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

PROTOCOL NO.: A4061030

PROTOCOL TITLE: Randomized Phase 2 Trial of AG-013736 or Bevacizumab in Combination With Paclitaxel and Carboplatin as First-Line Treatment for Patients With Advanced Non-Small Cell Lung Cancer

Study Centers: A total of 30 centers took part in the study and randomized subjects; 12 in the United States (US), 5 in Poland, 4 in the United Kingdom (UK) and 3 each in the Czech Republic, France and Spain.

Study Initiation and Final Completion Dates: 22 April 2008 to 16 October 2012; Primary Completion Date: 22 April 2011

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To assess progression-free survival (PFS) of axitinib in combination with paclitaxel and carboplatin (Group A) versus (vs) bevacizumab in combination with paclitaxel and carboplatin (Group B).

Secondary Objectives:

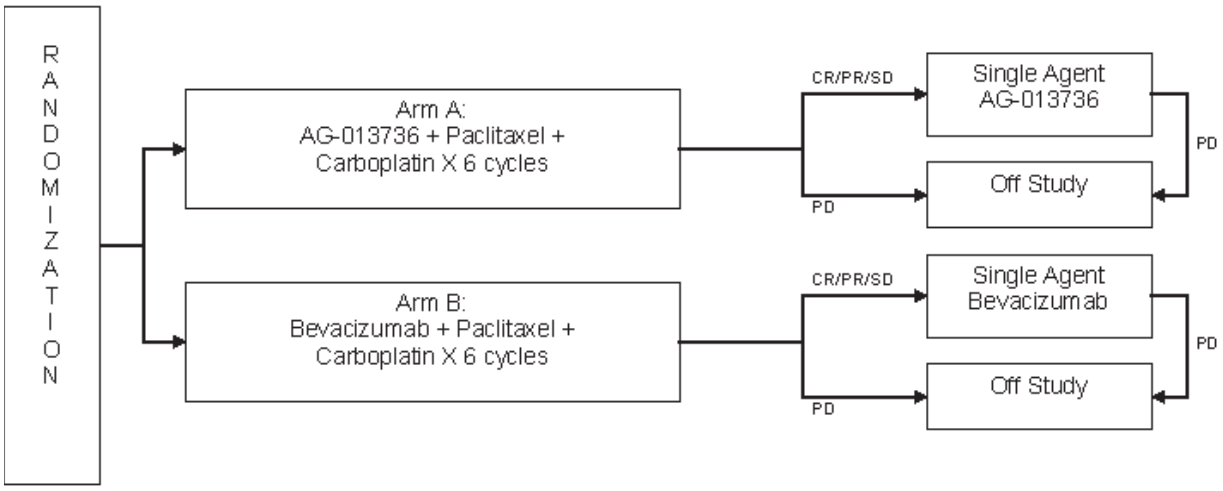
- Assess the overall survival (OS) in each group;
- To assess the overall response rate (ORR) in each group;
- Estimate the duration of response (DR) in each group;
- Evaluate the safety and tolerability of axitinib in combination with paclitaxel and carboplatin;
- Conduct population pharmacokinetic (PK) analysis using axitinib plasma concentrations;
- Evaluate the health-related quality of life (HRQoL) and lung cancer/treatment-related symptoms of subjects in each group according to European Organization for the Research

and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Quality of Life Questionnaire Lung Cancer-13 (QLQ-LC-13).

METHODS

Study Design: This was a Phase 2, multicenter, randomized, open-label study. Subjects were randomized in a 1:1 fashion to 1 of 2 treatment groups: axitinib in combination with paclitaxel and carboplatin (Group A) or bevacizumab in combination with paclitaxel and carboplatin (Group B). The arms of the study are depicted in Figure 1.

Figure 1. Overview of Study Design



AG-013736 = Axitinib

CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease.

Group A (Investigational Treatment): Paclitaxel and carboplatin were administered in 3-week cycles and axitinib was administered at a starting dose of 5 mg twice daily (BID) continuously. Chemotherapy treatment was continued for a maximum of 6 cycles. After completion or discontinuation of chemotherapy for reasons other than disease progression, subjects continued to receive single agent axitinib BID maintenance therapy.

Group B (Control Treatment): Paclitaxel, carboplatin and bevacizumab (15 mg/kg) were administered in 3-week cycles. Chemotherapy treatment was continued for a maximum of 6 cycles. After completion or discontinuation of chemotherapy for reasons other than disease progression, subjects continued to receive every 3 week single agent bevacizumab maintenance therapy.

Subjects were stratified based on history of adjuvant/neoadjuvant therapy (yes/no) and by gender. Crossover between treatment groups was not permitted.

Individual dose adjustments of the study drugs were made on the basis of the adverse events (AEs) observed. Treatment continued until progression of disease, unmanageable AEs, or withdrawal of subject consent. Subjects who tolerated axitinib with no AEs related to axitinib above Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 for

consecutive 2-week periods had their dose increased by 1 dose level unless their blood pressure (BP) was >150/90 mm Hg or the subject was receiving antihypertensive medication. In cases where it was not obvious as to which drug was the major contributor to AEs, dose titrations remained at the Investigator's discretion.

Once a subject had a dose reduction for study drug related toxicity, the dose was not re-escalated unless the toxicity was later determined to be unrelated to the study drug. The schedule of activities for this study is summarized in Table 1.

Table 1. Schedule of Activities[a]

		Study Treatment			Maintenance Phase		
		Cycles 1-6			Single Agent Maintenance or Off Therapy Surveillance	Final Study Visit[b]	Follow Up for Survival[c]
Activity	**Baseline[d]**	**Day 1[e]**	**Day8**	**Day 15**	**Every 3 Weeks**		**Bimonthly**
Informed consent	X						
Medical and oncologic history	X						
ECOG performance status	X						
12-Lead ECG[f]	X						
Physical examination[g]	X	X			X		
Weight, temperature, BP[h], pulse	X	X			X		
Laboratory assessments:							
Hematology[i]	X	X	X	X	X	X	
Coagulation[i]	X						
Serum chemistry[i]	X	X			X	X	
Urine[i]	X	X			X	X	
Thyroid function tests[j]	X	X			X	X	
Pregnancy test (serum/urine)[k]	X						
CT or MRI of brain[l]	X						
Tumor assessments	X[m]	Every 6 weeks			Every 6 weeks until disease progression or initiation of subsequent anticancer therapy	X[m]	
Assessments for tumor cavitation (chest X-ray)	X[n]	X[n]					
Adverse events assessment[o]		X			X	X	
Concomitant medications	X	X	Continuous				
Randomization	X						
Study treatment:							
Chemotherapy[p]		X					
Axitinib[q] (Group A only)		Twice daily continuously					
Bevacizumab IV (Group B only)		X			Every 3 weeks		
EORTC QLQ-C30 and QLQ-LC13[r]		X			X	X	
Pharmacogenomics[s] (optional)	X						
Whole blood RNA expression (optional)[s]		X		X			
CECs and CEPs[t]		X		X	X		
Soluble protein analyses[u]		X		X	X		

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Activity	**Baseline[d]**	**Day 1[e]**	**Day8**	**Day 15**	**Every 3 Weeks**		**Bimonthly**
Population pharmacokinetics (Group A only)[v]		X					
UGT1A1 testing[w]		X					
Survival information[x]							X

AE = adverse event; BP = blood pressure; C = cycle; CEC = circulating endothelial cell; CEP = circulating endothelial cell progenitor; CR = complete response; CT = computed tomography; CXR = chest x-ray; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; IEC = independent ethics committee; INR = International Normalized Ratio; IRB = institutional review board; MRI = magnetic resonance imaging; PA = posteroanterior; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; PTT = partial thromboplastin time; QLQ-C30 = quality of life questionnaire Core 30; QLQ-LC-13 = Quality of Life questionnaire Lung Cancer 13; RNA = ribonucleic acid; T3 = liothryoxine; T4 = levothyroxine; TSH = thyroid stimulating hormone; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1; VEGF = vascular endothelial growth factor.

a. Schedules could vary ±3 days to allow flexibility. Each cycle was 3 weeks in length unless delayed.
b. Assessments were only performed if the prior assessment was performed >7 days previously. Every effort was made to obtain a final tumor assessment.
c. Started at time of final study visit.
d. Assessments performed within 7 days of treatment, except informed consent and medical history, which were performed within 14 days and where noted (tumor assessments and pregnancy test).
e. Cycle 1 Day 1 assessments repeated only if the assessment was not performed in the previous 7 days.
f. Repeated during the course of the study as medically warranted.
g. Included height on initial examination. After the initial complete examination, targeted examinations based on signs and symptoms were performed.
h. BP was taken with the subject in the seated position after the subject had been sitting quietly for 5 minutes. All subjects received BP monitoring devices. Subjects took BP measurements at least once daily (prior to taking a dose of axitinib for subjects in Group A) and recorded results in the subject diary.
i. Analyzed by a center designated local laboratory. Day 8 and Day 15 hematology laboratories were only required during Cycle 1. If urine protein ≥2+ by semiquantitative method (eg, dipstick) then quantitate by urine protein: creatinine ratio. INR and PTT were required at Screening and if clinically indicated.
j. TSH, T3 (free) and free T4 at Baseline. TSH was performed at the beginning of every chemotherapy cycle (every 21 days). Additional T3 (free or total) and/or free T4 could be performed as clinically indicated. During the maintenance phase, TSH was recommended every 8 weeks. Hypothyroidism could be treated to maintain euthyroid state.
k. Performed within 72 hours of treatment only for women of childbearing potential. Repeated during the study, if requested by the IEC/IRB or if required by local regulations. Analyzed by a center designated local laboratory.
l. Baseline brain assessments performed within 28 days prior to start of treatment.
m. Performed at Baseline within 28 days prior to start of treatment. PFS was the primary endpoint for this study and tumor assessments were performed by

Table 1. Schedule of Activities[a]

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		Cycles 1-6			Single Agent Maintenance or Off Therapy Surveillance	Final Study Visit[b]	Follow Up for Survival[c]
Activity	**Baseline[d]**	**Day 1[e]**	**Day8**	**Day 15**	**Every 3 Weeks**		**Bimonthly**

calendar regardless of cycle length. Subjects with PR or CR had responses confirmed by repeat disease assessment no sooner than 4 weeks. Assessments repeated at the end of study visit if >4 weeks had passed since the last evaluation (including CR/PR confirmation, if needed). If any tumor cavitation was observed, axitinib was discontinued. Consideration of restarting axitinib was discussed between the Sponsor and the Investigator. Subjects either receiving single agent axitinib or bevacizumab or off therapy without progressive disease continued to have tumor assessments as indicated.

n. Required at beginning of each cycle unless a CT scan has been done within 7 days prior to Day 1 of that cycle. If any tumor cavitation was observed, axitinib was discontinued immediately. Restarting of axitinib could be considered following discussion between the Sponsor and the Investigator. If apparent tumor progression was observed by chest x-ray, CT or MRI was performed as soon as possible to confirm tumor progression.

o. 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 was followed up until resolution, return to baseline, chronicity or initiation of subsequent anticancer treatment. The serious AEs reporting period ends 28 days after the last study treatment dose, irrespectively of start of any new anticancer treatment. Serious-related AE was reported at any time.

p. Efforts were made to initiate study treatment within 7 days of randomization.

q. Twice daily continuously with dose titration upward or downward according to dose adjustment guidelines. Each time axitinib was dispensed, the Investigator or designee (eg, site coordinator or pharmacist) documented that: 1) no cavitating tumor was observed in most recent CXR or chest CT scan (performed within prior 4 weeks during chemotherapy, within prior 8 weeks during maintenance); and 2) no hemoptysis ≥0.5 teaspoon (2.5 mL) of blood has 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.

r. Health-related quality of life and disease/treatment-related symptoms questionnaire was collected Day 1 of each cycle during chemotherapy, every 3 weeks during the maintenance phase, and at the end of chemotherapy or single agent maintenance phase, whichever was later.

s. Optional blood samples were collected at Baseline (for pharmacogenomics), or Cycle 1 Day 1 (C1D1), C1D15, C2D1, C3D1, C4D1, C5D1 (for RNA expression analysis in whole blood) for subjects in both Group A and Group B.

t. Blood was collected to analyze effects of therapy on the number, viability/apoptotic state, and/or target activity/expression in CECs and CEPs at C1D1, C1D15, C2D1, C3D1, C4D1, C5D1. During the maintenance phase, collection was completed every 6 weeks.

u. Blood was collected to analyze effects of therapy on plasma VEGF, soluble VEGF receptors and soluble receptor tyrosine kinase receptors associated with tyrosine kinase inhibition at C1D1, C1D15, C2D1, C3D1, C4D1, C5D1. During the maintenance phase, collection was completed every 6 weeks.

v. Population PK samples for axitinib were obtained (Arm A only) on Cycle 2 Day 1 and Cycle 3 Day 1. On both scheduled visits 2 samples were 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.

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

x. Collected bimonthly after final study visit.

Number of Subjects (Planned and Analyzed): A total of 108 subjects were planned for the study. A total 118 subjects (30 in the US, 29 in Poland, 24 in the UK, 22 in the Czech Republic, 6 in France and 7 in Spain) were randomized and 117 received study treatment (58 in Group A and 59 in Group B).

