects (Planned and Analyzed): As planned, 168 subjects were enrolled and included in the randomized part of the study. A total of 168 subjects (27 in Canada, 2 in Czech Republic, 14 in Germany, 5 in India, 23 in Italy, 32 in Spain, 12 in UK and 53 in the US) were enrolled in Phase 2 portion of the study.

Diagnosis and Main Criteria for Inclusion: Females aged ≥18 years with a life expectancy ≥12 weeks, who had histologically/cytologically proven metastatic breast carcinoma (Stage IV, or recurrent with local or regional spread or distant metastatic disease) without HER-2/Neu over-expression were eligible for enrollment. Subjects had not been treated with chemotherapy, had completed chemotherapy at least 12 months before documentation of metastatic disease, had at least 1 target lesion as defined by RECIST, had adequate bone marrow, renal, and liver function, had no evidence of pre-existing uncontrolled hypertension, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 could be included in the study.

Study Treatment: Axitinib 5 mg was given twice daily (BID) in the initial cohort at approximately 12-hour intervals to fasting subjects. Axitinib was administered approximately 48 hours after the first docetaxel infusion to allow baseline docetaxel PK to be determined. Individual dose adjustments were made on the basis of the adverse events (AEs) observed.

Efficacy and Pharmacokinetic Endpoints:

Primary Efficacy Endpoint:

- Time to disease progression (Phase 2 portion of the study).

Secondary Efficacy and Pharmacokinetic Endpoints:

- Response rate according to RECIST criteria and duration of response of the combination.
- Response rate and duration of response of single-agent axitinib in subjects who progressed on docetaxel plus placebo.
- Pharmacokinetic parameters of axitinib and docetaxel when given in combination during the Phase 1 portion and population PK of axitinib when given in combination in the Phase 2 portion or as a single agent in the single-agent portion of the study.

Safety Evaluations:

Safety evaluations included analysis of study medication safety profiles, based on physical examinations, laboratory tests, and assessment of AEs.

Adverse Events: AEs included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the Investigator recorded as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (eg, Electrocardiogram (ECG), laboratory).

All AEs were assessed for whether they met the criteria for classification as serious adverse events (SAEs). If the SAE or its sequelae persisted, follow-up was required until resolution or stabilization occurred at a level acceptable to the Investigator and Sponsor.

Serious Adverse Events: All SAEs regardless of treatment group or suspected relationship to study drug were reported.

Physical Examination: A complete physical examination included the assessment of all body systems, the measurement of body weight, height, ECG, pulse, and assessment of ECOG performance status. Body surface area (BSA) was determined for docetaxel dosing. If a subject had ≥10% change in weight, the BSA was recalculated. All examinations were performed by qualified health care professionals. Findings of all physical examinations were recorded in the source documents, and any change from baseline considered by the Investigator to be clinically significant was recorded as an AE in the case report form.

Blood Pressure Assessments: BP readings were required at each clinic visit and collected in the seated position after the subject set quietly for 5 minutes. All subjects were issued a blood pressure monitor and blood pressure measurement diary. Subjects were asked to record their blood pressure measurements at least once each day. Subjects were instructed to call their physician if they record a systolic blood pressure reading greater than 150 mm Hg or a diastolic blood pressure reading greater than 90 mm Hg. Normal BP parameters were evaluated 15 mmHg higher for subjects whose hypertension was under control with occasional BP spikes.

Hematology: The following hematology tests were performed at the intervals described in Table 1, Table 2 and Table 3: Plasma hematocrit, levels of hemoglobin, red blood cell count, white blood cell count with differential, and platelet count. Prothrombin time and partial thromboplastin time were required at Screening and if clinically indicated.

Clinical Chemistry: Levels of the following chemical entities were assessed at the intervals described in the Table 1, Table 2 and Table 3: blood urea nitrogen (BUN), creatinine, sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-) or carbon dioxide (CO_2), alkaline phosphatase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT, or SGPT), aspartate aminotransferase (AST, or SGOT), total protein, albumin, total bilirubin, and glucose.

Urinalysis: The following tests on urine were performed by semiquantitative (dipstick) or routine laboratory at the intervals described in Table 1, Table 2 and Table 3: protein, glucose, and blood. Subjects with ≥1+ proteinuria, had protein quantitated by 24-hour urine protein determination.

Statistical Methods: The randomized Phase 2 portion of the study was designed to determine if there was sufficient activity of the combination of axitinib plus docetaxel to warrant larger scale comparative trials in subjects with metastatic breast cancer. Time to progression was the primary endpoint. Median TTP for subjects on docetaxel plus placebo was projected at 6 months and for the combination at 9 months. For an individual subject, TTP was measured from randomization to determination of progression.

Data from subjects enrolled in the Phase 1 portion of the study were analyzed separately using descriptive statistics only. Data from the single-agent, open-label axitinib portion of the study from subjects who crossed over after progressing on docetaxel plus placebo were analyzed separately using descriptive statistics.

The final analyses were conducted when at least 1 of the following conditions were met:

- When approximately 111 progression events (documented progression during treatment or follow-up or cancer-related death during treatment) occurred; or

- All subjects discontinued study medication and were followed to progression, death, withdrawal, or were lost to follow-up. All subjects followed for progression until the investigator was notified by the sponsor or its designee that no additional follow-up was requested in any subject.

RESULTS

Subject Disposition and Demography: Six subjects enrolled in the Phase 1 portion of the study, 168 subjects enrolled in the Phase 2, randomized portion, and 16 subjects enrolled in the Phase 2, open-label single-agent portion. One subject in the Phase 2, double-blind portion discontinued before receiving treatment. In the double-blind portion, the treatment arms were generally well-balanced with regard to demography and malignancy history.

Phase 1 Disposition and Demography: Overall, 6 subjects received a combination of axitinib and docetaxel in Phase 1. One (16.7%) subject discontinued axitinib because of an AE; 4 (66.7%) subjects discontinued axitinib because of lack of efficacy, and one (16.7%) subject discontinued because of clinical progression.

Demographic is summarized for the all treated population of Phase 1 in Table 4. The mean age 50.8 years, and most (66.7%) subjects were White.

Table 4. Demographics and Baseline Characteristics of Subjects in Phase 1 (All Treated Population)

Variable	Axitinib + Docetaxel (N=6)
Age (years)	
Mean (std)	50.8 (9.7)
Median (range)	51.0 (38.0–64.0)
Race(n [%])	
Caucasian	4 (66.7%)
Black	1 (16.7%)
Hispanic/Latino	1 (16.7%)

Std = standard deviation; N = total number in population set; n = number of subjects with pre-specified criteria.

Phase 2 Disposition and Demography:

In Phase 2, 168 subjects were randomized; 112 subjects were randomized to axitinib in combination with docetaxel (axitinib +docetaxel) and 56 were randomized to docetaxel plus placebo (placebo + docetaxel). Sixteen subjects crossed over to open-label, single-agent axitinib and were treated. Seven subjects (43.8%) had at least 1 dose reduction. Eleven subjects (68.8%) discontinued because of lack of efficacy, 2 (12.5%) because of AEs, and 1 subject (6.3%) refused to participate further; therefore, disposition data were missing for 2 subjects.

Overall summary of demography and disposition of subjects in Phase 2 (All randomized population) are summarized in Table 5.

Table 5. Overall Summary of Demography and Disposition of Subjects in Phase 2 (All Randomized Population)

Variable	Axitinib + Docetaxel (N=112)	Placebo + Docetaxel (N=56)
Demography		
Age (years)		
Mean (std)	54.1 (10.4)	54.7 (10.1)
Median (range)	55.0 (30.0 – 79.0)	56.0 (34.0 – 71.0)
Race (n [%])		
Caucasian	92 (82.1)	49 (87.5)
Black	5 (4.5)	2 (3.6)
Asian	8 (7.1)	3 (5.4)
Hispanic/Latino	6 (5.4)	2 (3.6)
Other	1 (0.9)	0 (0.0)
Disposition		
Never received study tablet (n [%])	1 (0.9%)	0 (0.0%)
At least one dose reduction of study tablet (n [%])	74 (66.1%)	28 (50.0%)
Primary reason for discontinuation of Study Tablet (n [%])		
Non-fatal AE	25 (22.3%)	6 (10.7%)
Lack of efficacy	59 (52.7%)	40 (71.4%)
Refusal to participate further	13 (11.6%)	4 (7.1%)
Other	15 (13.4%)	6 (10.7%)
Never received docetaxel (n [%])	1 (0.9%)	0 (0.0%)
At least one dose reduction of docetaxel (n [%])	62 (55.4%)	10 (17.9%)
Primary reason for discontinuation of docetaxel (n [%])		
Death[a]	1 (0.9%)	0 (0.0%)
Non-fatal AE	31 (27.7%)	9 (16.1%)
Lack of efficacy	32 (28.6%)	27 (48.2%)
Refusal to participate further	15 (13.4%)	4 (7.1%)
Other	32 (28.6%)	16 (28.6%)

n = number of subjects with prespecified criteria; N = total number in population set; AE = adverse event; SAE = serious adverse event.

a Death took precedence over adverse event.