Diagnosis and Main Criteria for Inclusion: Male and Female subjects aged ≥18 years with advanced nonsquamous cell, lung cancer and no prior treatment for lung cancer, except prior adjuvant therapy if the last dose was >12 months prior to enrollment, were included in the study.

Exclusion Criteria: Subjects with prior therapy for advanced lung cancer, the need for blood-thinners or those coughing up blood were excluded from the study.

Study Treatment: Commercially available paclitaxel, carboplatin, and bevacizumab were supplied by the study center; axitinib was supplied by the Sponsor as 1 mg and 5 mg film-coated tablets for oral administration.

Treatments consisted of axitinib (5 mg BID), administered orally with food on a continuous schedule, in combination with paclitaxel (200 mg/m^2) and carboplatin (dosed to an area under the concentration-time curve [AUC] = 6) given on Day 1 of a 3-week cycle or bevacizumab (15 mg/kg) in combination with paclitaxel (200 mg/m^2) and carboplatin (AUC = 6) given on Day 1 of a 3-week cycle. The recommended order of chemotherapy administration was: Premedications; paclitaxel; carboplatin; axitinib (Group A) or bevacizumab (Group B).

Paclitaxel (200 mg/m^2) was infused over 3 hours, or as per institutional guidelines, every 3 weeks (21 days).

Carboplatin (AUC of 6 mg∗minute/mL) was infused over 30 minutes, or as per institutional guidelines, every 3 weeks (21 days) following the infusion of paclitaxel.

Subjects received bevacizumab 15 mg/kg, as an intravenous (IV) infusion every 3 weeks. The initial dose was administered over a minimum of 90 minutes.

Efficacy, Parmacokinetic and Pharmacodynamic Endpoints:

Primary Endpoint:

- PFS defined as the time from randomization to the date of progression or death due to any cause, whichever occurred first.

Efficacy Secondary Endpoints:

- OS defined as the time from randomization to the date of death due to any cause;
- Overall confirmed ORR defined as the proportion of randomized 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] guidelines). Confirmed responses were those that persisted on a follow-up imaging assessment ≥4 weeks after the initial objective documentation of response;

- DR defined as the time from first documentation of response to the date of progression or death due to any cause, whichever occurred first;

- Overall safety profile characterized by type, frequency, severity (as graded using National Cancer Institute (NCI) CTCAE, version 3.0 and relationship to study therapy of AEs and laboratory abnormalities;

- Population PK analysis using axitinib plasma concentrations;

- Patient reported outcome (PRO) changes in scores for HRQoL and lung cancer/treatment-related symptoms according to EORTC QLQ-C30 and QLQ-LC-13;

- Molecular profiling and biomarkers of axitinib mechanism of action and clinical benefit was explored with optional pharmacogenomic and gene expression profiling in whole blood. Vascular endothelial growth factor (VEGF) receptor and associated signaling pathways was explored using circulating endothelial cells and soluble proteins in blood.

Safety Evaluations: Safety evaluations included physical examinations, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) score, vital signs monitoring (including weight, temperature, BP, and pulse), hematology tests, serum chemistry, urine protein, and thyroid function monitoring, AEs monitoring at all study visits, and monitoring of concomitant medications at each visit.

Statistical Methods: The intent-to-treat (ITT) 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. This was the primary population for evaluating all efficacy endpoints as well as subject characteristics.

The as-treated (AT) population consisted of all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety.

Primary Efficacy Analysis: PFS was summarized in the ITT population using Kaplan-Meier methods. The median event time for each treatment group and corresponding 2-sided 95% confidence interval (CI) for the median was provided for PFS. The hazard ratio and 95% CI were estimated. A log-rank test (1-sided, α=0.20) stratified on gender and prior adjuvant therapy was used to compare PFS between the 2 treatment groups. An unstratified log-rank test (1-sided) was also calculated. Cox regression models were used to explore the potential influences of the stratification factors on the primary PFS endpoint.

Secondary Analyses: 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 were provided for each endpoint. The hazard ratio and its 95% CI were estimated for OS. For DR, the number of subjects experiencing CR and PR may be small and thereby limit use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics or listings were provided.

The overall survival probability at 1 year was estimated for each treatment group 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 number and percent of subjects achieving objective response (CR or PR) were 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 test stratified by Baseline stratification factors were used to compare ORR between the 2 treatment groups.

The EORTC QLQ-C30 and LC-13 subscales and single item subscores were summarized by the mean (and 95% CI) and median (and ranges) for each group and plotted by time. PROs were assessed using the validated, self-administered EORTC QLQ-C30 and the LC-13 questionnaires.

The significance of changes in plasma proteins from Baseline levels was determined from analysis of the ratio to Baseline values using the Wilcoxon signed-rank test and a hypothetical median ratio to Baseline of 1.0.

The significance of changes in circulating endothelial cell (CEC) values from Baseline levels was determined from analysis of the ratio to Baseline values using the Wilcoxon signed-rank test and a hypothetical median ratio to Baseline of 1.0.

RESULTS

Subject Disposition and Demography: A total of 118 subjects were screened and assigned to treatment, of which 117 subjects received treatment. Disposition of study subjects is summarized in Table 2.

Table 2. Subject Disposition and Subject Analyzed

	Axitinib n (%)	Bevacizumab n (%)
Screened (N=118)		
Assigned study treatment	58	60
Treated	58	59
Completed	0	0
Discontinued study	57 (98.3)	56 (93.3)
Ongoing at data cutoff date (20 April 2011)	1 (0.7)	3 (5.0)
Primary reasons for discontinuation from study (ITT)		
Died	45 (77.6)	46 (76.7)
Lost to follow-up	2 (3.4)	2 (3.3)
Study terminated by Sponsor	8 (13.8)	6 (10.0)
Objective progression or relapse	0	1 (1.7)
Subject refused continued treatment for reason other than AE	1 (1.7)	1 (1.7)
Other	2 (3.4)	1 (1.7)
Data sets analyzed		
Intent-to-Treat (full analysis population)	58	60
As-Treated (safety analysis population)	58	59
Analyzed for safety		
Adverse events	58 (100.0)	59 (98.3)
Laboratory data	57 (98.3)	58 (96.7)
Analyzed for CEC biomarkers	58 (100.0)	59 (98.3)
Analyzed for soluble protein biomarkers	57 (98.3)	58 (96.7)

AE = adverse event; CEC = circulating endothelial cell; ITT = intent-to-treat; N = total number of subjects in treatment group; n = number of subjects.

In both treatment groups, approximately two-thirds of subjects were male and subjects were primarily white. Most subjects were between the ages of 45 and 64 and had an ECOG score of 0 or 1 (Table 3).

Table 3. Summary of Demographic Characteristics

	Axitinib (N=58) n (%)	Bevacizumab (N=60) n (%)
Gender		
Male	36 (62.1)	37 (61.7)
Female	22 (37.9)	23 (38.3)
Age (years)		
<18	0	0
18-44	1 (1.7)	2 (3.3)
45-64	33 (56.9)	44 (73.3)
≥65	24 (41.4)	14 (23.3)
Mean (SD)	61.7 (8.6)	59.9 (8.4)
Median (range)	60.5 (41, 79)	60.5 (40, 79)
n	58	60
Race		
White	54 (93.1)	56 (93.3)
Black	1 (1.7)	3 (5.0)
Asian	1 (1.7)	0
Other	2 (3.4)	1 (1.7)
n	58	60
Weight (kg)		
Mean (SD)	70.2 (15.5)	72.1 (16.5)
Median (range)	66.63 (46, 109)	68.88 (42, 112)
n	56	60
Height (cm)		
Mean (SD)	168.5 (9.5)	169.1 (10.3)
Median (range)	168.00 (150, 194)	170.00 (142, 192)
n	57	60
ECOG score		
0	16 (27.59)	16 (26.67)
1	42 (72.41)	43 (71.67)
Not reported	0	1 (1.67)
n	58	60
Smoking status		
Never smoked	6 (10.3)	8 (13.3)
Ex-smoker	34 (58.6)	34 (56.7)
Current smoker	18 (31.0)	18 (30.0)
n	58	60

ECOG = Eastern Cooperative Oncology Group; N = total number of subjects in treatment group; n = number of subjects; SD = standard deviation.

Efficacy, Pharmacokinetic and Pharmacodynamic Results:

PFS: A summary of PFS by treatment (stratified and unstratified analysis) for the ITT population is provided in Table 4. The primary hypothesis was tested using a 1-sided log rank test, stratified by gender and prior adjuvant therapy; the p-value was 0.639, demonstrating no statistical difference between the treatment groups.

Table 4. Progression-Free Survival (Stratified and Unstratified; ITT)

	Axitinib (N=58) n (%)	Bevacizumab (N=60) n (%)
Number with Event	37 (63.8)	36 (60.0)
Objective progression	27 (73.0)	32 (88.9)
Death without objective progression	10 (27.0)	4 (11.1)
Number censored	21 (36.2)	24 (40.0)
Reason for censorship		
No Baseline or on-study assessment	5 (23.8)	4 (16.7)
Alive, on-study, and progression free at time of analysis	11 (52.4)	14 (58.3)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on study	2 (9.5)	2 (8.3)
PD occurred after ≥2 consecutive missed assessments	1 (4.8)	0
PD occurred after given new antitumor treatment	1 (4.8)	4 (16.7)
Lost to follow-up	1 (4.8)	0
Kaplan-Meier estimates of time to event (month)		
Quartile (95% CI)[a]		
25%	2.6 (1.7, 4.7)	3.2 (2.7, 5.7)
50%	5.7 (4.1, 7.5)	6.1 (4.2, 8.7)
75%	8.3 (6.9, 12.2)	9.7 (8.3, 9.8)
Axitinib versus bevacizumab		
Stratified - hazard ratio[b]	1.093	
95% CI of hazard ratio	0.679, 1.761	
p-value[c]	0.639	
Unstratified - hazard ratio[d]	1.130	
95% CI of hazard ratio	0.712, 1.792	
p-value[e]	0.699	

CI = confidence interval; ITT = intent-to-treat; N = total number of subjects in treatment group; n = number of subjects; PD = progressive disease.

a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox Proportional hazards model stratified by gender and prior adjuvant therapy.
c. One-sided p-value from log-rank test stratified by gender and prior adjuvant therapy.
d. Based on the Cox Proportional hazards model.
e. One-sided p-value from unstratified log-rank test.

OS: A summary of OS by treatment (stratified and unstratified analysis) for the ITT population is provided in Table 5. Using a 1-sided log-rank test stratified by gender and prior adjuvant therapy, the p-value was 0.699, failing to demonstrate a statistically significant difference between the treatment groups.

Table 5. Overall Survival (Stratified and Unstratified; ITT)

	Axitinib (N=58) n (%)	Bevacizumab (N=60) n (%)
Deaths	45 (77.6)	46 (76.7)
Cause of death		
Disease under study	38 (84.4)	40 (87.0)
Study treatment toxicity	0	2 (4.3)
Unknown reason	3 (6.7)	2 (4.3)
Other	4 (8.9)	3 (6.5)
Number censored	13 (22.4)	14 (23.3)
Reason for censorship		
Alive	10 (76.9)	9 (64.3)
Subject no longer willing to participate	1 (7.7)	2 (14.3)
Lost to follow-up	2 (15.4)	3 (21.4)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[a]		
25%	5.7 (3.2, 7.5)	5.8 (3.8, 10.4)
50%	10.6 (7.5, 16.4)	13.3 (10.4, 17.6)
75%	22.5 (16.1, 26.3)	25.5 (17.6, 28.0)
Axitinib versus bevacizumab		
Stratified - hazard ratio[b]	1.117	
95% CI of hazard ratio	0.739, 1.689	
p-value[c]	0.699	
Unstratified - hazard ratio[d]	1.164	
95% CI of hazard ratio	0.770, 1.759	
p-value[e]	0.763	

CI = confidence interval; ITT = intent-to-treat; N = total number of subjects in treatment group; n = number of subjects; PD = progressive disease.

a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox proportional hazards model stratified by gender and prior adjuvant therapy.
c. 1-sided p-value from the log-rank test stratified by gender and prior adjuvant therapy.
d. Based on the Cox proportional hazards model.
e. One-sided p-value from unstratified log-rank test.

ORR: Best overall response (stratified and unstratified analysis) is summarized in Table 6. There was no statistically significant difference in ORR between treatment groups (stratified p=0.9422).

Table 6. Summary of Best Overall Response (Stratified and Unstratified; ITT)

	Axitinib (N=58) n (%)	Bevacizumab (N=60) n (%)
Subjects with Baseline assessment	58 (100)	60 (100)
Subjects with measurable disease at Baseline	58 (100)	60 (100)
Best overall response		
Complete response	0	1 (1.7)
Partial response	17 (29.3)	25 (41.7)
Stable disease	15 (25.9)	11 (18.3)
Progressive disease	10 (17.2)	11 (18.3)
Not assessed	0	0
Indeterminate	16 (27.6)	12 (20.0)
Overall confirmed ORR (CR + PR)	17 (29.3)	26 (43.3)
95% Exact CI[a]	18.1% - 42.7%	30.6% - 56.8%
Treatment comparison (axitinib versus bevacizumab)		
Stratified - risk ratio[b]	0.676	
95% CI of risk ratio[b]	0.412 - 1.107	
p-value	0.9422[c]	
Unstratified - treatment difference	-14 %	
95% CI of difference[d]	-31.2 % - 3.1 %	
p-value	0.9432[e]	

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

a. Using exact method based on F-distribution.
b. Risk Ratio and CI based on the Mantel-Haenszel estimator; risk ratio is adjusted for same stratification factors as Cochran-Mantel-Haenszel test.
c. The p-value is from a 1-sided Cochran-Mantel-Haenszel test of treatment stratified by prior adjuvant therapy and gender.
d. Calculated based on a normal distribution.
e. p-value is from a 1-sided Pearson chi-square test.