Efficacy and Pharmacokinetic Results:

Efficacy Results:

Primary Endpoint: The primary endpoint of this study was to compare the TTP associated with axitinib in combination with docetaxel versus that associated with placebo + docetaxel. The primary analysis was based on the Investigator's assessment and also on data collected from the disease assessment method used starting at baseline. A sensitivity analysis with discontinuation due to lack of efficacy considered progression was also performed.

The primary analysis is summarized in Table 6; the influence of baseline factors on the treatment effect was analyzed using a Cox proportional hazards model stratified by the baseline factors ER status ± any prior adjuvant therapy, and screening ECOG performance (≤1 or 2). Seventy-six (67.9 %) versus 39 subjects (70.9 %) on axitinib + docetaxel vs placebo + docetaxel, respectively, were known to have progressed at the time of this analysis. The median TTP was 247.0 days (95 % CI: 208.0 to 265.0 days) vs 215.0 days (95 % CI: 191.0 to 247.0 days). The stratified Cox hazard ratio was 1.237 (95 % CI: 0.819 to 1.867) with a 1-sided p-value =0.156 based on the stratified log-rank test. This indicated there was no statistically significant improvement in TTP for axitinib + docetaxel vs placebo + docetaxel when controlling for baseline stratification factors. Based on an unstratified Cox proportional hazards model of TTP and unstratified log-rank test, the hazard ratio (placebo + docetaxel: axitinib + docetaxel) was 1.167 (95 % CI: 0.790 to 1.725) with a 1-sided p-value =0.218.

Table 6. Summary of Analyses of Time to Progression in Phase 2 (Modified All Randomized Population)

Variable	Axitinib + Docetaxel (N=112)	Placebo + Docetaxel (N=55)	p-Value
Progression status (n [%])			
Progressed	76 (67.9%)	39 (70.9)	
Did not progress	36 (32.1)	16 (29.1)	
Median (95% CI) TTP (days)	247.0 (208.0-265.0)	215.0 (191.0–247.0)	
Hazard ratio (placebo + docetaxel vs axitinib + docetaxel; 95% CI)[a]	1.237 (0.819–1.867)		0.156[b]
Sensitivity Analysis (unstratified):			
Hazard ratio (placebo + docetaxel vs axitinib +docetaxel; 95% CI)[c]	1.167 (0.790-1.725)		0.218[d]

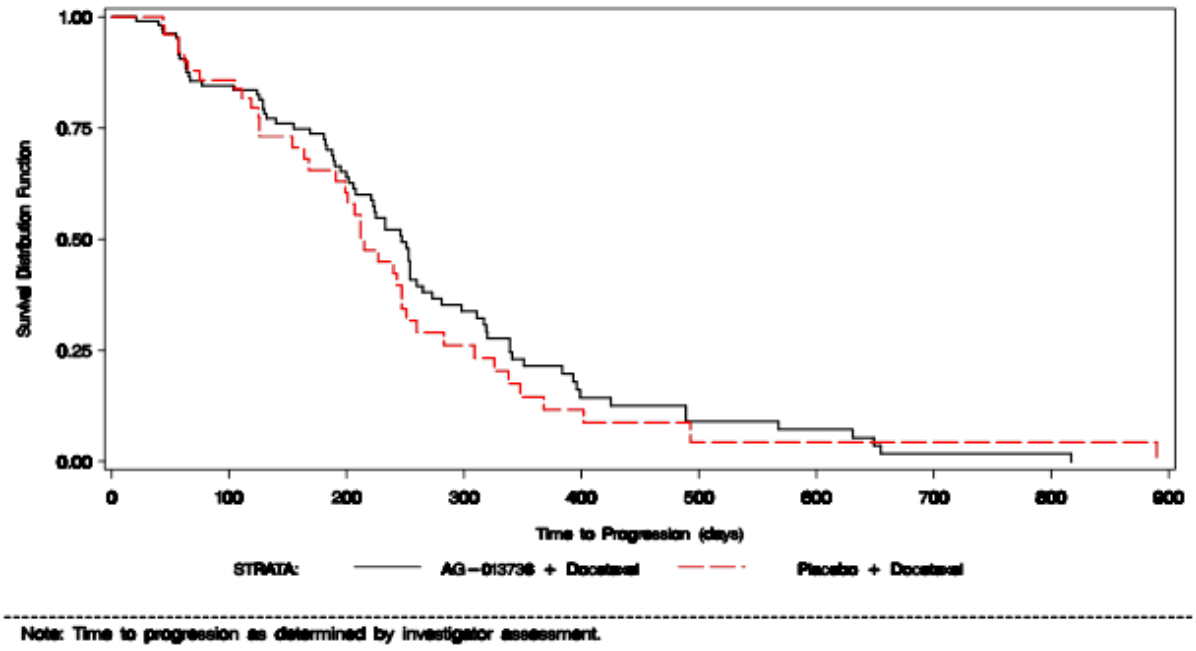
CI = confidence interval; n = number of subjects with specified criteria; N = total number in population set; TTP = time to progression.

a. Based on the Cox proportional hazards model stratified by ER status, prior adjuvant therapy, and screening ECOG performance.
b. One-sided p-value from the log-rank test stratified by estrogen receptor status, prior adjuvant therapy, and screening ECOG.
c Based on the unstratified Cox proportional hazards model.
d One-sided p-value from the unstratified log-rank test.

In the sensitivity analysis in which discontinuation due to lack of efficacy was considered progression, 79 (70.5%) vs 44 subjects (80.0%) on axitinib +docetaxel versus placebo + docetaxel, respectively, were known to have progressed at the time of this analysis.

The median TTP was 246.0 days (95% CI: 195.0 to 254.0 days) versus 184.0 days (95% CI: 132.0 to 243.0 days). The stratified Cox hazard ratio was 1.365 (95% CI: 0.923 to 2.020) with a 1-sided p-value =0.059 based on the stratified log-rank test. This indicated a statistically and clinically significant improvement in TTP for axitinib +docetaxel versus placebo + docetaxel, when controlling for baseline factors; the hazard ratio indicated a 36.5% greater risk of progressing on treatment with placebo + docetaxel compared with treatment on axitinib +docetaxel. The treatment effect was most clear in the strata with prior adjuvant therapy and less so in the strata without prior adjuvant therapy. The treatment effect was also statistically significant based on an unstratified Cox proportional hazard model (hazard ratio: 1.290 [95% CI: 0.888 to 1.873]) with a 1-sided p-value =0.089 based on the unstratified log-rank test. The Kaplan-Meier curve of TTP is presented in Figure 1.

Figure 1. Kaplan-Meier Curve of TTP in Phase 2 (Modified All Randomized Population)



Note: Time to progression as determined by investigator assessment.

Secondary Endpoints:

Response Rate: According to RECIST criteria and duration of response of the combination:

Overall objective response rate (ORR), stratified for baseline factors, in the randomized portion of Phase 2 is summarized in Table 7. Forty-six (41.1%) vs 13 subjects (23.6%) responded on axitinib +docetaxel vs placebo + docetaxel, respectively; 1 (0.9%) vs 0 subjects (0.0%) had a CR; 45 (40.2%) vs 13 subjects (23.6%) had a PR. These results indicate a statistically significant higher response rate on treatment with axitinib + docetaxel (treatment difference: 17.4%; 95% CI: 3.0 to 31.9; p=0.038). The risk ratio for objective response, stratified by the baseline factors (ER status, prior adjuvant therapy, and screening ECOG) was also significant; the risk ratio was 1.761 (95% CI: 1.048 to 2.960; p=0.021) indicating a

clinically and statistically significant increase in likelihood of objective response for subjects treated with axitinib + docetaxel.

Table 7. Summary of Analyses of Objective Response Rate in Phase 2 (Modified All Randomized Population)

Variable	Axitinib + Docetaxel (N=112)	Placebo + Docetaxel (N=55)
Complete response	1 (0.9%)	0
Partial response	45 (40.2%)	13 (23.6%)
Stable disease	8 (7.1%)	7 (12.7%)
Progressive disease	35 (31.3%)	23 (41.8%)
Indeterminate disease	17 (15.2%)	10 (18.2%)
Missing	6 (5.4%)	2 (3.6%)
Overall response rate[a]	46 (41.1%)	13 (23.6%)
95% CI[b]	(31.9, 50.8)	(13.2, 37.0)
Difference in response rates (95% CI)[c]	17.4 (3.0, 31.9)	
p-Value[d]	0.038	

CI = confidence interval; N = total number in population set; RECIST = Response Evaluation Criteria in Solid Tumors.

a. Overall Response Rate = Complete Responders + partial responders according to RECIST.
b. Exact confidence interval for the overall response rate based on the F-distribution.
c. Asymptotic confidence interval for difference in response rates based on a normal distribution.
d. p-value from Fisher's exact test (two-sided) comparing treatment group response rates.