DR: The median DR (95% CI) for the axitinib and bevacizumab groups was 4.4 months (4.2, 6.7 months) and 7.0 months (4.8, 8.3 months), respectively. DR is summarized in Table 7.

Table 7. Duration of Objective Response Among Responders (ITT)

	Axitinib (N=17) n (%)	Bevacizumab (N=26) n (%)
Subjects with event	13 (76.5)	17 (65.4)
Objective progression	12 (92.3)	15 (88.2)
Death without objective progression	1 (7.7)	2 (11.8)
Number censored	4 (23.5)	9 (34.6)
Reason for censorship		
Alive, on-study, and progression free at time of analysis	3 (75.0)	7 (77.8)
At least 1 on-study disease assessment and discontinued treatment prior to documented PD on study	0	2 (22.2)
PD occurred after given new antitumor treatment	1 (25.0)	0
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[a]		
25%	4.2 (2.9, 4.4)	4.4 (2.8, 6.6)
50%	4.4 (4.2, 6.7)	7.0 (4.8, 8.3)
75%	6.7 (4.4, 10.6)	8.3 (7.2, --)

CI = confidence interval; ITT = intent-to-treat; N = total number of subjects in treatment group; n = number of subjects; PD = progressive disease.
a. Based on the Brookmeyer and Crowley method.

PK: Results from population PK modeling using data from this study (pooled with data from other axitinib clinical studies) are not included in this report.

PRO: Absolute mean scores for all functioning scales and symptoms of the EORTC QLQ-C30/LC-13 at Baseline for both treatment groups are summarized in Table 8. Mean scores for the EORTC QLQ-C30 and LC-13 for all items and scales were similar between the 2 treatment groups at Baseline.

Table 8. Mean (SD) Baseline Scores for EORTC QLQ-C30 and LC-13 (ITT)

Function or Symptom	Axitinib		Bevacizumab	
	Sample Size	Score (Mean [SD])	Sample Size	Score (Mean [SD])
EORTC QLQ-C30				
Global health status/ QoL	57	53.22 (22.03)	57	54.97 (21.06)
Functioning scales				
Cognitive functioning	57	80.12 (24.28)	57	83.33 (19.16)
Emotional functioning	57	69.74 (23.45)	57	63.74 (27.44)
Physical functioning	58	66.29 (22.04)	59	75.00 (22.21)
Role functioning	58	60.92 (31.15)	58	60.63 (31.79)
Social functioning	57	71.35 (27.59)	57	65.50 (32.25)
Symptom scales				
Fatigue	57	40.45 (23.94)	58	38.89 (28.02)
Nausea and vomiting	57	8.77 (17.85)	59	9.89 (21.91)
Pain	57	31.29 (31.82)	59	35.31 (30.02)
Dyspnea	56	32.74 (30.15)	58	36.21 (33.21)
Insomnia	57	46.20 (33.19)	58	37.93 (31.50)
Appetite Loss	57	29.82 (28.65)	59	31.64 (34.14)
Constipation	56	15.48 (23.75)	57	21.05 (31.89)
Diarrhea	55	6.67 (17.45)	57	5.85 (14.26)
Financial difficulties	56	22.62 (31.85)	57	21.64 (27.09)
EORTC QLQ-LC-13				
Cough	56	37.50 (31.18)	59	38.42 (24.62)
Haemoptysis	56	2.98 (11.51)	59	3.39 (10.16)
Dyspnea	56	29.17 (20.60)	58	31.42 (28.85)
Sore mouth	56	3.57 (12.19)	58	1.15 (6.13)
Dysphagia	56	6.55 (17.31)	59	6.78 (14.88)
Peripheral neuropathy	56	9.52 (19.81)	59	15.25 (26.50)
Alopecia	56	2.98 (11.51)	59	2.26 (10.48)
Chest pain	56	23.81 (28.93)	59	20.90 (25.45)
Arm/shoulder pain	56	20.83 (27.39)	59	20.34 (29.04)
Other pain	52	28.85 (32.36)	57	25.15 (34.09)
Any medication for pain	37	60.36 (29.23)	35	66.67 (28.01)

Baseline was defined as Cycle1/Day1.
Higher score on functioning or global health status/QoL scales = better functioning or QoL.
Higher score on symptoms scale = higher symptomology or more problems.
Range of score by domain/symptom is 0-100.
EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ITT = intent-to-treat; LC-13 = 13-item supplement module for Lung cancer; QoL = quality of life; SD = standard deviation.

The summary of changes from Baseline by treatment cycle for the EORTC QLQ-C30 and EORTC QLQ-LC-13 is presented in Table 9 and Table 10 respectively.

Table 9. Change From Baseline by Cycle, for EORTC QLQ-C30 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	Standard Deviation	95% CI for Mean
Change from Baseline Score at Cycle 2/Day 1										
Global health status / QoL										
Global QoL	48	-3.82	0	21.54	(-10.07, 2.43)	50	6.67	8.33	22.53	(0.27,13.07)
Functioning scales										
Cognitive functioning	49	-2.04	0	23.97	(-8.92, 4.84)	51	1.96	0	18.45	(-3.23, 7.15)
Emotional functioning	49	2.55	0	19.56	(-3.07, 8.17)	51	11.17	8.34	23.9	(4.44, 17.89)
Physical functioning	51	-2.32	0	18.66	(-7.57, 2.93)	52	2.18	0	14.2	(-1.77, 6.13)
Role functioning	51	-5.23	0	28.58	(-13.27, 2.81)	52	5.77	8.33	26.17	(-1.52, 13.06)
Social functioning	49	-10.88	0	31.47	(-19.92, -1.85)	50	11	0	28.29	(2.96, 19.04)
Symptoms										
Fatigue	51	3.59	0	21.94	(-2.58, 9.77)	52	-2.99	0	23.91	(-9.65, 3.67)
Nausea and vomiting	51	-0.33	0	13.54	(-4.13, 3.48)	52	-3.85	0	24.17	(-10.57, 2.88)
Pain	51	-1.96	0	25.31	(-9.08, 5.16)	52	-8.65	0	28.1	(-16.48, -0.83)
Dyspnoea	50	0	0	24.28	(-6.9, 6.9)	51	-11.76	0	26.52	(-19.22, -4.31)
Insomnia	51	-7.19	0	34.84	(-16.99, 2.61)	52	-9.62	0	30.49	(-18.1, -1.13)
Appetite loss	51	-4.57	0	29.07	(-12.75, 3.6)	52	-10.26	0	39.35	(-21.21, 0.7)
Constipation	49	7.48	0	31.38	(-1.53, 16.5)	50	-0.67	0	28.16	(-8.67, 7.34)
Diarrhoea	48	4.86	0	23.81	(-2.05, 11.77)	51	2.61	0	23.89	(-4.11, 9.33)
Financial difficulties	48	-2.08	0	28.69	(-10.41, 6.25)	51	-3.92	0	21.75	(-10.04, 2.2)
Change from Baseline Score at Cycle 3/Day 1										
Global health status / QoL										
Global QoL	43	-2.52	0	24.9	(-10.18, 5.14)	45	3.33	8.33	19.58	(-2.55, 9.22)
Functioning scales										
Cognitive functioning	43	-2.32	0	27.84	(-10.89, 6.24)	46	1.45	0	17.51	(-3.75, 6.65)
Emotional functioning	43	1.36	0	19.24	(-4.56, 7.28)	46	14.8	8.34	23.85	(7.71, 21.88)
Physical functioning	44	-4.05	-6.67	21.69	(-10.65, 2.54)	46	3.33	0	16.38	(-1.53, 8.2)
Role functioning	44	-9.85	0	34.35	(-20.29, 0.59)	46	10.14	16.66	27.99	(1.83, 18.46)
Social functioning	43	-7.75	0	29.62	(-16.87, 1.36)	46	8.7	0	25.03	(1.26, 16.13)
Symptoms										
Fatigue	44	6.19	0	23.76	(-1.04, 13.41)	46	-2.66	0	27.03	(-10.69, 5.37)
Nausea and vomiting	44	3.03	0	14.94	(-1.51, 7.57)	46	-2.9	0	23.12	(-9.76, 3.97)
Pain	44	-2.65	0	29.63	(-11.66, 6.36)	47	-14.18	-16.66	28.01	(-22.41, -5.96)
Dyspnoea	43	5.43	0	34.06	(-5.06, 15.91)	46	-15.94	0	29.6	(-24.73, -7.15)
Insomnia	44	-18.94	0	40.92	(-31.38, -6.5)	46	-7.25	0	33.64	(-17.24, 2.74)
Appetite loss	43	2.33	0	35.93	(-8.73, 13.38)	46	-13.04	0	34.77	(-23.37, -2.72)
Constipation	43	3.88	0	28.37	(-4.85, 12.61)	44	-8.33	0	33.04	(-18.38, 1.71)
Diarrhoea	42	6.35	0	25.75	(-1.68, 14.37)	46	2.17	0	25.73	(-5.47, 9.81)

Table 9. Change From Baseline by Cycle, for EORTC QLQ-C30 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	Standard Deviation	95% CI for Mean
Financial difficulties	43	1.55	0	36.34	(-9.63, 12.73)	46	-3.62	0	24.57	(-10.92, 3.67)
Change from Baseline Score at Cycle 4/Day 1										
Global health status / QoL										
Global QoL	36	-3.7	-8.33	23.35	(-11.61, 4.2)	46	0.91	0	23.32	(-6.02, 7.83)
Functioning scales										
Cognitive functioning	36	-0.93	0	27	(-10.06, 8.21)	46	-0.73	0	23.03	(-7.56, 6.11)
Emotional functioning	36	3.09	0	16.44	(-2.48, 8.65)	46	11.59	8.34	29.05	(2.97, 20.22)
Physical functioning	36	-5.37	-6.67	19.7	(-12.04, 1.3)	47	-2.38	-6.67	22.78	(-9.06, 4.31)
Role functioning	36	-3.7	0	34.3	(-15.31, 7.9)	47	5.67	0	29.95	(-3.12, 14.47)
Social functioning	36	-5.09	0	27.84	(-14.51, 4.33)	46	4.35	0	32.29	(-5.24, 13.94)
Symptoms										
Fatigue	36	2.62	0	26.18	(-6.23, 11.48)	47	2.25	0	28.44	(-6.1, 10.6)
Nausea and vomiting	36	6.02	0	18.32	(-0.18, 12.22)	47	-1.06	0	20.97	(-7.22, 5.09)
Pain	36	-4.17	0	32.46	(-15.15, 6.82)	47	-7.8	0	35.07	(-18.1, 2.5)
Dyspnoea	35	4.76	0	31.46	(-6.04, 15.57)	47	-12.06	0	32.17	(-21.5, -2.61)
Insomnia	36	-20.37	0	40.06	(-33.93, -6.82)	47	-7.8	0	34.9	(-18.05, 2.45)
Appetite loss	36	-0.93	0	28.16	(-10.45, 8.6)	47	-5.67	0	36.33	(-16.34, 4.99)
Constipation	35	4.76	0	34.43	(-7.07, 16.59)	45	-9.63	0	32.27	(-19.33, 0.07)
Diarrhoea	36	4.63	0	28.9	(-5.15, 14.41)	45	-2.22	0	17.98	(-7.62, 3.18)
Financial difficulties	36	-2.78	0	34.16	(-14.33, 8.78)	46	0.72	0	34.06	(-9.39, 10.84)
Change from Baseline Score at Cycle 5/Day 1										
Global health status / QoL										
Global QoL	31	-1.61	0	24.67	(-10.66, 7.43)	36	2.78	0	26.58	(-6.21, 11.77)
Functioning scales										
Cognitive functioning	31	0	0	22.77	(-8.35, 8.35)	36	-0.46	0	27.16	(-9.65, 8.73)
Emotional functioning	31	3.76	0	16.36	(-2.24, 9.77)	36	15.74	16.67	28.99	(5.93, 25.55)
Physical functioning	33	-10.66	-6.67	23.5	(-18.99, -2.32)	37	-1.62	0	23.59	(-9.49, 6.24)
Role functioning	33	-10.61	0	33.8	(-22.59, 1.38)	37	5.86	16.66	36.69	(-6.38, 18.09)
Social functioning	31	-12.9	0	26.07	(-22.47, -3.34)	36	8.8	0	28.03	(-0.69, 18.28)
Symptoms										
Fatigue	33	4.04	11.11	27.58	(-5.74, 13.82)	37	4.2	0	32.85	(-6.75, 15.16)
Nausea and vomiting	33	8.59	0	25.39	(-0.42, 17.59)	37	0.9	0	24.2	(-7.17, 8.97)
Pain	33	-8.59	0	32.84	(-20.23, 3.06)	37	-8.11	0	37.4	(-20.58, 4.36)
Dyspnoea	32	9.38	0	36.15	(-3.66, 22.41)	37	-5.41	0	34.71	(-16.98, 6.17)
Insomnia	33	-19.19	-33.33	40.85	(-33.68, -4.71)	37	-11.71	0	35.33	(-23.49, 0.07)
Appetite loss	33	2.02	0	35.3	(-10.49, 14.54)	37	-3.6	0	33.13	(-14.65, 7.44)
Constipation	31	4.3	0	30.72	(-6.97, 15.57)	35	-2.86	0	34.65	(-14.76, 9.05)