Response Rate and Duration: Single-agent axitinib in subjects who progressed on docetaxel plus placebo:

Duration of response (for all responding subjects) is summarized for subjects in the randomized portion of Phase 2 in Table 8. Thirty-seven (80.4%) vs 13 subjects (100.0%) on axitinib + docetaxel vs placebo + docetaxel, respectively, responded (CR or PR) and subsequently progressed or died. The median duration of response was 211.0 days (95% CI: 190.0 to 276.0 days) vs 149.0 days (95% CI: 120.0 to 238.0 days).

Table 8. Summary of Duration of Objective Response Rate in Phase 2 (All Responding Subjects[a])

Variable	Axitinib + Docetaxel (N=46)	Placebo + Docetaxel (N=13)
Status		
Subject had progressive disease or died	37 (80.4%)	13 (100.0%)
Subject did not show progressive disease or die; subject showed partial or complete response to study drug[b,c]	9 (19.6%)	0
Median duration of response (days)[d]	211.0	149.0
95% CI of duration of response (days)[e]	(190.0, 276.0)	(120.0, 238.0)

CI = confidence interval; CR = complete response; N = total number in population set; PR = partial response.

a. The "All Responding Subject" study population included all randomized subjects who had a baseline assessment of disease and the correct histological cancer type, excluding subjects with missing stratification variables.

b. Assessed from the first date that criteria was met for partial response or complete response was met (+ 1 day).

c. Subjects who achieved a PR or CR and who did not experience disease progression during the treatment and follow-up periods and who did not die during the treatment period will have their event times censored on the last study date that objective tumor assessments verified lack of disease progression.

d. Assessed from the first date that disease progression criteria was met or the subject died due to any cause.

e. Estimated from the Kaplan-Meier curve, based on the Brookmeyer and Crowley method (95% CI for median survival time = 192 to 230).

Sixteen subjects received open-label, single-agent axitinib after progressing on treatment with placebo + docetaxel in the blinded portion of Phase 2 of this study. The baseline tumor measurements for the purpose of establishing response were those from the last tumor assessment on the blinded portion of the study.

Objective response rate for subjects taking open-label, single-agent axitinib in Phase 2 of this study is summarized in Table 9; 1 subject (6.3%) responded (PR); 11 subjects (68.8%) had disease progression, 2 subjects (12.5%) had an evaluation of indeterminate, and 2 subjects (12.5%) were missing.

Table 9. Summary of Objective Response Rate for Subjects Taking Open-Label, Single-Agent Axitinib in Phase 2 (Modified All Treated Subjects)

Best Overall Response	Axitinib (N=16)
Complete response	0
Partial response	1 (6.3%)
Stable disease	0
Progressive disease	11 (68.8%)
Indeterminate	2 (12.5%)
Missing	2 (12.5%)
Overall response rate[a]	1 (6.3%)
95% CI[b]	(0.2, 30.2)

CI = confidence interval; N = total number in population set; RECIST = Response Evaluation Criteria in Solid Tumors.

a. Overall Response Rate = Complete Responders + Partial Responders according to RECIST criteria.

b. Exact confidence interval for the overall response rate based on F-distribution.

Of the subjects with progressive disease, 9 subjects (56.3%) had a new lesion, 4 subjects (25.0%) had a 20% increase in sum of the longest diameters of target lesions, 3 subjects (18.8%) had unequivocal progression on non-target lesions, and 2 subjects (12.5%) had clinical deterioration (Table 10).

Table 10. Summary of Reason for Disease Progression - RECIST Assessment All Treated Subjects

Reason	Axitinib (N=16)
Progressive disease	11 (68.8%)
Twenty (20)% increase in sum of longest diameters of target lesions	4 (25.0%)
New lesion	9 (56.3%)
Unequivocal progression of non-target lesions	3 (18.8%)
Clinical deterioration	2 (12.5%)
Death due to disease under study	0
Missing	0

N = total number in population set.

Pharmacokinetic Results: Axitinib plasma PK and plasma profiles were similar in the absence and presence of docetaxel. PK parameters are summarized in Table 11.

Table 11. Phase 1 Summary of Axitinib Steady-State Plasma Pharmacokinetics When Administered Alone (Day 21) and When Administered With Docetaxel (Day 22)

Treatment	$AUC_{(0-24)}$ (ng*hr/mL)	AUC_{last} (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)	V_z/F (L)
Axitinib alone	646	326	89.3	2.17	3.22	15.5	66.3
(Day 21), n=6	(331–1261)	(166–640)	(59.1–135)	(1.00–5.65)	(2.11–4.32)	(7.93–30.2)	(33.8–130)
Axitinib+docetaxel	678	333	82.1	2.15	3.34	14.8	68.9
(Day 22), n=6	(348–1322)	(169–654)	(54.3–124)	(1.97–5.95)	(2.23–4.44)	(7.56–28.8)	(35.2–135)

$AUC_{(0-24)}$ = area under the plasma concentration versus time curve from 0 to 24 hour; AUC_{last} = area under the plasma concentration-time curve from zero to the time of last quantifiable concentration; C_{max} = maximal plasma concentration; CL/F = apparent plasma clearance; n = number of subjects in each treatment group; T_{max} = time of maximal plasma concentration; $t_{1/2}$ = plasma terminal elimination half-life; V_z/F = apparent oral volume of distribution during the elimination phase.

Docetaxel plasma PK parameters were not reported for 2 subjects because PK blood samples were collected immediately downstream from the vein through which docetaxel infusion was being administered and hence samples were likely contaminated with undiluted docetaxel. Plasma PK and plasma profiles for docetaxel in the remaining subjects (n=4) were similar in the absence and presence of axitinib. PK parameters are summarized in Table 12.

Table 12. Phase 1 Summary of Docetaxel Plasma Pharmacokinetics When Administered Alone (Day 1) and When Administered With Axitinib (Day 22)

Treatment	AUC_{inf} (ng*hr/mL)	AUC_{last} (ng*hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	CL (L/hr)	V_z (L)
Docetaxel alone	3815	3644.34	3424.07	16.4	37.0	778
(Day 1), n=4	(1436–10140)	(1341–9906)	(1830–6407)	(9.47–23.3)	(11.4–121)	(301–2010)
Axitinib + docetaxel	4727	4458	4090	21.7	29.3	913
(Day 22), n=4	(1779–12562)	(1640–12119)	(2186–7653)	(14.8–28.6)	(8.98–95.4)	(354–2358)

Geometric least square means with 95% CIs reported for AUC_{inf}, AUC_{last}, C_{max}, CL, and V_z; arithmetic least square means with 95% CIs reported for $t_{1/2}$.
Data from 2 subjects were not included in the summary statistics because plasma samples were collected from the same arm and downstream from docetaxel infusion line.
$AUC_{(0\text{-}inf)}$ = area under the plasma concentration versus time curve from 0 to infinite time; AUC_{last} = area under the plasma concentration-time curve from zero to the time of last quantifiable concentration; C_{max} = maximal plasma concentration; CI = confidence interval; CL= plasma systemic; clearance; n = number of subjects in each treatment group; T_{max} = time of maximal plasma concentration; $t_{1/2}$ = plasma terminal elimination half-life; V_z= volume of distribution of the drug during the elimination phase.

Safety Results:

Phase 1: Axitinib 5 mg BID + docetaxel 80 mg/m^2 was the maximum tolerated dose, with 1 out of the 6 subjects with dose-limiting toxicity of stomatitis, dysphagia, and neutropenic fever. All 6 subjects in Phase 1 experienced at least 1 AE including at least 1 AE that was considered to be related to the study drug. One subject (16.7%) experienced a SAE; this was considered related to treatment. No subject discontinued both axitinib and docetaxel because of an AE. One subject (16.7%) had a dose reduction of both axitinib and docetaxel due to an AE. No subjects died while on treatment; 1 subject died more than 28 days after her last dose due to disease progression. Nonhematological AEs were generally Grade 1 or 2 in severity, though all Phase 1 subjects experienced at least 1 Grade 3 or 4 event. The only Grade 3 or 4 AE experienced by more than 2 subjects was neutropenia (4 subjects [66.7%]). Grade 4 neutrophil count was experienced by 2 subjects (33.3%), and Grade 4 febrile neutropenia, back pain, chest wall pain, and lung disorder were each experienced by 1 subject (16.7%); other Grade 3 AEs were hypertension (2 subjects [33.3%]); diarrhea, dysphagia, fatigue, stomatitis, vomiting, weight decreased, and white blood cell (WBC) count decreased (each 1 subject [16.7%]). WBC, neutrophils, and platelets all showed a notable decrease from Day 1 to Day 8 of each cycle (following the docetaxel infusion) and recovered by Day 1 of the subsequent cycles. Grade 3 or 4 toxicities were common for WBC and neutrophils. Proteinuria was generally asymptomatic and reversible, and hypertension was adequately managed.