Table 9. Change From Baseline by Cycle, for EORTC QLQ-C30 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	Standard Deviation	95% CI for Mean
Diarrhoea	31	13.98	0	41.07	(-1.09, 29.04)	36	0	0	22.54	(-7.63, 7.63)
Financial difficulties	31	-2.15	0	42.11	(-17.6, 13.29)	36	1.85	0	25.13	(-6.65, 10.35)
Change from Baseline Score at Cycle 6/Day 1										
Global health status / QoL										
Global QoL	28	-6.85	-8.34	25.16	(-16.6, 2.91)	30	0.83	0	25.74	(-8.78, 10.44)
Functioning scales										
Cognitive functioning	28	-1.19	0	25.63	(-11.13, 8.75)	30	-1.67	0	19.74	(-9.04, 5.71)
Emotional functioning	28	3.27	0	17.02	(-3.33, 9.88)	30	13.89	12.5	28.98	(3.07, 24.71)
Physical functioning	30	-7.22	-6.67	21.21	(-15.14, 0.7)	32	-2.08	0	22.43	(-10.17, 6)
Role functioning	30	-6.67	0	31.74	(-18.52, 5.19)	32	7.29	16.66	37.85	(-6.35, 20.94)
Social functioning	28	-7.74	0	31.59	(-19.99, 4.51)	30	5	0	30.68	(-6.46, 16.46)
Symptoms										
Fatigue	30	7.22	5.56	25.24	(-2.2, 16.65)	32	0.87	0	29.54	(-9.78, 11.52)
Nausea and vomiting	30	8.89	0	25.42	(-0.6, 18.38)	32	5.73	0	17.77	(-0.68, 12.13)
Pain	30	-3.89	0	33.81	(-16.52, 8.74)	32	-7.81	0	34.65	(-20.3, 4.68)
Dyspnoea	30	8.89	0	42.83	(-7.1, 24.88)	32	-7.29	0	30.21	(-18.19, 3.6)
Insomnia	30	-21.11	-33.33	37.64	(-35.16, -7.06)	32	-12.5	0	37.63	(-26.07, 1.07)
Appetite loss	30	3.33	0	33.16	(-9.05, 15.72)	32	1.04	0	37.37	(-12.43, 14.52)
Constipation	27	9.88	0	25.84	(-0.35, 20.1)	31	-3.23	0	34.81	(-15.99, 9.54)
Diarrhoea	28	10.71	0	35.2	(-2.93, 24.36)	30	3.33	0	28.16	(-7.18, 13.85)
Financial difficulties	28	0	0	32.71	(-12.68, 12.68)	30	0	0	32.75	(-12.23, 12.23)
Change from Baseline Score at Cycle 7/Day 1										
Global health status / QoL										
Global QoL	26	-5.13	-12.5	25.94	(-15.6, 5.35)	29	-3.16	0	24.44	(-12.46, 6.14)
Functioning scales										
Cognitive functioning	26	-7.69	-8.34	30.27	(-19.92, 4.53)	29	2.3	0	20.76	(-5.6,10.2)
Emotional functioning	26	3.21	0	21.61	(-5.52, 11.93)	29	13.79	16.67	26.94	(3.55, 24.04)
Physical functioning	26	-5.64	-3.33	26.24	(-16.24, 4.96)	30	-4	0	23.92	(-12.93, 4.93)
Role functioning	27	-16.05	-16.67	34.74	(-29.79, -2.31)	30	2.22	0	36.81	(-11.52, 15.97)
Social functioning	26	-14.74	-8.34	32.77	(-27.98, -1.51)	29	1.73	0	27.22	(-8.63, 12.08)
Symptoms										
Fatigue	27	9.06	11.11	31.09	(-3.24, 21.35)	30	10.74	0	28.51	(0.09, 21.39)
Nausea and vomiting	27	9.88	0	25.84	(-0.35, 20.1)	30	5	0	18.65	(-1.96, 11.96)
Pain	27	-8.64	0	36.8	(-23.2, 5.91)	30	0	0	30.32	(-11.32, 11.32)
Dyspnoea	27	8.64	0	38.78	(-6.7, 23.98)	30	-3.33	0	23.73	(-12.2, 5.53)
Insomnia	27	-20.99	-33.33	39.38	(-36.57, -5.41)	30	-10	0	26.48	(-19.89, -0.11)
Appetite loss	27	14.82	0	36.2	(0.5, 29.14)	30	2.22	0	34.94	(-10.83, 15.27)

Table 9. Change From Baseline by Cycle, for EORTC QLQ-C30 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	Standard Deviation	95% CI for Mean
Constipation	26	10.26	0	30.94	(-2.24, 22.75)	29	-11.49	0	28.56	(-22.36, -0.63)
Diarrhoea	26	3.85	0	38.1	(-11.54, 19.23)	29	2.3	0	21.69	(-5.95, 10.55)
Financial difficulties	26	1.28	0	34.62	(-12.7, 15.27)	29	4.6	0	35.33	(-8.84, 18.03)
Change from Baseline Score at Cycle 8/Day 1										
Global health status / QoL										
Global QoL	20	-4.17	-12.5	26.28	(-16.47, 8.13)	28	-1.19	0	22.42	(-9.88, 7.5)
Functioning scales										
Cognitive functioning	20	-1.67	0	25.31	(-13.51, 10.18)	28	5.95	0	19.88	(-1.76, 13.66)
Emotional functioning	20	2.92	0	16.95	(-5.01, 10.85)	28	15.48	16.67	24.82	(5.85, 25.1)
Physical functioning	21	-10.16	-6.67	22.27	(-20.3, -0.02)	28	-1.19	0	22.81	(-10.04, 7.65)
Role functioning	21	-7.14	0	24.48	(-18.29, 4)	28	9.52	8.33	30.57	(-2.33, 21.38)
Social functioning	20	-6.67	0	21.9	(-16.92, 3.58)	28	1.79	0	27.72	(-8.96, 12.53)
Symptoms										
Fatigue	21	9	0	30.76	(-5, 23)	28	1.98	0	24.2	(-7.4, 11.37)
Nausea and vomiting	21	8.73	0	26.15	(-3.17, 20.63)	28	1.79	0	18.34	(-5.32, 8.9)
Pain	21	-9.52	0	41.36	(-28.35, 9.3)	28	-4.76	0	28.99	(-16, 6.48)
Dyspnoea	21	0	0	34.96	(-15.91, 15.91)	28	-8.33	0	19.51	(-15.9, -0.77)
Insomnia	21	-23.81	-33.33	41.02	(-42.48, -5.14)	28	-15.48	0	29.37	(-26.87, -4.09)
Appetite loss	21	14.29	0	30.86	(0.24, 28.33)	28	-3.57	0	37.78	(-18.22, 11.08)
Constipation	20	11.67	0	27.09	(-1.01, 24.34)	28	-15.48	0	26.42	(-25.72, -5.23)
Diarrhoea	20	13.33	0	31.34	(-1.34, 28)	28	-4.76	0	21.69	(-13.17, 3.65)
Financial difficulties	19	10.53	0	31.53	(-4.67, 25.73)	28	1.19	0	37.93	(-13.52, 15.9)
Change from Baseline Score at Cycle 9/Day 1										
Global health status / QoL										
Global QoL	16	-9.38	-4.17	25.25	(-22.83, 4.08)	22	1.14	4.17	23.33	(-9.21, 11.48)
Functioning scales										
Cognitive functioning	16	-7.29	0	22.75	(-19.41, 4.83)	23	2.9	0	25.94	(-8.32, 14.12)
Emotional functioning	16	-2.61	0	25.77	(-16.34, 11.13)	23	10.39	8.33	28.24	(-1.83, 22.6)
Physical functioning	17	-7.45	0	31.52	(-23.66, 8.76)	23	-5.73	0	18.82	(-13.86, 2.41)
Role functioning	17	-8.82	0	25.08	(-21.72, 4.07)	23	5.07	0	36.73	(-10.81, 20.96)
Social functioning	16	-9.37	0	21.92	(-21.05, 2.3)	23	10.87	0	28.25	(-1.35, 23.09)
Symptoms										
Fatigue	17	5.88	0	29.16	(-9.11, 20.88)	23	-0.48	0	25.18	(-11.37, 10.4)
Nausea and vomiting	17	4.9	0	12.86	(-1.71, 11.51)	23	0	0	24.1	(-10.42, 10.42)
Pain	17	-6.86	-16.66	30.65	(-22.62, 8.9)	23	0.72	0	35.7	(-14.71, 16.16)
Dyspnoea	17	1.96	0	36.27	(-16.69, 20.61)	23	-2.9	0	22.28	(-12.53, 6.73)
Insomnia	17	-13.72	0	37.38	(-32.94, 5.49)	23	-10.14	0	35.44	(-25.47, 5.18)

Table 9. Change From Baseline by Cycle, for EORTC QLQ-C30 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	Standard Deviation	95% CI for Mean
Appetite loss	17	9.81	0	22.87	(-1.95, 21.56)	23	-8.7	0	36.54	(-24.5, 7.11)
Constipation	16	-4.17	0	26.87	(-18.49, 10.15)	23	-13.04	0	29.71	(-25.89, -0.2)
Diarrhoea	16	20.83	16.67	31.91	(3.83, 37.84)	23	-2.9	0	22.28	(-12.53, 6.73)
Financial difficulties	16	6.25	0	30.35	(-9.92, 22.43)	23	-1.45	0	32.53	(-15.52, 12.62)
Change from Baseline Score at Cycle 10/Day 1										
Global health status / QoL										
Global QoL	15	-9.44	-16.67	32.25	(-27.31, 8.42)	20	-4.17	-8.33	24.41	(-15.59, 7.26)
Functioning scales										
Cognitive functioning	15	-2.22	0	25.09	(-16.12, 11.67)	20	5.83	0	21.81	(-4.38, 16.04)
Emotional functioning	15	0	0	21.82	(-12.08, 12.08)	20	11.67	8.33	27.76	(-1.32, 24.66)
Physical functioning	16	-4.58	-6.67	27.62	(-19.3, 10.13)	20	-0.67	0	22.68	(-11.28, 9.94)
Role functioning	16	-4.17	0	23.17	(-16.52, 8.18)	20	3.33	0	41.04	(-15.87, 22.54)
Social functioning	15	-8.89	0	28.08	(-24.44, 6.66)	20	5	0	30.15	(-9.11, 19.11)
Symptoms										
Fatigue	16	8.34	5.56	27.37	(-6.25, 22.92)	20	2.22	0	26.15	(-10.02, 14.46)
Nausea and vomiting	16	5.21	0	13.22	(-1.84, 12.25)	20	6.67	0	18.26	(-1.88, 15.21)
Pain	16	-11.46	-8.33	31.46	(-28.22, 5.3)	20	3.33	0	30.4	(-10.89, 17.56)
Dyspnoea	16	2.08	0	33.27	(-15.64, 19.81)	20	-5	0	22.36	(-15.47, 5.46)
Insomnia	16	-10.42	-16.67	37.95	(-30.64, 9.8)	20	-16.67	0	31.53	(-31.42, -1.91)
Appetite loss	16	16.67	0	27.22	(2.16, 31.17)	20	1.67	0	36.64	(-15.48, 18.81)
Constipation	15	4.44	0	30.52	(-12.45, 21.34)	20	-11.67	0	31.11	(-26.23, 2.89)
Diarrhoea	15	15.56	0	35.34	(-4.01, 35.12)	20	5	0	27.09	(-7.68, 17.68)
Financial difficulties	15	6.67	0	36.08	(-13.31, 26.65)	19	7.02	0	42.43	(-13.43, 27.47)
Change from Baseline Score at Cycle 11/Day 1										
Global health status / QoL										
Global QoL	14	-16.67	-16.67	30.49	(-34.27, 0.94)	19	-2.19	0	24.19	(-13.85, 9.47)
Functioning scales										
Cognitive functioning	14	-9.52	0	14.19	(-17.72, -1.33)	19	2.63	0	26.21	(-10, 15.27)
Emotional functioning	14	-4.76	-8.33	18.11	(-15.22, 5.7)	19	17.54	16.67	30.29	(2.94, 32.14)
Physical functioning	14	-13.1	-13.33	24.82	(-27.43, 1.24)	19	-2.81	-6.66	20.65	(-12.76, 7.14)
Role functioning	14	-11.91	0	29.55	(-28.97, 5.16)	19	4.39	0	38.42	(-14.13, 22.91)
Social functioning	14	-14.28	-16.67	19.45	(-25.52, -3.05)	19	6.14	0	33.43	(-9.97, 22.25)
Symptoms										
Fatigue	14	8.34	-5.56	34.23	(-11.43, 28.1)	19	-1.17	0	24.82	(-13.13, 10.79)
Nausea and vomiting	14	9.52	0	21.4	(-2.83, 21.88)	19	3.51	0	11.89	(-2.22, 9.24)
Pain	14	7.14	0	29.03	(-9.62, 23.9)	19	-2.63	0	31.56	(-17.84, 12.58)
Dyspnoea	14	14.29	0	25.2	(-0.26, 28.84)	19	-7.02	0	23.78	(-18.48, 4.44)