Phase 2: All subjects (111 [100.0%] and 56 subjects [100.0%] on axitinib + docetaxel vs placebo + docetaxel, respectively) experienced AEs (Table 13), and 109 (98.2%) and 55 subjects (98.2%) experienced AEs that were considered to be related to the study drug (Table 14). Fifty-four (48.6%) versus 17 subjects (30.4%) experienced serious AEs, and 40 (36.0%) vs 15 subjects (26.8%) experienced SAEs considered to be related to the study drug (Table 15 and Table 16). Thirty-four (30.6%) vs 9 subjects (16.1%) discontinued the study tablet due to an AE, and 36 (32.4%) vs 10 subjects (17.9%) discontinued docetaxel due

to an AE. Twenty-three (20.7%) vs 2 subjects (3.6%) had a dose reduction of the study tablet due of an AE; 42 (37.8%) vs 8 subjects (14.3%) had a dose reduction of docetaxel due of an AE. Thirty-two (28.8%) vs 9 subjects (16.1%) died; 4 (3.6%) vs 1 subject (1.8%) died on treatment or within 28 days the last dose of study drug; 1 (0.9%) vs 0 subjects (0.0%) died more than 28 days after the last dose of study drug of an event considered treatment-related. SAEs, treatment-related SAEs, and discontinuation and dose reductions of study tablet and of docetaxel, were more common in axitinib + docetaxel.

Phase 2, Open-Label: Twelve of 16 subjects (75.0%) experienced at least 1 AE and at least 1 AE that was considered to be related to the study drug (Table 14). Two subjects (12.5%) experienced at least 1 SAE, and 1 subject (6.3%) experienced at least 1 SAE considered to be related to treatment (Table 15 and Table 16). Four subjects (25.0%) discontinued axitinib due to an AE. The AE profile during the open-label, single-agent portion of the study was similar to that during the randomized portion. There were no Grade 5 AEs reported by subjects during open-label axitinib treatment. Six subjects (37.5%) experienced treatment-related AEs with maximum severity of Grade 3; these events were hypertension (4 subjects [25.0%]) and acquired hypothyroidism, vomiting, and dyspnea (each 1 subject [6.3%]); Grade 3 acquired hypothyroidism was the only serious treatment-related AE.

A summary of all-causality AEs at no higher than a 5% threshold is presented in Table 13.

Table 13. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) N=6	Axitinib + Docetaxel (Phase 2, Double-blind) N=111	Docetaxel + Placebo (Phase 2, Double-blind) N=56	Axitinib (Phase 2, Open-label) N=16
	n (%)	n (%)	n (%)	n (%)
Number (%) of Subjects				
Evaluable for adverse events	6	111	56	16
Blood and lymphatic system disorders	4 (66.7)	50 (45.0)	24 (42.9)	2 (12.5)
Anaemia	2 (33.3)	10 (9.0)	13 (23.2)	1 (6.3)
Febrile neutropenia	0	9 (8.1)	1 (1.8)	0
Leukopenia	0	15 (13.5)	12 (21.4)	0
Lymphadenopathy	0	0	2 (3.6)	1 (6.3)
Neutropenia	4 (66.7)	39 (35.1)	20 (35.7)	0
Cardiac disorders	2 (33.3)	9 (8.1)	8 (14.3)	3 (18.8)
Bradycardia	0	0	1 (6.3)	1 (16.7)
Tachycardia	1 (16.7)	5 (4.5)	3 (5.4)	2 (12.5)
Eye disorders	4 (66.7)	55 (49.5)	22 (39.3)	1 (6.3)
Conjunctivitis	0	15 (13.5)	4 (7.1)	0
Dacryostenosis acquired	1 (16.7)	1 (0.9)	0	0
Eye pain	0	2 (1.8)	3 (5.4)	0
Eyelid oedema	0	0	0	1 (6.3)
Glaucoma	1 (16.7)	0	0	0
Keratitis	1 (16.7)	0	0	0
Lacrimation increased	3 (50.0)	33 (29.7)	11 (19.6)	0
Ocular hyperaemia	1 (16.7)	0	0	0
Vision blurred	1 (16.7)	3 (2.7)	1 (1.8)	1 (6.3)
Gastrointestinal disorders	6 (100.0)	101 (91.0)	48 (85.7)	12 (75.0)
Abdominal discomfort	2 (33.3)	2 (1.8)	2 (3.6)	1 (6.3)
Abdominal distension	0	2 (1.8)	3 (5.4)	0
Abdominal pain	4 (66.7)	26 (23.4)	5 (8.9)	2 (12.5)
Abdominal pain upper	0	2 (12.5)	6 (10.7)	2 (12.5)
Constipation	2 (33.3)	37 (33.3)	12 (21.4)	2 (12.5)
Dental caries	1 (16.7)	1 (0.9)	0	0
Diarrhoea	5 (83.3)	69 (62.2)	24 (42.9)	4 (25.0)
Dry mouth	0	9 (8.1)	4 (7.1)	1 (6.3)
Dyspepsia	3 (50.0)	16 (14.4)	6 (10.7)	0
Dysphagia	2 (33.3)	6 (5.4)	16 (14.4)	1 (6.3)
Flatulence	2 (33.3)	3 (2.7)	3 (5.4)	0
Gastrooesophageal reflux disease	0	7 (6.3)	0	0
Glossodynia	3 (50.0)	8 (7.2)	4 (7.1)	3 (18.8)
Haemorrhoidal haemorrhage	1 (16.7)	0	1 (1.8)	0
Haemorrhoids	1 (16.7)	8 (7.2)	2 (3.6)	0
Nausea	5 (83.3)	54 (48.6)	19 (33.9)	10 (62.5)
Odynophagia	1 (16.7)	4 (3.6)	0	0
Oral discomfort	0	0	1 (1.8)	1 (6.3)
Oral pain	4 (66.7)	11 (9.9)	5 (8.9)	3 (18.8)
Rectal haemorrhage	0	8 (7.2)	0	0
Retching	0	1 (0.9)	1 (1.8)	1 (6.3)
Stomatitis	3 (50.0)	47 (42.3)	6 (10.7)	1 (6.3)
Toothache	1 (16.7)	2 (1.8)	4 (7.1)	1 (6.3)

Table 13. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) N=6	Axitinib + Docetaxel (Phase 2, Double-blind) N=111	Docetaxel + Placebo (Phase 2, Double-blind) N=56	Axitinib (Phase 2, Open-label) N=16
	n (%)	n (%)	n (%)	n (%)
Vomiting	4 (66.7)	42 (37.8)	17 (30.4)	5 (31.3)
General disorders and administration site conditions	5 (83.3)	100 (90.1)	51 (91.1)	9 (56.3)
Asthenia	0	39 (35.1)	10 (17.9)	1 (6.3)
Axillary pain	1 (16.7)	3 (2.7)	0	0
Catheter site erythema	0	0	0	1 (6.3)
Catheter site pain	0	1 (0.9)	4 (7.1)	0
Chest discomfort	0	1 (0.9)	2 (3.6)	1 (6.3)
Chest pain	0	6 (5.4)	7 (12.5)	1 (6.3)
Chills	1 (16.7)	8 (7.2)	6 (10.7)	1 (6.3)
Face oedema	0	4 (3.6)	4 (7.1)	0
Fatigue	4 (66.7)	52 (46.8)	24 (42.9)	7 (43.8)
Influenza like illness	0	3 (2.7)	2 (3.6)	1 (6.3)
Irritability	1 (16.7)	1 (0.9)	0	0
Mucosal inflammation	3 (50.0)	42 (37.8)	12 (21.4)	1 (6.3)
Oedema	0	3 (2.7)	5 (8.9)	0
Oedema peripheral	1 (16.7)	18 (16.2)	13 (23.2)	1 (6.3)
Pain	1 (16.7)	7 (6.3)	9 (16.1)	0
Pyrexia	1 (16.7)	22 (19.8)	10 (17.9)	0
Immune system disorders	1 (16.7)	4 (3.6)	1 (1.8)	0
Seasonal allergy	1 (16.7)	0	0	0
Infections and infestations	5 (83.3)	64 (57.7)	30 (53.6)	1 (6.3)
Cellulitis	1 (16.7)	3 (2.7)	2 (3.6)	0
Infected sebaceous cyst	1 (16.7)	0	0	0
Influenza	0	1 (0.9)	0	1 (6.3)
Nasopharyngitis	0	8 (7.2)	6 (10.7)	0
Oral candidiasis	2 (33.3)	4 (3.6)	2 (3.6)	0
Rhinitis	1 (16.7)	1 (0.9)	1 (1.8)	0
Sinusitis	0	2 (1.8)	0	1 (6.3)
Tooth abscess	1 (16.7)	1 (0.9)	0	0
Tooth infection	1 (16.7)	1 (0.9)	0	0
Upper respiratory tract infection	1 (16.7)	7 (6.3)	4 (7.1)	0
Urinary tract infection	3 (50.0)	14 (12.6)	4 (7.1)	0
Vulvovaginal candidiasis	1 (16.7)	0	1 (1.8)	0
Vulvovaginal mycotic infection	1 (16.7)	2 (1.8)	0	0
Injury, poisoning and procedural complications	1 (16.7)	12 (10.8)	3 (5.4)	0
Skin laceration	1 (16.7)	0	0	0
Investigations	3 (50.0)	34 (30.6)	13 (23.2)	2 (12.5)
Alanine aminotransferase	1 (16.7)	1 (0.9)	0	0
Aspartate aminotransferase	1 (16.7)	1 (0.9)	0	0
Haemoglobin	1 (16.7)	0	0	0
Neutrophil count	1 (16.7)	1 (0.9)	0	0
Neutrophil count decreased	2 (33.3)	4 (3.6)	2 (3.6)	0
Weight decreased	2 (33.3)	16 (14.4)	2 (3.6)	1 (6.3)