Table 9. Change From Baseline by Cycle, for EORTC QLQ-C30 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	Standard Deviation	95% CI for Mean
Insomnia	14	-7.14	0	35.03	(-27.37, 13.08)	19	-10.53	0	33.43	(-26.64, 5.59)
Appetite loss	14	9.53	0	37.96	(-12.39, 31.44)	19	-1.76	0	34.2	(-18.24, 14.73)
Constipation	14	7.14	0	32.5	(-11.62, 25.91)	19	-8.77	0	24.45	(-20.56, 3.01)
Diarrhoea	14	16.67	0	31.35	(-1.44, 34.77)	19	-3.51	0	15.3	(-10.88, 3.86)
Financial difficulties	14	2.38	0	27.63	(-13.57, 18.33)	19	1.75	0	37.64	(-16.39, 19.89)
Change from Baseline Score at Cycle 12/Day 1										
Global health status / QoL										
Global QoL	9	-7.41	-8.34	21.02	(-23.56, 8.75)	17	-4.9	0	17.45	(-13.87, 4.07)
Functioning scales										
Cognitive functioning	9	-5.55	0	16.67	(-18.36, 7.26)	17	4.9	0	22.64	(-6.74, 16.54)
Emotional functioning	9	4.63	8.33	18.22	(-9.37, 18.63)	17	12.26	8.34	26.54	(-1.39, 25.9)
Physical functioning	9	-5.19	-6.67	19.94	(-20.51, 10.14)	17	-4.31	0	21.98	(-15.61, 6.99)
Role functioning	9	-3.7	0	21.69	(-20.38, 12.97)	17	1.96	0	36.74	(-16.93, 20.85)
Social functioning	9	-7.41	0	18.84	(-21.89, 7.07)	17	4.9	0	24.84	(-7.87, 17.67)
Symptoms										
Fatigue	9	1.24	0	20.37	(-14.42, 16.9)	17	0.65	0	23.72	(-11.55, 12.85)
Nausea and vomiting	9	5.56	0	14.43	(-5.54, 16.65)	17	4.9	0	16.42	(-3.54, 13.34)
Pain	9	7.41	0	23.73	(-10.84, 25.65)	17	0	0	31.73	(-16.32, 16.32)
Dyspnoea	9	7.41	0	22.22	(-9.67, 24.49)	17	-3.92	0	26.04	(-17.31, 9.47)
Insomnia	9	-3.7	0	26.06	(-23.73, 16.33)	17	-9.8	0	36.83	(-28.74, 9.13)
Appetite loss	9	-11.11	0	16.67	(-23.92, 1.7)	17	9.8	0	32.84	(-7.08, 26.69)
Constipation	9	3.7	0	30.93	(-20.07, 27.48)	17	-13.73	0	20.61	(-24.32, -3.13)
Diarrhoea	9	25.93	33.33	27.78	(4.57, 47.28)	17	-3.92	0	16.17	(-12.24, 4.39)
Financial difficulties	9	-3.7	0	20.03	(-19.1, 11.7)	17	-1.96	0	32.21	(-18.52, 14.6)
Change from Baseline Score at Cycle 13/Day 1										
Global health status / QoL										
Global QoL	7	-5.95	0	25.78	(-29.8, 17.89)	14	-10.12	-8.33	16.73	(-19.77, -0.46)
Functioning scales										
Cognitive functioning	7	-9.52	0	18.9	(-27,7.95)	14	11.91	0	23.95	(-1.93, 25.74)
Emotional functioning	7	7.14	8.33	19.5	(-10.89, 25.18)	14	19.05	16.67	28.58	(2.55, 35.55)
Physical functioning	7	-4.76	-13.33	36.25	(-38.29, 28.77)	14	-3.81	0	22.75	(-16.95, 9.33)
Role functioning	7	-11.9	0	34.31	(-43.64, 19.83)	14	15.48	8.34	38.38	(-6.68, 37.64)
Social functioning	7	-19.05	-33.33	36.55	(-52.85, 14.76)	14	4.76	0	26.5	(-10.53, 20.06)
Symptoms										
Fatigue	7	14.29	11.11	37.25	(-20.16, 48.74)	14	-2.38	0	26.21	(-17.52, 12.75)
Nausea and vomiting	7	9.52	0	13.11	(-2.6, 21.65)	14	3.57	0	16.25	(-5.81, 12.95)
Pain	7	2.38	0	24.4	(-20.18, 24.94)	14	-9.52	0	33.15	(-28.66, 9.62)

Table 9. Change From Baseline by Cycle, for EORTC QLQ-C30 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	Standard Deviation	95% CI for Mean
Dyspnoea	7	23.81	33.33	31.71	(-5.51, 53.13)	14	-4.76	0	25.68	(-19.59, 10.06)
Insomnia	7	-9.52	-33.33	31.7	(-38.84, 19.8)	14	-16.67	0	36.4	(-37.68, 4.35)
Appetite loss	7	4.76	0	23	(-16.51, 26.04)	14	2.38	0	35.72	(-18.24, 23.01)
Constipation	7	9.52	0	31.71	(-19.8, 38.85)	14	-19.05	0	25.2	(-33.6, -4.5)
Diarrhoea	7	19.05	33.33	32.53	(-11.04, 49.13)	14	2.38	0	24.33	(-11.67, 16.43)
Financial difficulties	7	4.76	0	29.99	(-22.97, 32.5)	14	-2.38	0	35.72	(-23.01, 18.24)
Change from Baseline Score at EOT_C30										
Global health status / QoL										
Global QoL	26	-13.46	-16.67	26.25	(-24.07, -2.86)	36	-1.85	0	24.73	(-10.22, 6.52)
Functioning scales										
Cognitive functioning	26	-10.26	0	28.7	(-21.85, 1.34)	37	-4.05	0	21.66	(-11.28, 3.17)
Emotional functioning	26	-8.33	0	24.61	(-18.27, 1.61)	37	6.31	0	30.77	(-3.95, 16.57)
Physical functioning	26	-7.69	-6.67	21.23	(-16.27, 0.88)	38	-8.6	-6.67	26.39	(-17.27, 0.08)
Role functioning	26	-16.03	-16.67	33.49	(-29.55, -2.5)	38	-1.75	0	35.89	(-13.55, 10.04)
Social functioning	26	-14.74	-8.34	32.77	(-27.98, -1.51)	37	-0.45	0	32.27	(-11.21, 10.31)
Symptoms										
Fatigue	26	16.24	22.22	24.79	(6.23, 26.26)	38	2.19	0	30.28	(-7.76, 12.15)
Nausea and vomiting	26	8.33	0	20.14	(0.2, 16.47)	38	-2.63	0	28.87	(-12.12, 6.86)
Pain	26	7.69	0	22.23	(-1.29, 16.67)	38	-2.63	0	35.63	(-14.34, 9.08)
Dyspnoea	26	2.56	0	38.79	(-13.1, 18.23)	38	-5.26	0	39.16	(-18.13, 7.61)
Insomnia	26	-17.95	0	42.41	(-35.08, -0.82)	37	-6.31	0	33.18	(-17.37, 4.76)
Appetite loss	26	15.39	0	37.98	(0.05, 30.73)	38	7.9	0	35.88	(-3.9, 19.69)
Constipation	26	10.26	0	29.47	(-1.65, 22.16)	37	-9.01	0	32.06	(-19.7, 1.68)
Diarrhoea	26	12.82	0	36.61	(-1.97, 27.61)	37	-2.7	0	19.84	(-9.32, 3.91)
Financial difficulties	26	2.56	0	28.16	(-8.81, 13.94)	36	1.85	0	33.75	(-9.57, 13.27)

Higher score on functioning or global health status/QoL scales = better functioning or QoL. Range of score by domain/symptom is (-100, 100). Higher score on symptoms scale = higher symptomology or more problems. 95% CI of mean absolute score is truncated to be in (0, 100). Sample size for treatment 1 and treatment 2 should be ≥6.
CI = confidence interval; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = end of treatment; QoL = quality of life; N = number of subjects in treatment group, SD = standard deviation.

Table 10. Change From Baseline by Cycle, for EORTC QLQ-LC-13 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	SD	95% CI for Mean
Change from Baseline Score at Cycle 2/Day 1										
Cough	48	-2.78	0	26.48	(-10.47, 4.91)	52	-7.69	0	26.91	(-15.18, -0.2)
Haemoptysis	48	0	0	13.75	(-3.99, 3.99)	52	0	0	9.33	(-2.6, 2.6)
Dyspnoea	46	0.72	0	18.95	(-4.9, 6.35)	51	-8.93	0	22.56	(-15.28, -2.59)
Sore mouth	49	15.65	0	27.3	(7.8, 23.49)	51	8.5	0	20.92	(2.61, 14.38)
Dysphagia	49	6.8	0	25.44	(-0.5, 14.11)	52	-0.64	0	22.37	(-6.87, 5.59)
Peripheral neuropathy	49	16.33	0	26.46	(8.73, 23.93)	52	17.95	16.67	36.43	(7.81, 28.09)
Alopecia	48	67.36	66.67	36.7	(56.7, 78.02)	52	69.23	66.67	32.23	(60.26, 78.21)
Chest pain	49	-4.76	0	21.52	(-10.94, 1.42)	52	-10.9	0	26.17	(-18.18, -3.61)
Arm/shoulder pain	49	-0.68	0	29.26	(-9.08, 7.72)	52	-0.64	0	32.67	(-9.74, 8.45)
Other pain	44	0	0	37.35	(-11.36, 11.36)	45	2.96	0	28.27	(-5.53, 11.46)
Any medicine for pain	22	3.03	0	32.38	(-11.33, 17.39)	25	5.33	0	31.45	(-7.65, 18.31)
Change from Baseline Score at Cycle 3/Day 1										
Cough	43	-8.53	0	30.94	(-18.05, 1)	46	-10.15	0	27.1	(-18.19, -2.1)
Haemoptysis	41	-1.63	0	12.8	(-5.67, 2.42)	46	2.9	0	9.5	(0.08, 5.72)
Dyspnoea	42	5.03	0	20.71	(-1.43, 11.48)	42	-7.94	0	23.32	(-15.2, -0.67)
Sore mouth	42	15.08	0	31.41	(5.29, 24.87)	45	8.15	0	19.01	(2.44, 13.86)
Dysphagia	43	8.53	0	26.32	(0.43, 16.63)	46	-0.72	0	17.9	(-6.04, 4.59)
Peripheral neuropathy	43	29.46	33.33	36.52	(18.22, 40.7)	46	21.01	0	40.59	(8.96, 33.07)
Alopecia	43	71.32	100	38.2	(59.56, 83.07)	44	66.67	100	41.92	(53.92, 79.41)
Chest pain	42	-8.73	0	23.35	(-16.01, -1.45)	46	-13.77	0	23.91	(-20.87, -6.67)
Arm/shoulder pain	43	-0.78	0	30.42	(-10.14, 8.59)	46	-8.7	0	29.34	(-17.41, 0.02)
Other pain	39	2.56	0	39.28	(-10.17, 15.3)	42	-1.59	0	39.61	(-13.93, 10.76)
Any medicine for pain	19	7.02	0	36.14	(-10.4, 24.44)	18	-1.85	0	44.97	(-24.22, 20.51)
Change from Baseline Score at Cycle 4/Day 1										
Cough	35	-1.9	0	31.25	(-12.64, 8.83)	47	-9.93	0	22.96	(-16.67, -3.19)
Haemoptysis	34	-2.94	0	12.63	(-7.35, 1.46)	47	2.13	0	10.78	(-1.04, 5.29)
Dyspnoea	34	4.57	0	17.75	(-1.62, 10.77)	44	-1.26	0	22.64	(-8.15, 5.62)
Sore mouth	35	17.14	0	33.7	(5.57, 28.72)	46	7.25	0	22.13	(0.68, 13.82)
Dysphagia	35	2.86	0	20.41	(-4.15, 9.87)	47	-3.55	0	15.9	(-8.21, 1.12)
Peripheral neuropathy	35	38.1	33.33	42.12	(23.63, 52.56)	47	24.82	33.33	35.76	(14.32, 35.32)
Alopecia	35	65.71	66.67	37.47	(52.84, 78.59)	44	58.33	66.67	43.21	(45.2, 71.47)
Chest pain	34	-4.9	0	28.58	(-14.87, 5.07)	47	-10.64	0	27.89	(-18.83, -2.45)
Arm/shoulder pain	35	-0.95	0	27.4	(-10.36, 8.46)	46	-3.62	0	32.38	(-13.24, 5.99)
Other pain	32	-1.04	0	35.4	(-13.81, 11.72)	40	-0.83	0	44.33	(-15.01, 13.34)
Any medicine for pain	14	2.38	0	42.29	(-22.04, 26.8)	21	4.76	0	35.41	(-11.36, 20.88)