Table 13. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) N=6	Axitinib + Docetaxel (Phase 2, Double-blind) N=111	Docetaxel + Placebo (Phase 2, Double-blind) N=56	Axitinib (Phase 2, Open-label) N=16
	n (%)	n (%)	n (%)	n (%)
White blood cell count decreased	2 (33.3)	3 (2.7)	3 (5.4)	0
Metabolism and nutrition disorders	5 (83.3)	48 (43.2)	17 (30.4)	5 (31.3)
Decreased appetite	3 (50.0)	36 (32.4)	13 (23.2)	5 (31.3)
Dehydration	4 (66.7)	12 (10.8)	1 (1.8)	1 (6.3)
Hyperglycaemia	0	6 (5.4)	1 (1.8)	1 (6.3)
Hypoalbuminaemia	1 (16.7)	4 (3.6)	1 (1.8)	0
Hypokalaemia	0	6 (5.4)	2 (3.6)	1 (6.3)
Hyponatraemia	0	6 (5.4)	1 (1.8)	0
Musculoskeletal and connective tissue disorders	4 (66.7)	72 (64.9)	28 (50.0)	7 (43.8)
Arthralgia	3 (50.0)	21 (18.9)	10 (17.9)	1 (6.3)
Back pain	1 (16.7)	21 (18.9)	11 (19.6)	2 (12.5)
Bone pain	1 (16.7)	18 (16.2)	11 (19.6)	2 (12.5)
Flank pain	0	0	0	1 (6.3)
Groin pain	0	1 (0.9)	1 (1.8)	1 (6.3)
Muscle fatigue	0	0	0	1 (6.3)
Muscle spasms	0	6 (5.4)	2 (3.6)	1 (6.3)
Muscular weakness	2 (33.3)	10 (9.0)	3 (5.4)	2 (12.5)
Musculoskeletal chest pain	2 (33.3)	6 (5.4)	3 (5.4)	1 (6.3)
Musculoskeletal pain	2 (33.3)	9 (8.1)	5 (8.9)	2 (12.5)
Myalgia	2 (33.3)	22 (19.8)	7 (12.5)	0
Neck pain	0	6 (5.4)	2 (3.6)	0
Pain in extremity	0	25 (22.5)	10 (17.9)	6 (37.5)
Pain in jaw	1 (16.7)	2 (1.8)	2 (3.6)	0
Neoplasms benign, malignant and unspecified(including cysts and polyps)	0	5 (4.5)	0	0
Nervous system disorders	6 (100.0)	78 (70.3)	37 (66.1)	7 (43.8)
Balance disorder	0	0	0	1 (6.3)
Dizziness	1 (16.7)	22 (19.8)	6 (10.7)	3 (18.8)
Dysgeusia	4 (66.7)	25 (22.5)	10 (17.9)	1 (6.3)
Dyskinesia	1 (16.7)	0	0	0
Facial neuralgia	0	0	0	1 (6.3)
Headache	3 (50.0)	27 (24.3)	13 (23.2)	6 (37.5)
Hyperaesthesia	1 (16.7)	1 (0.9)	1 (1.8)	0
Hypoaesthesia	1 (16.7)	9 (8.1)	3 (5.4)	0
Migraine	1 (16.7)	1 (0.9)	1 (1.8)	1 (6.3)
Neuropathy peripheral	4 (66.7)	14 (12.6)	8 (14.3)	0
Paraesthesia	0	13 (11.7)	5 (8.9)	0
Peripheral sensory neuropathy	2 (33.3)	16 (14.4)	6 (10.7)	1 (6.3)
Sinus headache	0	1 (0.9)	0	1 (6.3)
Psychiatric disorders	2 (33.3)	38 (34.2)	18 (32.1)	2 (12.5)
Anxiety	2 (33.3)	9 (8.1)	5 (8.9)	0
Depression	0	7 (6.3)	4 (7.1)	1 (6.3)
Insomnia	0	20 (18.0)	7 (12.5)	1 (6.3)
Renal and urinary disorders	3 (50.0)	20 (18.0)	9 (16.1)	1 (6.3)

Table 13. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) N=6	Axitinib + Docetaxel (Phase 2, Double-blind) N=111	Docetaxel + Placebo (Phase 2, Double-blind) N=56	Axitinib (Phase 2, Open-label) N=16
	n (%)	n (%)	n (%)	n (%)
Dysuria	1 (16.7)	8 (7.2)	3 (5.4)	0
Haematuria	2 (33.3)	3 (2.7)	1 (1.8)	0
Micturition urgency	1 (16.7)	2 (1.8)	1 (1.8)	1 (6.3)
Pollakiuria	0	7 (6.3)	1 (1.8)	0
Proteinuria	0	2 (1.8)	2 (3.6)	1 (6.3)
Urinary incontinence	1 (16.7)	0	1 (1.8)	0
Reproductive system and breast disorders	4 (66.7)	12 (10.8)	6 (10.7)	0
Vaginal discharge	1 (16.7)	0	0	0
Vaginal haemorrhage	2 (33.3)	1 (0.9)	2 (3.6)	0
Vulvovaginal discomfort	1 (16.7)	1 (0.9)	0	0
Vulvovaginal pain	1 (16.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	5 (83.3)	62 (55.9)	30 (53.6)	7 (43.8)
Cough	3 (50.0)	18 (16.2)	14 (25.0)	2 (12.5)
Dysphonia	1 (16.7)	10 (9.0)	4 (7.1)	4 (25.0)
Dyspnoea	1 (16.7)	23 (20.7)	10 (17.9)	5 (31.3)
Dyspnoea exertional	0	5 (4.5)	3 (5.4)	0
Epistaxis	3 (50.0)	30 (27.0)	10 (17.9)	0
Nasal congestion	1 (16.7)	4 (3.6)	2 (3.6)	0
Nasal discomfort	1 (16.7)	2 (1.8)	0	0
Oropharyngeal pain	3 (50.0)	20 (18.0)	8 (14.3)	1 (6.3)
Pleural effusion	0	3 (2.7)	5 (8.9)	0
Postnasal drip	0	0	0	1 (6.3)
Productive cough	1 (16.7)	1 (0.9)	0	1 (6.3)
Rhinitis allergic	1 (16.7)	0	0	0
Rhinorrhoea	0	7 (6.3)	5 (8.9)	0
Sputum discoloured	1 (16.7)	0	0	0
Upper-airway cough syndrome	1 (16.7)	1 (0.9)	0	0
Wheezing	1 (16.7)	2 (1.8)	0	1 (6.3)
Skin and subcutaneous tissue disorders	6 (100.0)	90 (81.1)	43 (76.8)	4 (25.0)
Alopecia	4 (66.7)	56 (50.5)	30 (53.6)	1 (6.3)
Blister	2 (33.3)	7 (6.3)	0	0
Dry skin	1 (16.7)	14 (12.6)	7 (12.5)	2 (12.5)
Eczema	0	0	1 (1.8)	2 (12.5)
Erythema	0	9 (8.1)	4 (7.1)	0
Hirsutism	1 (16.7)	0	0	0
Hyperkeratosis	0	0	0	1 (6.3)
Nail discolouration	0	6 (5.4)	2 (3.6)	0
Nail disorder	5 (83.3)	23 (20.7)	14 (25.0)	0
Onychalgia	1 (16.7)	4 (3.6)	1 (1.8)	0
Onycholysis	0	8 (7.2)	2 (3.6)	0
Pain of skin	1 (16.7)	2 (1.8)	0	1 (6.3)
Palmar-plantar erythrodysaesthesia syndrome	1 (16.7)	11 (9.9)	0	0
Pruritus	0	13 (11.7)	5 (8.9)	0

Table 13. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) N=6	Axitinib + Docetaxel (Phase 2, Double-blind) N=111	Docetaxel + Placebo (Phase 2, Double-blind) N=56	Axitinib (Phase 2, Open-label) N=16
	n (%)	n (%)	n (%)	n (%)
Rash	2 (33.3)	26 (23.4)	7 (12.5)	2 (12.5)
Rash erythematous	1 (16.7)	0	0	0
Skin exfoliation	0	10 (9.0)	1 (1.8)	0
Skin reaction	1 (16.7)	0	0	0
Umbilical erythema	1 (16.7)	0	0	0
Urticaria	1 (16.7)	0	0	0
Vascular disorders	4 (66.7)	48 (43.2)	15 (26.8)	8 (50.0)
Flushing	1 (16.7)	2 (1.8)	2 (3.6)	0
Hot flush	0	2 (1.8)	4 (7.1)	0
Hypertension	4 (66.7)	36 (32.4)	3 (5.4)	8 (50.0)
Hypotension	1 (16.7)	5 (4.5)	5 (8.9)	1 (6.3)
Lymphoedema	0	4 (3.6)	6 (10.7)	0
Nail discolouration	0	6 (5.4)	2 (3.6)	0
Nail disorder	5 (83.3)	23 (20.7)	14 (25.0)	0
Onychalgia	1 (16.7)	4 (3.6)	1 (1.8)	0
Onycholysis	0	8 (7.2)	2 (3.6)	0
Pain of skin	1 (16.7)	2 (1.8)	0	1 (6.3)
Palmar-plantar erythrodysaesthesia syndrome	1 (16.7)	11 (9.9)	0	0
Pruritus	0	13 (11.7)	5 (8.9)	0
Rash	2 (33.3)	26 (23.4)	7 (12.5)	2 (12.5)
Rash erythematous	1 (16.7)	0	0	0

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

A summary of treatment-related AEs in greater than or equal to 5% of subjects are presented in Table 14.

Table 14. Treatment-Related Adverse Events For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) (N=6)	Axitinib + Docetaxel (Phase 2, Double-Blind) (N=111)	Docetaxel + Placebo (Phase 2, Double-Blind) (N=56)	Axitinib (Phase 2, Open-Label) (N=16)
	n (%)	n (%)	n (%)	n (%)
Number (%) of subjects:				
At least one treatment-related AE	6 (100)	109 (98.2)	55 (98.2)	12 (75.0)
Blood and lymphatic system	4 (66.7)	64 (57.7)	26 (46.4)	1 (6.3)
Neutropenia	4 (66.7)	48 (43.2)	22 (39.3)	0 (0.0)
Febrile neutropenia	1 (16.7)	17 (15.3)	4 (7.1)	0 (0.0)
Leukopenia NOS	0 (0.0)	15 (13.5)	11 (19.6)	0 (0.0)
Anaemia NOS	2 (33.3)	11 (9.9)	13 (23.2)	1 (6.3)
Cardiac disorders	1 (16.7)	7 (6.3)	0 (0.0)	1 (6.3)
Tachycardia NOS	0 (0.0)	2 (1.8)	0 (0.0)	1 (6.3)
Bradycardia NOS	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	1 (16.7)	1 (0.9)	0 (0.0)	1 (6.3)
Hirsutism	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Acquired hypothyroidism	0 (0.0)	1 (0.9)	0 (0.0)	1 (6.3)
Eye disorders	3 (50.0)	45 (40.5)	20 (35.7)	0 (0.0)
Dacryostenosis acquired	1 (16.7)	1 (0.9)	0 (0.0)	0 (0.0)
Lacrimation increased	3 (50.0)	29 (26.1)	11 (19.6)	0 (0.0)
Conjunctivitis	0 (0.0)	11 (9.9)	3 (5.4)	0 (0.0)
Gastrointestinal disorders	6 (100)	97 (87.4)	37 (66.1)	10 (62.5)
Abdominal discomfort	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea NOS	5 (83.3)	65 (58.6)	17 (30.4)	3 (18.8)
Dry mouth	0 (0.0)	5 (4.5)	2 (3.6)	1 (6.3)
Nausea	6 (100)	51 (45.9)	18 (32.1)	8 (50.0)
Stomatitis	4 (66.7)	50 (45.0)	8 (14.3)	2 (12.5)
Flatulence	1 (16.7)	3 (2.7)	0 (0.0)	0 (0.0)
Vomiting NOS	3 (50.0)	34 (30.6)	14 (25.0)	2 (12.5)
Constipation	0 (0.0)	18 (16.2)	3 (5.4)	0 (0.0)
Abdominal pain NOS	2 (33.3)	18 (16.2)	2 (3.6)	2 (12.5)
Dyspepsia	1 (16.7)	11 (9.9)	4 (7.1)	0 (0.0)
Loose stools	1 (16.7)	0 (0.0)	1 (1.8)	0 (0.0)
Oral discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Oral pain	3 (50.0)	10 (9.0)	3 (5.4)	2 (12.5)
Odynophagia	1 (16.7)	5 (4.5)	0 (0.0)	0 (0.0)
Glossodynia	3 (50.0)	8 (7.2)	3 (5.4)	2 (12.5)
Dysphagia	2 (33.3)	6 (5.4)	0	1 (6.3)
General disorders and administration site conditions	4 (66.7)	94 (84.7)	43 (76.8)	5 (31.3)
Chest pressure sensation	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Chest tightness	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Fatigue	3 (50.0)	49 (44.1)	24 (42.9)	4 (25.0)
Mucosal inflammation NOS	3 (50.0)	42 (37.8)	12 (21.4)	1 (6.3)
Asthenia	0 (0.0)	35 (31.5)	9 (16.1)	0 (0.0)

Table 14. Treatment-Related Adverse Events For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) (N=6)	Axitinib + Docetaxel (Phase 2, Double-Blind) (N=111)	Docetaxel + Placebo (Phase 2, Double-Blind) (N=56)	Axitinib (Phase 2, Open-Label) (N=16)
	n (%)	n (%)	n (%)	n (%)
Pyrexia	1 (16.7)	13 (11.7)	6 (10.7)	0 (0.0)
Oedema peripheral	1 (16.7)	8 (7.2)	8 (14.3)	0 (0.0)
Pain NOS	1 (16.7)	5 (4.5)	5 (8.9)	0 (0.0)
Oedema NOS	0 (0.0)	2 (1.8)	5 (8.9)	0 (0.0)
Weakness	0 (0.0)	6 (5.4)	1 (1.8)	0 (0.0)
Infections and infestations	1 (16.7)	23 (20.7)	9 (1.6)	0 (0.0)
Oral candidiasis	1 (16.7)	4 (3.6)	0 (0.0)	0 (0.0)
Vaginal candidiasis	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (16.7)	8 (7.2)	2 (3.6)	0 (0.0)
Blister	1 (16.7)	4 (3.6)	0 (0.0)	0 (0.0)
Investigations	2 (33.3)	28 (25.2)	7 (12.5)	1 (6.3)
Haemoglobin	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count	2 (33.3)	2 (1.8)	0 (0.0)	0 (0.0)
Weight decreased	1 (16.7)	14 (12.6)	1 (1.8)	1 (6.3)
White blood cell count decreased	2 (33.3)	3 (2.7)	3 (5.4)	0 (0.0)
Metabolism and nutrition disorders	3 (50.0)	43 (38.7)	15 (26.8)	6 (37.5)
Anorexia	2 (33.3)	33 (29.7)	13 (23.2)	4 (25.0)
Dehydration	3 (50.0)	8 (7.2)	1 (1.8)	0 (0.0)
Hypoalbuminaemia	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Appetite decreased NOS	0 (0.0)	0 (0.0)	1 (1.8)	2 (12.5)
Musculoskeletal and connective tissue disorders	2 (33.3)	42 (37.8)	11 (19.6)	3 (18.8)
Muscle cramps	0 (0.0)	4 (3.6)	1 (1.8)	1 (6.3)
Myalgia	2 (33.3)	20 (18.0)	3 (5.4)	0 (0.0)
Bone pain	1 (16.7)	3 (2.7)	2 (3.6)	0 (0.0)
Pain in limb	0 (0.0)	15 (13.5)	3 (5.4)	3 (18.8)
Arthralgia	1 (16.7)	13 (11.7)	1 (1.8)	0 (0.0)
Nervous system disorders	4 (66.7)	66 (59.5)	30 (53.6)	3 (18.8)
Dysgeusia	4 (66.7)	24 (21.6)	11 (19.6)	1 (6.3)
Paraesthesia	0 (0.0)	13 (11.7)	6 (10.7)	0 (0.0)
Dizziness	0 (0.0)	13 (11.7)	3 (5.4)	2 (12.5)
Peripheral sensory neuropathy	1 (16.7)	12 (10.8)	5 (8.9)	1 (6.3)
Peripheral neuropathy NOS	4 (66.7)	10 (9.0)	5 (8.9)	0 (0.0)
Neuropathy NOS	1 (16.7)	10 (9.0)	4 (7.1)	0 (0.0)
Headache NOS	0 (0.0)	10 (9.0)	2 (3.6)	1 (6.3)
Hyperaesthesia	1 (16.7)	2 (1.8)	1 (1.8)	0 (0.0)
Hypoaesthesia	1 (16.7)	6 (5.4)	2 (3.6)	0 (0.0)
Renal and urinary disorders	0 (0.0)	6 (5.4)	1 (1.8)	1 (6.3)
Proteinuria	0 (0.0)	3 (2.7)	1 (1.8)	1 (6.3)
Respiratory, thoracic and mediastinal disorders	5 (83.3)	54 (48.6)	18 (32.1)	5 (31.3)
Epistaxis	3 (50.0)	24 (21.6)	6 (10.7)	0 (0.0)
Dyspnoea NOS	1 (16.7)	13 (11.7)	3 (5.4)	2 (12.5)