Table 10. Change From Baseline by Cycle, for EORTC QLQ-LC-13 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	SD	95% CI for Mean
Change from Baseline Score at Cycle 5/Day 1										
Cough	31	-9.68	0	28.79	(-20.24, 0.88)	37	-5.41	0	22.92	(-13.05, 2.24)
Haemoptysis	31	-3.23	0	15.76	(-9.01, 2.56)	37	2.7	0	14.44	(-2.11, 7.52)
Dyspnoea	31	1.79	0	19.05	(-5.2, 8.78)	36	-1.85	0	21.98	(-9.29, 5.59)
Sore mouth	31	17.2	0	37.39	(3.49, 30.92)	36	10.19	0	24.97	(1.74, 18.63)
Dysphagia	30	1.11	0	25.5	(-8.41, 10.63)	37	0	0	15.71	(-5.24, 5.24)
Peripheral neuropathy	31	41.94	33.34	46.32	(24.94, 58.93)	37	27.93	33.33	39.69	(14.7, 41.16)
Alopecia	31	54.84	66.67	45.99	(37.97, 71.71)	34	60.78	100	46.04	(44.72, 76.85)
Chest pain	31	-10.75	0	23.39	(-19.33, -2.17)	37	-10.81	0	23.64	(-18.69, -2.93)
Arm/shoulder pain	31	-6.45	0	26.41	(-16.14, 3.24)	37	-4.51	0	31.59	(-15.04, 6.03)
Other pain	29	-1.15	0	36.17	(-14.91, 12.61)	34	-2.94	0	54.66	(-22.01, 16.13)
Any medicine for pain	13	2.57	0	39.59	(-21.36, 26.49)	15	4.45	0	37.52	(-16.33, 25.22)
Change from Baseline Score at Cycle 6/Day 1										
Cough	27	-7.41	0	28.24	(-18.58, 3.76)	32	-8.33	0	22.4	(-16.41, -0.26)
Haemoptysis	27	-1.23	0	11.25	(-5.69, 3.22)	32	2.08	0	11.79	(-2.17, 6.33)
Dyspnoea	26	7.27	11.11	23.3	(-2.14, 16.68)	30	1.11	0	19.43	(-6.15, 8.37)
Sore mouth	26	12.82	0	32.77	(-0.41, 26.05)	32	4.17	0	20.3	(-3.15, 11.49)
Dysphagia	26	5.13	0	29.35	(-6.73, 16.98)	32	3.13	0	19.6	(-3.94, 10.19)
Peripheral neuropathy	27	48.15	66.67	44.66	(30.48, 65.82)	32	39.58	33.33	36.36	(26.48, 52.69)
Alopecia	26	66.67	100	41.1	(50.07, 83.27)	31	56.99	66.67	44.88	(40.53, 73.45)
Chest pain	26	-8.97	0	25.92	(-19.44, 1.5)	32	-12.5	0	18.45	(-19.15, -5.85)
Arm/shoulder pain	27	-6.17	0	26.21	(-16.54, 4.19)	32	-15.63	0	32.77	(-27.44, -3.81)
Other pain	25	1.33	0	39.06	(-14.79, 17.46)	29	-4.6	0	43.39	(-21.1, 11.91)
Any medicine for pain	13	7.69	0	33.76	(-12.71, 28.09)	12	-2.78	0	36.12	(-25.73, 20.17)
Change from Baseline Score at Cycle 7/Day 1										
Cough	26	-6.41	0	31.3	(-19.05, 6.23)	29	-6.9	0	22.5	(-15.45, 1.66)
Haemoptysis	25	-4	0	14.66	(-10.05, 2.05)	29	2.3	0	12.38	(-2.41, 7.01)
Dyspnoea	25	4.45	0	27.78	(-7.02, 15.91)	27	1.23	0	22.92	(-7.84, 10.3)
Sore mouth	26	15.38	0	32.97	(2.07, 28.7)	29	5.75	0	17.97	(-1.09, 12.58)
Dysphagia	26	3.85	0	27.21	(-7.14, 14.83)	28	1.19	0	19.21	(-6.26, 8.64)
Peripheral neuropathy	26	43.59	33.33	42.97	(26.23, 60.94)	29	43.68	33.33	37.91	(29.26, 58.1)
Alopecia	26	38.46	16.67	49.61	(18.42, 58.5)	28	36.9	0	47.44	(18.51, 55.3)
Chest pain	26	-12.82	0	25.08	(-22.95, -2.69)	28	-13.09	0	20.96	(-21.22, -4.97)
Arm/shoulder pain	26	-5.13	0	29.35	(-16.98, 6.73)	29	-4.6	0	29.17	(-15.7, 6.5)
Other pain	26	-2.56	0	41.01	(-19.13, 14)	25	6.67	0	39.68	(-9.71, 23.04)
Any medicine for pain	11	12.12	0	40.2	(-14.89, 39.13)	10	3.34	0	33.15	(-20.38, 27.05)

Table 10. Change From Baseline by Cycle, for EORTC QLQ-LC-13 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	SD	95% CI for Mean
Change from Baseline Score at Cycle 8/Day 1										
Cough	20	-6.67	0	31.71	(-21.51, 8.18)	27	-13.58	0	23.13	(-22.73, -4.43)
Haemoptysis	20	-1.67	0	7.45	(-5.15, 1.82)	27	0	0	9.24	(-3.66, 3.66)
Dyspnoea	20	0	0	21.63	(-10.12, 10.12)	26	2.14	0	19.38	(-5.69, 9.96)
Sore mouth	20	15	0	31.48	(0.27, 29.74)	27	2.47	0	12.83	(-2.61, 7.54)
Dysphagia	20	10	0	26.71	(-2.5, 22.5)	27	-3.7	0	14.12	(-9.29, 1.88)
Peripheral neuropathy	20	53.33	66.67	43.8	(32.84, 73.83)	27	39.51	33.33	39.26	(23.97, 55.04)
Alopecia	19	45.61	33.34	44.74	(24.05, 67.18)	27	40.74	0	49.21	(21.27, 60.21)
Chest pain	20	-5	0	19.57	(-14.16, 4.16)	27	-11.11	0	24.46	(-20.79, -1.43)
Arm/shoulder pain	20	-8.33	0	37.27	(-25.78, 9.11)	26	-3.85	0	27.21	(-14.84, 7.14)
Other pain	20	-15	0	39.7	(-33.58, 3.58)	24	-2.78	0	40.43	(-19.85, 14.29)
Any medicine for pain	10	3.33	0	36.68	(-22.91, 29.58)	13	5.13	0	32.9	(-14.75, 25.01)
Change from Baseline Score at Cycle 9/Day 1										
Cough	16	0	0	29.81	(-15.89, 15.89)	23	-8.69	0	18.03	(-16.49, -0.9)
Haemoptysis	16	0	0	0	(., .)	23	-1.45	0	6.95	(-4.45, 1.56)
Dyspnoea	16	5.56	5.56	25.34	(-7.94, 19.06)	21	0.53	0	18.75	(-8.01, 9.06)
Sore mouth	16	8.33	0	14.91	(0.39, 16.28)	23	4.35	0	18.27	(-3.55, 12.25)
Dysphagia	16	2.08	0	19.12	(-8.11, 12.27)	23	-4.35	0	15.26	(-10.94, 2.25)
Peripheral neuropathy	15	44.45	66.67	46.58	(18.65, 70.24)	23	46.38	33.34	42.33	(28.07, 64.68)
Alopecia	16	29.17	0	45.34	(5.01, 53.33)	23	27.54	0	47.83	(6.85, 48.22)
Chest pain	16	-8.33	0	19.24	(-18.59, 1.92)	23	-8.7	0	27	(-20.37, 2.98)
Arm/shoulder pain	16	-12.5	0	23.96	(-25.27, 0.27)	23	-10.15	0	30.87	(-23.5, 3.2)
Other pain	13	15.39	0	29.24	(-2.28, 33.05)	20	6.67	0	55.78	(-19.44, 32.77)
Change from Baseline Score at Cycle 10/Day 1										
Cough	15	6.67	0	38.21	(-14.5, 27.83)	20	-8.33	0	21.29	(-18.3, 1.63)
Haemoptysis	15	0	0	0	(., .)	20	-1.67	0	7.45	(-5.15, 1.82)
Dyspnoea	15	5.93	0	23.71	(-7.2,19.06)	19	0.58	0	22.67	(-10.35, 11.51)
Sore mouth	15	17.78	0	35.34	(-1.79,37.35)	20	8.33	0	21.29	(-1.63, 18.3)
Dysphagia	15	15.56	0	24.77	(1.84, 29.28)	20	0	0	24.18	(-11.32, 11.32)
Peripheral neuropathy	15	42.22	33.33	49.55	(14.78, 69.66)	20	38.33	33.33	44.95	(17.3, 59.37)
Alopecia	15	33.33	0	45.43	(8.18, 58.49)	20	6.67	0	27.78	(-6.34, 19.67)
Chest pain	15	-8.89	0	23.46	(-21.88, 4.1)	20	-8.33	0	30.35	(-22.54, 5.87)
Arm/shoulder Pain	15	-15.56	0	24.78	(-29.28, -1.84)	20	-5	0	39.4	(-23.44, 13.44)
Other pain	14	0	0	39.23	(-22.65, 22.65)	17	3.92	0	48.42	(-20.98, 28.82)
Any medicine for pain	8	8.34	0	34.5	(-20.51, 37.18)	8	-8.34	0	29.55	(-33.04, 16.37)
Change from Baseline Score at Cycle 11/Day 1										
Cough	14	2.38	0	38.04	(-19.58, 24.34)	19	-3.51	0	18.91	(-12.62, 5.6)

Table 10. Change From Baseline by Cycle, for EORTC QLQ-LC-13 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	SD	95% CI for Mean
Haemoptysis	14	0	0	0	(., .)	19	-1.75	0	7.65	(-5.44, 1.93)
Dyspnoea	14	6.35	0	15.54	(-2.62, 15.32)	18	-0.62	0	15.93	(-8.54, 7.3)
Sore mouth	14	21.43	0	38.36	(-0.72, 43.58)	19	7.02	0	17.84	(-1.58, 15.62)
Dysphagia	14	16.67	16.67	25.32	(2.05, 31.28)	19	-5.26	0	12.49	(-11.28, 0.76)
Peripheral neuropathy	13	48.72	33.33	44.34	(21.92, 75.51)	19	38.6	33.33	35.6	(21.44, 55.75)
Alopecia	13	15.38	0	32.25	(-4.1, 34.87)	18	11.11	0	37.92	(-7.75, 29.97)
Chest pain	14	2.38	0	33.24	(-16.81, 21.57)	19	-10.53	0	22.37	(-21.31, 0.25)
Arm/shoulder pain	13	-2.57	0	34.59	(-23.47, 18.34)	19	-10.53	0	29.51	(-24.75, 3.7)
Other pain	13	25.64	0	33.76	(5.24, 46.04)	16	8.33	0	49.44	(-18.01, 34.68)
Any medicine for pain	8	-16.67	-16.67	30.86	(-42.47, 9.13)	7	4.76	0	23	(-16.51, 26.04)
Change from Baseline Score at Cycle 12/Day 1										
Cough	9	-3.71	0	35.14	(-30.71, 23.3)	17	0	0	26.35	(-13.55, 13.55)
Haemoptysis	9	0	0	0	(., .)	17	-1.96	0	8.08	(-6.12, 2.2)
Dyspnoea	9	3.7	0	17.57	(-9.8, 17.21)	17	0.65	0	19.03	(-9.13, 10.44)
Sore mouth	9	11.11	0	23.57	(-7.01, 29.23)	17	5.88	0	13.1	(-0.85, 12.62)
Dysphagia	9	0	0	0	(., .)	17	-3.92	0	23.22	(-15.86, 8.02)
Peripheral neuropathy	8	58.33	66.67	42.73	(22.61, 94.05)	17	43.14	33.33	43.73	(20.66, 65.62)
Alopecia	9	11.11	0	23.57	(-7.01, 29.23)	17	3.92	0	26.04	(-9.47, 17.31)
Chest pain	9	-7.41	0	14.7	(-18.7, 3.89)	16	-18.75	0	24.25	(-31.67, -5.83)
Arm/shoulder pain	9	0	0	16.67	(-12.81, 12.81)	17	-3.92	0	30.92	(-19.82, 11.97)
Other pain	9	14.81	0	24.22	(-3.8, 33.43)	15	13.33	0	46.8	(-12.59, 39.25)
Change from Baseline Score at Cycle 13/Day 1										
Cough	7	9.52	0	37.09	(-24.78, 43.83)	14	-4.76	0	12.11	(-11.75, 2.23)
Haemoptysis	7	4.76	0	12.6	(-6.89, 16.41)	14	-2.38	0	8.91	(-7.52, 2.76)
Dyspnoea	7	17.46	22.22	15.53	(3.1, 31.82)	14	-1.59	0	18.42	(-12.22, 9.05)
Sore mouth	7	9.52	0	25.2	(-13.78, 32.83)	14	2.38	0	15.82	(-6.75, 11.51)
Dysphagia	7	4.76	0	12.6	(-6.89, 16.41)	14	-2.38	0	24.33	(-16.43, 11.67)
Peripheral neuropathy	7	66.67	66.67	38.49	(31.07, 102.26)	14	38.1	33.33	36.65	(16.93, 59.26)
Alopecia	7	9.52	0	25.2	(-13.78, 32.83)	14	4.76	0	28.81	(-11.87, 21.4)
Chest pain	6	0	0	21.08	(-22.12, 22.13)	14	-16.67	0	25.32	(-31.29, -2.05)
Arm/shoulder pain	7	-4.76	0	23	(-26.04, 16.51)	14	-11.91	0	36.06	(-32.73, 8.92)
Other pain	7	4.76	0	48.8	(-40.37, 49.89)	12	5.55	0	48.89	(-25.51, 36.62)
Change from Baseline Score at EOT_L13										
Cough	25	-5.33	0	28.35	(-17.04, 6.37)	38	-5.26	0	28.5	(-14.63, 4.11)
Haemoptysis	25	-5.33	0	15.75	(-11.84, 1.17)	38	2.63	0	9.11	(-0.36, 5.63)
Dyspnoea	24	7.87	11.11	20.59	(-0.82, 16.56)	37	-2.1	0	32.06	(-12.79, 8.59)
Sore mouth	25	6.67	0	28.87	(-5.25, 18.58)	38	3.51	0	15.09	(-1.45, 8.47)