Table 14. Treatment-Related Adverse Events For Events Having a Frequency Rate ≥5%

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1, Lead-in) (N=6)	Axitinib + Docetaxel (Phase 2, Double-Blind) (N=111)	Docetaxel + Placebo (Phase 2, Double-Blind) (N=56)	Axitinib (Phase 2, Open-Label) (N=16)
	n (%)	n (%)	n (%)	n (%)
Hoarseness	1 (16.7)	4 (3.6)	1 (1.8)	3 (18.8)
Pharyngitis	3 (50.0)	11 (9.9)	4 (7.1)	0 (0.0)
Cough	0 (0.0)	8 (7.2)	2 (3.6)	0 (0.0)
Pharyngolaryngeal pain	0 (0.0)	8 (7.2)	1 (1.8)	1 (6.3)
Rhinorrhoea	0 (0.0)	6 (5.4)	3 (5.4)	0 (0.0)
Wheezing	0 (0.0)	1 (0.9)	0 (0.0)	1 (6.3)
Nasal passage irritation	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis allergic NOS	1 (16.7)	1 (0.9)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	6 (100.0)	84 (75.7)	39 (69.6)	4 (25.0)
Alopecia	4 (66.7)	57 (51.4)	31 (55.4)	1 (6.3)
Nail disorder NOS	5 (83.3)	23 (20.7)	15 (26.8)	1 (6.3)
Nail bed tenderness	1 (16.7)	2 (1.8)	0 (0.0)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	2 (33.3)	12 (10.8)	0 (0.0)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Pain of skin	0 (0.0)	1 (0.9)	0 (0.0)	1 (6.3)
Skin irritation	1 (16.7)	1 (0.9)	0 (0.0)	0 (0.0)
Urticaria NOS	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Scalp pain	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rash NOS	2 (33.3)	19 (17.1)	6 (10.7)	1 (6.3)
Dry skin	1 (16.7)	14 (12.6)	5 (8.9)	2 (12.5)
Face oedema	0 (0.0)	2 (1.8)	4 (7.1)	0 (0.0)
Pruritus NOS	0 (0.0)	10 (9.0)	0 (0.0)	0 (0.0)
Onycholysis	0 (0.0)	8 (7.2)	2 (3.6)	0 (0.0)
Dermatitis exfoliative NOS	0 (0.0)	7 (6.3)	0	0 (0.0)
Erythema	0 (0.0)	6 (5.4)	1 (1.8)	0 (0.0)
Vascular disorders	5 (83.3)	40 (36.0)	4 (7.1)	8 (50.0)
Hypertension NOS	5 (83.3)	31 (27.9)	0 (0.0)	8 (50.0)
Hypotension NOS	0 (0.0)	3 (2.7)	2 (3.6)	1 (6.3)
Flushing	1 (16.7)	1 (0.9)	1 (1.8)	0 (0.0)

AEs and SAEs are not separated out.
N = total number of subjects; n = number of subjects with specified criteria; NOS = not otherwise specified.

A summary of all-causality SAEs (100% of SAEs) are summarized in Table 15.

Table 15. Serious Adverse Events by System Organ Class and Preferred Term (All-Causality)

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1 Lead-in)	Axitinib + Docetaxel (Phase 2, Double-Blind)	Docetaxel + Placebo (Phase 2, Double-Blind)	Axitinib (Phase 2, Open-Label)
	n (%)	n (%)	n (%)	n (%)
Number (%) of Subjects:				
Evaluable for adverse events	6	111	56	16
With adverse events	1 (16.7)	54 (48.6)	17 (30.4)	2 (12.5)
Blood and lymphatic system disorders	1 (16.7)	19 (17.1)	7 (12.5)	0
Agranulocytosis	0	0	1 (1.8)	0
Febrile neutropenia	1 (16.7)	9 (8.1)	3 (5.4)	0
Neutropenia	0	10 (9.0)	3 (5.4)	0
Cardiac disorders	0	3 (2.7)	0	0
Arrhythmia supraventricular	0	1 (0.9)	0	0
Left ventricular dysfunction	0	1 (0.9)	0	0
Palpitations	0	1 (0.9)	0	0
Pericardial effusion	0	1 (0.9)	0	0
Restrictive cardiomyopathy	0	1 (0.9)	0	0
Endocrine disorders	0	0	0	1 (6.3)
Hypothyroidism	0	0	0	1 (6.3)
Eye disorders	0	2 (1.8)	1 (1.8)	0
Angle closure glaucoma	0	1 (0.9)	0	0
Diplopia	0	0	1 (1.8)	0
Uveitis	0	1 (0.9)	0	0
Gastrointestinal disorders	1 (16.7)	14 (12.6)	2 (3.6)	0
Abdominal distension	0	1 (0.9)	0	0
Abdominal pain	0	1 (0.9)	0	0
Diarrhoea	0	4 (3.6)	1 (1.8)	0
Duodenal ulcer	0	1 (0.9)	0	0
Dysphagia	0	1 (0.9)	0	0
Haemorrhoids	0	1 (0.9)	0	0
Nausea	0	4 (3.6)	2 (3.6)	0
Odynophagia	0	1 (0.9)	0	0
Stomatitis	1 (16.7)	5 (4.5)	0	0
Volvulus	0	1 (0.9)	0	0
Vomiting	0	4 (3.6)	2 (3.6)	0
General disorders and administration site conditions	0	15 (13.5)	1 (1.8)	0
Asthenia	0	3 (2.7)	0	0
Chest pain	0	2 (1.8)	0	0
Haemorrhagic cyst	0	1 (0.9)	0	0
Mucosal inflammation	0	3 (2.7)	0	0
Pyrexia	0	6 (5.4)	1 (1.8)	0
Thrombosis in device	0	1 (0.9)	0	0
Hepatobiliary disorders	0	3 (2.7)	0	0
Cholecystitis	0	1 (0.9)	0	0
Cholecystitis acute	0	1 (0.9)	0	0
Hyperbilirubinaemia	0	1 (0.9)	0	0
Infections and infestations	0	10 (9.0)	4 (7.1)	0
Anal abscess	0	1 (0.9)	0	0

Table 15. Serious Adverse Events by System Organ Class and Preferred Term (All-Causality)

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1 Lead-in)	Axitinib + Docetaxel (Phase 2, Double-Blind)	Docetaxel + Placebo (Phase 2, Double-Blind)	Axitinib (Phase 2, Open-Label)
	n (%)	n (%)	n (%)	n (%)
Breast abscess	0	1 (0.9)	0	0
Bronchopneumonia	0	1 (0.9)	0	0
Catheter site infection	0	2 (1.8)	0	0
Clostridial infection	0	1 (0.9)	0	0
Enterobacter infection	0	1 (0.9)	0	0
Groin abscess	0	1 (0.9)	0	0
Herpes zoster	0	0	1 (1.8)	0
Infection	0	1 (0.9)	1 (1.8)	0
Influenza	0	0	1 (1.8)	0
Lower respiratory tract infection	0	1 (0.9)	0	0
Neutropenic sepsis	0	1 (0.9)	1 (1.8)	0
Oral candidiasis	0	1 (0.9)	0	0
Pneumonia	0	2 (1.8)	0	0
Respiratory tract infection	0	1 (0.9)	0	0
Urinary tract infection	0	0	1 (1.8)	0
Investigations	0	3 (2.7)	1 (1.8)	0
Gamma-glutamyltransferase increased	0	1 (0.9)	0	0
Neutrophil count decreased	0	1 (0.9)	0	0
Weight decreased	0	1 (0.9)	0	0
White blood cell count decreased	0	0	1 (1.8)	0
Metabolism and nutrition disorders	0	4 (3.6)	1 (1.8)	0
Dehydration	0	4 (3.6)	1 (1.8)	0
Hyponatraemia	0	1 (0.9)	0	0
Musculoskeletal and connective tissue disorders	0	1 (0.9)	0	0
Back pain	0	1 (0.9)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	5 (4.5)	0	0
Malignant neoplasm progression	0	1 (0.9)	0	0
Malignant pleural effusion	0	1 (0.9)	0	0
Metastases to liver	0	1 (0.9)	0	0
Metastases to meninges	0	1 (0.9)	0	0
Metastases to nervous system	0	1 (0.9)	0	0
Nervous system disorders	0	2 (1.8)	3 (5.4)	1 (6.3)
Convulsion	0	0	0	1 (6.3)
Lethargy	0	1 (0.9)	0	0
Radiculopathy	0	1 (0.9)	0	0
Syncope	0	0	2 (3.6)	0
Respiratory, thoracic and mediastinal disorders	0	9 (8.1)	3 (5.4)	0
Dyspnoea	0	2 (1.8)	1 (1.8)	0
Epistaxis	0	1 (0.9)	0	0
Haemothorax	0	0	1 (1.8)	0
Nasal septum perforation	0	1 (0.9)	0	0
Pleural effusion	0	0	2 (3.6)	0
Pneumonitis	0	1 (0.9)	0	0
Pneumothorax	0	1 (0.9)	1 (1.8)	0