Table 10. Change From Baseline by Cycle, for EORTC QLQ-LC-13 (Intent to Treat)

	Axitinib (N=58)					Bevacizumab (N=60)				
	Sample Size	Mean	Median	SD	95% CI for Mean	Sample Size	Mean	Median	SD	95% CI for Mean
Dysphagia	25	4	0	27.76	(-7.46, 15.46)	38	0	0	25.7	(-8.45, 8.45)
Peripheral neuropathy	24	29.17	33.33	43.2	(10.93, 47.41)	38	25.44	16.67	46.13	(10.27, 40.6)
Alopecia	25	30.67	0	46.07	(11.65, 49.68)	37	23.42	0	37.57	(10.9, 35.95)
Chest pain	25	14.67	0	30.55	(2.06, 27.28)	37	-9.91	0	36.74	(-22.16, 2.34)
Arm/shoulder pain	25	1.33	0	33.99	(-12.7, 15.37)	38	2.63	0	37.47	(-9.69, 14.95)
Other pain	24	11.11	0	42.47	(-6.82, 29.04)	35	2.86	0	44.55	(-12.45, 18.16)
Any medicine for pain	12	-5.56	0	31.25	(-25.41, 14.3)	17	1.96	0	34.3	(-15.68, 19.6)

Higher score on functioning or global health status/QoL scales = better functioning or QoL. Range of score by domain/symptom is (-100, 100). Higher score on symptoms scale = higher symptomology or more problems. 95% CI of mean absolute score is truncated to be in (0, 100). Sample size for treatment 1 and treatment 2 should be ≥6.
CI = confidence interval; EORTC QLQ-LC-13 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-supplement module for Lung Cancer-13; EOT = end of treatment; QoL = quality of life; N = number of subjects in treatment group, SD = standard deviation.

Pharmacodynamic Results:

Plasma Levels of VEGF-A, soluble vascular endothelial growth factor receptor (sVEGFR)-2, sVEGFR-3, and sKIT, at Baseline, and Ratios to Baseline: Baseline plasma protein concentrations and ratios to Baseline at each time point are summarized for the axitinib and bevacizumab groups in Table 11 and Table 12, respectively.

Table 11. Summary of Levels of Soluble Protein Biomarkers and Ratios to Baseline by Timepoint: Axitinib

Variable	Axitinib (N=57)								
	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C7D1	C9D1	C11D1
SKIT (pg/mL)									
n	52	42	41	40	32	27	18	12	11
Mean	49740.29	53095.48	52979.39	53817.75	56961.41	58305	50701.11	48680.42	49251.82
STD	16998.69	18233.85	18018.73	19638.72	20828.07	20311.85	17927.98	14791.32	19469.45
Ratio to Baseline (SKIT)[a]									
n	-	42	41	40	32	27	18	12	11
Mean	-	1.06	1.06	1.09	1.13	1.14	1.06	0.99	0.95
STD	-	0.19	0.18	0.20	0.25	0.28	0.22	0.26	0.20
VEGF (pg/mL)	-								
n	50	40	39	39	30	25	18	12	11
Mean	95.14	117.08	127.46	148.06	197.16	184.77	226.62	273.17	339.86
STD	66.6	98.05	128.06	159.8	282.49	175.32	202.53	207.22	303.71
Ratio to Baseline (VEGF) [a]									
n	-	40	39	39	30	25	18	12	11
Mean	-	1.48	1.51	1.73	2.33	2.8	2.78	3.72	3.41
STD	-	0.96	1.11	1.67	3.63	2.86	2.5	3.1	1.93
VEGFR2 (pg/mL)									
n	52	42	41	40	32	27	18	12	11
Mean	9587.31	7828.1	7477.8	7058.5	6885.94	6565.93	6401.11	6291.67	5696.36
STD	1570.27	1959.39	2146.89	2037.12	1754.19	1755.75	2360.24	2235.24	2724.57
Ratio to Baseline (VEGFR2) [a]									
n	-	42	41	40	32	27	18	12	11
Mean	-	0.81	0.77	0.72	0.69	0.68	0.62	0.59	0.53
STD	-	0.17	0.19	0.17	0.17	0.19	0.20	0.15	0.19
VEGFR3 (pg/mL)									
n	52	42	41	40	32	27	18	12	11
Mean	44390.77	33684.29	35780.49	34147	19730.94	17452.59	17896.67	21449.17	22332.73
STD	75118.17	52617.02	68287.68	74220.3	9237.69	8614.99	8360.82	12806.75	12408.37
Ratio to Baseline (VEGFR3) [a]									
n	-	42	41	40	32	27	18	12	11
Mean	-	0.85	0.83	0.74	0.73	0.67	0.68	0.74	0.86
STD	-	0.28	0.25	0.27	0.28	0.23	0.26	0.37	0.52

Only biomarker evaluable subjects with soluble protein Baseline data >0 are shown.
C = Cycle; D = Day; N = number of participants analyzed; n = participants evaluated at specific time point for each group; SKIT = soluble v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; STD = standard deviation; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.
a. Baseline was Cycle 1 Day 1 result.

Table 12. Summary of Levels of Soluble Protein Biomarkers and Ratios to Baseline by Timepoint: Bevacizumab

Variable	Bevacizumab (N=58)								
	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C7D1	C9D1	C11D1
SKIT (pg/mL)									
n	47	36	43	38	38	34	23	16	13
Mean	49544.15	55801.39	55729.65	65634.14	72671.32	68677.21	75547.61	65990.78	66920.38
STD	14803.62	22058.63	21476.66	27097.91	33207.22	30073.83	24458.54	17003.08	12261.25
Ratio to Baseline (SKIT)[a]									
n	-	36	43	38	38	34	23	16	13
Mean	-	1.1	1.13	1.27	1.39	1.33	1.39	1.2	1.23
STD	-	0.21	0.23	0.27	0.39	0.43	0.32	0.27	0.21
VEGF (pg/mL)									
n	48	37	43	38	38	34	23	16	13
Mean	121.83	287.19	324.33	368.23	405.13	400.16	433.3	422.38	449.92
STD	141.22	171.77	153.65	151.2	173.86	165.69	172.14	157.76	144.5
Ratio to Baseline (VEGF)[a]									
n	-	37	43	38	38	34	23	16	13
Mean	-	4.03	4.41	4.67	5.59	5.38	5.5	6.1	6.77
STD	-	3.68	3.42	3.29	4.13	3.19	2.94	2.84	3.91
VEGFR2 (pg/mL)									
n	48	37	43	38	38	34	23	16	13
Mean	9995	10781.35	10330	10129.47	9934.21	10140.59	10339.57	9421.25	9222.31
STD	2185.61	2311.9	2511.23	2244.65	1785.78	2056.4	1897.95	2446.42	2727.04
Ratio to Baseline (VEGFR2)[a]									
n	-	37	43	38	38	34	23	16	13
Mean	-	1.09	1.04	1.02	1.01	1.05	1	0.88	0.91
STD	-	0.16	0.13	0.16	0.17	0.18	0.17	0.18	0.25
VEGFR3 (pg/mL)									
n	48	37	43	38	38	34	23	16	13
Mean	24718.33	17693.51	17798.37	15901.32	16307.37	16381.47	15626.3	14733.44	16048.46
STD	12494.07	9679.53	9710.23	8062.41	7409.61	6707.41	8873.31	6441.61	7064.47
Ratio to Baseline (VEGFR3)[a]									
n	-	37	43	38	38	34	23	16	13
Mean	-	0.75	0.72	0.68	0.7	0.73	0.67	0.65	0.76
STD	-	0.29	0.2	0.21	0.24	0.24	0.24	0.16	0.38

Only biomarker evaluable subjects with soluble protein Baseline data >0 are shown.
C = Cycle; D = Day; N = number of participants analyzed; n = participants evaluated at specific time point for each group; SKIT = soluble v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; STD = standard deviation; VEGFR = vascular endothelial growth factor receptor.
a. Baseline is Cycle 1 Day 1 result.

Plasma Levels of CECs at Baseline, and Ratios to Baseline: Baseline CEC values and ratios to Baseline at each time point are summarized for the axitinib and bevacizumab groups in Table 13 and Table 14, respectively.

Table 13. Summary of Levels of CEC Biomarkers and Ratios to Baseline by Timepoint: Axitinib

Variable	Axitinib (N=58)								
	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C7D1	C9D1	C11D1
Total CEC (cells/mL)									
n	39	27	32	24	20	18	11	7	6
Mean	46815.38	11780.15	29229.09	19517.5	24556.05	28266.22	71770.91	58680	116620.8
STD	131531.755	13127.85	55725	19793.72	22434.01	39480.21	94182.03	78138.79	129577.3
Ratio to Baseline (Total CEC)[a]									
n	-	27	32	24	20	18	11	7	6
Mean	-	4.78	5.08	2.24	3.65	4.18	22.95	26.68	19.34
STD	-	12.275	12.739	3.485	4.627	5.234	38.798	57.232	23.629
pVEGFR2+ (FIU)									
n	50	38	41	33	25	24	16	12	10
Mean	1936317.98	1822096	1767065	1715569	1472448	2208802	1405048	2280990	1828225
STD	1252665.9	1678888	1442193	1515662	970463.3	3098289	879770.9	1050679	1179020
Ratio to Baseline (pVEGFR2+)[a]									
n	-	38	41	33	25	24	16	12	10
Mean	-	1.68	1.26	1.11	1.02	1.06	0.84	1.85	0.87
STD	-	3.373	1.272	0.951	1.021	0.789	0.529	1.303	0.625
VEGFR2+ (FIU)									
n	50	38	41	33	25	24	16	12	10
Mean	1694522.56	1634957	1597042	1443987	1181667	1371956	1028231	1485820	1573299
STD	1534520.504	1285333	865675.1	843071.9	673860.4	948166.9	495059.4	953884.3	1152156
Ratio to Baseline (VEGFR2+)[a]									
n	-	38	41	33	25	24	16	12	10
Mean	-	1.64	1.6	1.51	1.32	1.3	1.23	2.02	1.68
STD	-	2.733	1.746	2.031	2.558	1.708	1.301	1.663	1.584
pPDGFRB+ (FIU)									
n	50	38	41	33	25	24	16	12	10
Mean	1646702.34	1253894	1395312	1470449	1046446	2253115	1380133	2172540	1580029
STD	1482336.244	894629.3	1111766	841336.4	588769.4	3314987	1002148	2323386	927582.4
Ratio to Baseline (pPDGFRB+)[a]									
n	-	38	41	33	25	24	16	12	10
Mean	-	1.09	1.32	1.49	0.92	1.42	1.07	2.03	0.87
STD	-	0.959	1.366	2.184	0.77	1.369	1.047	2.358	0.418
PDGFRB+ (FIU)									
n	50	38	41	33	25	24	16	12	10
Mean	1775826.12	1589914	1840678	1690163	1288625	1309640	1049351	1666414	1533606
STD	1485762.54	985828.9	1315689	1064816	641546.3	975890.6	587546.1	1465165	1258734
Ratio to Baseline (PDGFRB+)[a]									
n	-	38	41	33	25	24	16	12	10

Table 13. Summary of Levels of CEC Biomarkers and Ratios to Baseline by Timepoint: Axitinib

Variable	Axitinib (N=58)								
	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C7D1	C9D1	C11D1
Mean	-	1.35	1.64	1.52	1.32	1.34	1.07	1.92	1.47
STD	-	1.289	1.573	1.681	1.573	1.732	0.918	1.885	1.647

Only biomarker evaluable subjects with CEC Baseline data >0 were shown.
C = Cycle; D = Day; CEC = circulating endothelial cells; FIU = flourescent intensity unit; N = number of participants analyzed; PDGFR = platelet-derived growth factor receptor pPDGFRB+ = p-β-type platelet-derived growth factor receptor; pVEGFR2 = plasma-vascular endothelial growth factor receptor-2; STD = standard deviation; VEGFR = vascular endothelial growth factor receptor.
a. Baseline was Cycle 1 Day 1 result.