Table 15. Serious Adverse Events by System Organ Class and Preferred Term (All-Causality)

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase 1 Lead-in)	Axitinib + Docetaxel (Phase 2, Double-Blind)	Docetaxel + Placebo (Phase 2, Double-Blind)	Axitinib (Phase 2, Open-Label)
	n (%)	n (%)	n (%)	n (%)
Pulmonary embolism	0	3 (2.7)	0	0
Skin and subcutaneous tissue disorders	0	2 (1.8)	0	0
Dermatitis allergic	0	1 (0.9)	0	0
Palmar-plantar erythrodysaesthesia syndrome	0	1 (0.9)	0	0
Vascular disorders	0	5 (4.5)	0	0
Capillary leak syndrome	0	1 (0.9)	0	0
Deep vein thrombosis	0	2 (1.8)	0	0
Hypertension	0	1 (0.9)	0	0
Hypotension	0	1 (0.9)	0	0

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects; NOS = not otherwise specified;v = version.

A summary of treatment-related SAEs (100% of SAEs) is presented in Table 16.

Table 16. Treatment-Related Serious Adverse Events

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase-1 Lead-in) (N=6)	Axitinib + Docetaxel (Phase 2, Double-Blind) (N=111)	Docetaxel + Placebo (Phase 2, Double-Blind) (N=56)	Axitinib (Phase 2, Open-Label) (N=16)
	n (%)	n (%)	n (%)	n (%)
Number (%) of subjects:	1 (16.7)	40 (36.0)	15 (26.8)	1 (6.3)
At Least One Treatment-Related SAE				
Blood and lymphatic system disorders	1 (16.7)	18 (16.2)	7 (12.5)	0 (0.0)
Neutropenia	0 (0.0)	10 (9.0)	3 (5.4)	0 (0.0)
Febrile neutropenia	1 (16.7)	8 (7.2)	3 (5.4)	0 (0.0)
Agranulocytosis	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Cardiac disorders	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Restrictive cardiomyopathy	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Supraventricular arrhythmia NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Ventricular hypokinesia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Acquired hypothyroidism	0 (0.0)	0 (0.0%)	0 (0.0)	1 (6.3)
Eye disorders	0 (0.0)	1 (0.9)	1 (1.8)	0 (0.0)
Uveitis NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Diplopia	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Gastrointestinal disorders	1 (16.7)	11 (9.9)	2 (3.6)	0 (0.0)
Stomatitis	1 (16.7)	5 (4.5)	0 (0.0)	0 (0.0)
Diarrhoea NOS	0 (0.0)	4 (3.6)	0 (0.0)	0 (0.0)
Vomiting NOS	0 (0.0)	3 (2.7)	1 (1.8)	0 (0.0)
Nausea	0 (0.0)	2 (1.8)	1 (1.8)	0 (0.0)
Duodenal ulcer	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Haemorrhoids	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Odynophagia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	11 (9.9)	0 (0.0)	0 (0.0)
Mucosal inflammation NOS	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Weakness	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Lethargy	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Cholecystitis acute NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	3 (2.7)	2 (3.6)	0 (0.0)
Neutropenic sepsis	0 (0.0)	1 (0.9)	1 (1.8)	0 (0.0)
Abscess NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Bronchopneumonia NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Catheter related infection	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Lower respiratory tract infection NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Oral candidiasis	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Herpes zoster	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Infection NOS	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Investigations	0 (0.0)	2 (1.8)	1 (1.8)	0 (0.0)
Neutrophil count decreased	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)

Table 16. Treatment-Related Serious Adverse Events

System Organ Class Preferred Term	Axitinib + Docetaxel (Phase-1 Lead-in) (N=6)	Axitinib + Docetaxel (Phase 2, Double-Blind) (N=111)	Docetaxel + Placebo (Phase 2, Double-Blind) (N=56)	Axitinib (Phase 2, Open-Label) (N=16)
	n (%)	n (%)	n (%)	n (%)
Weight decreased	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
White blood cell count decreased	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Metabolism and nutrition disorder	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (0.9)	2 (3.6)	0 (0.0)
Radiculopathy NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Neurological disorder NOS	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	6 (5.4)	2 (3.6)	0 (0.0)
Dyspnoea NOS	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Capillary leak syndrome	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Nasal septum perforation	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Pneumonitis NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Pleural effusion	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)
Skin and subcutaneous tissue disorder	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	4 (3.6)	0 (0.0)	0 (0.0)
Deep venous thrombosis NOS	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Hypertension NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Hypotension NOS	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)

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

Permanent Discontinuations for Adverse Events:

Phase 1: No subjects discontinued both axitinib and docetaxel because of AEs during the phase 1 portion of the study. Only 1 subject in Phase 1 of this study experienced an AE for which the action taken was "dose permanently discontinued". One Subject discontinued axitinib because of Grade 3 treatment-related stomatitis.

Phase 2: In the blinded portion of Phase 2, 34 (30.6%) vs 9 subjects (16.1%) on axitinib + docetaxel vs placebo + docetaxel, respectively, discontinued the study tablet (axitinib/placebo) because of an AE for which the action taken was "dose permanently discontinued." Thirty-six (32.4%) vs 10 subjects (17.9%) discontinued docetaxel because of an AE for which the action taken was "dose permanently discontinued.

Subjects on axitinib + docetaxel more frequently discontinued study treatment because of AEs. Discontinuations because of gastrointestinal events (oral pain, stomatitis, nausea, diarrhea, abdominal pain, and vomiting not otherwise specified [NOS]), skin reactions (palmar-plantar erythrodysesthesia syndrome, dry skin, rash NOS, skin fissures, skin

desquamation NOS, onycholysis, and nail disorder), neuropathy (peripheral neuropathy NOS, peripheral motor neuropathy, radiculopathy, and polyneuropathy toxic), and hypertension were unique to the axitinib + docetaxel group. Skin toxicity and hypertension are known AEs associated with vascular endothelial growth factor (VEGF) inhibition; neuropathy and gastrointestinal toxicities are typically associated with docetaxel.

Phase 2 Open-Label: Four subjects (25.0%) discontinued because of an AE during the open-label phase. These AEs were considered related to study drug for 1 subject; 1 Subject discontinued open-label, single-agent axitinib because of Grade 3 treatment related hypertension NOS and Grade 1 nausea.

Temporary Discontinuations and Dose Reduction: Discontinuations and dose reductions of the study tablet and docetaxel were more common on axitinib + docetaxel.

Deaths:

Phase 1: There were no Grade 5 (fatal) AEs in Phase 1. One Subject, a 48-year-old white female, died due to progressive disease; her death was neither on-study nor within 28 days of her last dose of study drug, and was not related to an AE.

Phase 2: Thirty-two (28.8%) vs 9 subjects (16.1%), on axitinib + docetaxel vs placebo + docetaxel, respectively, died in Phase 2 of this study. Four (3.6%) vs 1 subject (1.8%) died on treatment or within 28 days after the last dose of study drug; these deaths were secondary to progressive disease with the exception of 1 death due to hemothorax. One subject (0.9%) on axitinib + docetaxel died after 28 days due to a treatment-related event (pneumonitis).

Phase 2 Open-Label: Seven subjects (43.8%) who participated in the open-label portion of Phase 2 died. All of the deaths were due to disease progression and none occurred within 28 days of the last dose of study drug.

CONCLUSIONS:

- Axitinib 5 mg administered BID in combination with docetaxel 80 mg/m^2 administered once intravenously every 3 weeks to subjects with metastatic breast cancer resulted in generally manageable toxicities and statistically and clinically significant improvement in ORR but not in TTP and appeared to prolong duration of response (DR).

- Preliminary findings from this study showed that the PK of axitinib and docetaxel were similar when administered alone and in combination.

- Discontinuations and dose reductions of the study tablet and docetaxel were more common on the axitinib +docetaxel arm than on the placebo + docetaxel arm.

- Hypertension, stomatitis, febrile neutropenia, dehydration, and palmar-plantar erythrodysesthesia syndrome were greater on the axitinib + docetaxel arm than on the placebo + docetaxel arm.