Table 14. Summary of Levels of CEC Biomarkers and Ratios to Baseline by Timepoint: Bevacizumab

Variable	Bevacizumab (N=59)								
	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C7D1	C9D1	C11D1
Total CEC (cells/mL)									
n	37	29	28	30	27	23	14	7	6
Mean	16960.41	21882.41	40507.36	25215.7	41944.59	37468.13	36964.36	107978.14	120847.67
STD	25527.526	67578.781	82161.06	42932.747	70239.938	82647.38	60577.084	206314.489	140674.394
Ratio to Baseline (Total CEC)[a]									
n	-	29	28	30	27	23	14	7	6
Mean	-	3.35	10.94	9.02	4.41	5.54	5.7	10.13	9.7
STD	-	7.913	31.078	22.389	6.406	10.516	8.065	11.484	10.21
pVEGFR2+ (FIU)									
n	42	37	35	34	32	26	16	11	9
Mean	1764577.67	1810049.32	2090673.6	1578940.53	1815402.16	1794843.58	1634128	2283985	2354939.11
STD	1331540.549	1330590.809	1659128.892	1274415.109	1263516.73	1458412.725	1443612.089	1093158.76	1116283.011
Ratio to Baseline (pVEGFR2+)[a]									
n	-	37	35	34	32	26	16	11	9
Mean	-	1.39	1.79	1.35	1.33	1.19	1.3	1.35	1.21
STD	-	1.377	1.771	1.508	1.153	1.17	2.005	1.109	0.633
VEGFR2+ (FIU)									
n	42	37	35	34	32	25	16	11	9
Mean	1841618.36	1740268.05	1444404.94	1504595.71	1259913.44	1447188.88	1317560.13	1476621	1332064.78
STD	1300088.201	1444881.394	1097875.465	1163469.112	765707.741	885864.695	720095.027	1688887.819	668964.428
Ratio to Baseline (VEGFR2+)[a]									
n	-	37	35	34	32	25	16	11	9
Mean	-	1.29	0.98	1.02	0.94	0.87	0.8	0.92	0.78
STD	-	1.273	0.711	0.764	0.872	0.533	0.434	1.058	0.461
pPDGFRB+ (FIU)									
n	42	37	35	34	32	26	16	11	9
Mean	1734853.24	1599671.65	1885684.31	1285439.44	1514713.97	2299459.38	2163313.88	2225289.18	3127640.22
STD	1485338.326	1669690.889	1356916.305	1083860.541	1150805.01	5140939.706	3720352.717	1126401.528	2817719.865
Ratio to Baseline (pPDGFRB+)[a]									
n	-	37	35	34	32	26	16	11	9
Mean	-	1.54	1.82	1.06	1.22	1.85	2.24	1.51	2.05
STD	-	2.659	2.036	1.077	1.239	3.75	5.44	1.054	1.538
PDGFRB+ (FIU)									
n	42	37	35	34	32	26	16	11	9
Mean	3176459.69	1819988.05	1586256.17	1518360.71	1408366.91	1364500.5	1287039.25	1625161.64	1959067.11
STD	3222201.986	1807664.991	1092406.544	1286285.813	1013859.81	1058758.211	922009.811	1467355.491	1973194.943
Ratio to Baseline (PDGFRB+)[a]									
n	-	37	35	34	32	26	16	11	9

Table 14. Summary of Levels of CEC Biomarkers and Ratios to Baseline by Timepoint: Bevacizumab

Variable	Bevacizumab (N=59)								
	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C7D1	C9D1	C11D1
Mean	-	1.21	0.76	0.83	0.81	0.68	0.59	1.11	1.06
STD	-	2.3	0.67	0.935	0.841	0.583	0.541	1.731	1.067

Only biomarker evaluable subjects with CEC Baseline data >0 were shown.
C = Cycle; D = Day; CEC = circulating endothelial cells; FIU = flourescent intensity unit; N = number of participants analyzed; PDGFR = platelet-derived growth factor receptor pPDGFRB+ = p-β-type platelet-derived growth factor receptor; pVEGFR2 = plasma-vascular endothelial growth factor receptor-2; STD = standard deviation; VEGFR = vascular endothelial growth factor receptor.
a. Baseline was Cycle 1 Day 1 result.

In the bevacizumab group, results for comparison of soluble protein concentrations at Baseline, and of ratios to Baseline at each time point, between subjects having a response and those without a response are presented in Table 15.

Table 15. Comparison of Levels of Soluble Protein Biomarkers at Baseline, and of Ratios to Baseline at Each Timepoint, after Stratification by CR/PR vs SD/PD: Bevacizumab

Variable	CR or PR			PD or SD			p-Value[a]
	Mean	Median	n	Mean	Median	n	Wilcoxon Rank Sum Test
SKIT Baseline[b] (pg/mL)	56511.43	53930	21	40392.11	38710	19	0.0006
C1D15:C1D1	1.11	1.13	16	1.07	1.04	15	0.5192
C2D1:C1D1	1.15	1.17	19	1.13	1.07	18	0.6621
C3D1:C1D1	1.31	1.31	19	1.26	1.16	13	0.519
C4D1:C1D1	1.45	1.28	21	1.33	1.23	13	0.2954
C5D1:C1D1	1.35	1.24	20	1.31	1.22	9	0.9814
C7D1:C1D1	1.42	1.25	16	1.25	1.16	5	0.3962
C9D1:C1D1	1.23	1.14	12	1.01	0.96	3	-
C11D1:C1D1	1.27	1.25	10	1.01	1.01	2	-
VEGF Baseline[b] (pg/mL)	77.4	62.7	21	184.96	91.5	19	0.0285
C1D15:C1D1	4.26	3.4	16	3.59	2.71	15	0.7099
C2D1:C1D1	4.97	3.39	19	3.87	3.37	18	0.3602
C3D1:C1D1	5.81	4.27	19	3.26	2.3	13	0.0643
C4D1:C1D1	6.76	4.89	21	3.93	3.17	13	0.0598
C5D1:C1D1	5.78	5.00	20	4.67	5.09	9	0.6917
C7D1:C1D1	5.58	5.14	16	5.28	6.14	5	0.9027
C9D1:C1D1	6.48	7.15	12	5.29	6.1	3	-
C11D1:C1D1	6.92	6.13	10	7.27	7.27	2	-
VEGFR2 Baseline[b] (pg/mL)	10121.9	10200	21	9893.68	9440	19	0.5819
C1D15:C1D1	1.11	1.07	16	1.05	1.04	15	0.5708
C2D1:C1D1	1.05	1.03	19	1.03	1.05	18	0.7745
C3D1:C1D1	1.02	0.99	19	1.00	0.95	13	0.6759
C4D1:C1D1	1.01	1.02	21	1.00	0.99	13	0.8056
C5D1:C1D1	1.06	1.02	20	1.00	0.97	9	0.4999
C7D1:C1D1	1.01	0.97	16	0.98	1.06	5	0.9675
C9D1:C1D1	0.92	0.95	12	0.86	0.87	3	-
C11D1:C1D1	1.00	0.94	10	0.63	0.63	2	-
VEGFR3 Baseline[b] (pg/mL)	23935.24	20730	21	25319.47	25100	19	0.1591
C1D15:C1D1	0.85	0.71	16	0.65	0.66	15	0.1594
C2D1:C1D1	0.76	0.72	19	0.67	0.7	18	0.262
C3D1:C1D1	0.71	0.68	19	0.59	0.62	13	0.2288
C4D1:C1D1	0.68	0.65	21	0.70	0.76	13	0.7518
C5D1:C1D1	0.73	0.75	20	0.71	0.68	9	0.6917
C7D1:C1D1	0.72	0.71	16	0.51	0.48	5	0.1639
C9D1:C1D1	0.63	0.63	12	0.78	0.77	3	-
C11D1:C1D1	0.78	0.65	10	0.79	0.79	2	-

The Wilcoxon rank sum p-value was not produced when the sample size was small in any input group (N<5). Only biomarker evaluable subjects with response data and soluble protein Baseline data >0 are shown.
C = cycle; CR = complete response; D = day; N = number of participants analyzed; n = participants evaluated at specific time point for each group; PD = progressive disease; PR = partial response; SD = stable disease; SKIT = soluble v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; vs = versus.
a. Two-sided normal approximated p-value.
b. Baseline is Cycle 1 Day 1 result.

In the axitinib group, results for the analysis of PFS by median soluble protein levels at Baseline and by median ratios to Baseline are presented in Table 16.

In the bevacizumab group, results for comparison of soluble protein concentrations at Baseline, and of ratios to Baseline at each time point, between subjects having a response and those without a response are shown in Table 17.

In the bevacizumab group, results for the analysis of PFS after stratification by median CEC values at Baseline and by median ratios to Baseline are presented in Table 18.

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Table 16. Comparison of Kaplan-Meier PFS Curves After Stratification by Less Than or Greater Than or Equal to Median Levels of Soluble Proteins at Baseline, and of Ratios to Baseline at Each Timepoint: Axitinib

Variable	Median BM Value	Median PFS (Weeks)				Logrank p-Value	Hazard Ratio (95% CI)
		N	Less Than Median BM Value (95% CI)	N	Greater Than or Equal to Median BM Value (95% CI)		
SKIT Baseline[a] pg/mL	46780.00	26	25.0 (12.43, 42.29)	26	24.0 (12.14, 35.71)	0.8775	0.9476 (0.4770, 1.8826)
C1D15:C1D1	1.04	21	26.6 (7.43, 46.29)	21	25.0 (12.14, 35.71)	0.4240	1.3943 (0.6139, 3.1670)
C2D1:C1D1	1.09	20	24.0 (12.43, 32.71)	21	23.4 (11.14, 35.71)	0.6400	1.1995 (0.5583, 2.5770)
C3D1:C1D1	1.13	20	26.6 (12.14, 35.71)	20	25.0 (17.86, 42.29)	0.8065	1.1043 (0.4987, 2.4455)
C4D1:C1D1	1.07	16	32.4 (12.43, 46.29)	16	26.6 (23.43, 42.29)	0.6220	0.8004 (0.3296, 1.9434)
C5D1:C1D1	1.07	13	26.6 (13.86, 35.71)	14	36.0 (24.00, 66.29)	0.1452	0.4929 (0.1859, 1.3068)
C7D1:C1D1	1.00	9	-	9	-	-	-
C9D1:C1D1	1.02	6	-	6	-	-	-
C11D1:C1D1	0.93	5	-	6	-	-	-
VEGF Baseline[a] pg/mL	81.45	25	23.4 (7.43, 35.71)	25	25.0 (11.14, 36.00)	0.9859	0.9936 (0.4837, 2.0411)
C1D15:C1D1	1.30	20	26.6 (12.14, 42.29)	20	20.3 (7.43, 35.71)	0.9470	1.0263 (0.4774, 2.2062)
C2D1:C1D1	1.19	19	23.4 (12.14, 26.57)	20	32.4 (9.57, 36.00)	0.6172	0.8192 (0.3736, 1.7964)
C3D1:C1D1	1.27	19	25.0 (17.57, 52.86)	20	26.1 (12.43, 32.71)	0.2970	1.4955 (0.6967, 3.2104)
C4D1:C1D1	1.25	15	36.0 (24.00, NA)	15	23.4 (13.71, 35.71)	0.1357	1.9650 (0.7963, 4.8490)
C5D1:C1D1	1.75	12	25.0 (17.57, 36.00)	13	32.7 (23.43, 52.86)	0.6512	0.8063 (0.3152, 2.0623)
C7D1:C1D1	1.82	9	-	9	-	-	-
C9D1:C1D1	2.41	6	-	6	-	-	-
C11D1:C1D1	2.58	5	-	6	-	-	-
VEGFR2 Baseline[a] pg/mL	9385.00	26	24.0 (10.57, 36.00)	26	25.0 (12.43, 35.71)	0.3496	0.7217 (0.3625, 1.4369)
C1D15:C1D1	0.79	21	26.1 (10.57, 35.71)	21	32.4 (17.57, 66.29)	0.0696	0.4694 (0.2032, 1.0843)
C2D1:C1D1	0.78	20	13.9 (10.57, 35.71)	21	24.0 (17.57, 26.57)	0.6804	0.8502 (0.3917, 1.8451)
C3D1:C1D1	0.69	20	17.9 (11.14, 26.14)	20	32.4 (23.43, 66.29)	0.0187	0.3905 (0.1730, 0.8815)
C4D1:C1D1	0.71	16	32.7 (13.86, 36.00)	16	26.1 (20.29, 52.86)	0.5473	0.7485 (0.2904, 1.9288)
C5D1:C1D1	0.64	13	32.4 (17.86, 35.71)	14	36.0 (20.29, 66.29)	0.1707	0.4893 (0.1719, 1.3930)
C7D1:C1D1	0.59	9	-	9	-	-	-
C9D1:C1D1	0.54	6	-	6	-	-	-
C11D1:C1D1	0.49	5	-	6	-	-	-

Table 16. Comparison of Kaplan-Meier PFS Curves After Stratification by Less Than or Greater Than or Equal to Median Levels of Soluble Proteins at Baseline, and of Ratios to Baseline at Each Timepoint: Axitinib

Variable	Median BM Value	Median PFS (Weeks)				Logrank p-Value	Hazard Ratio (95% CI)
		N	Less Than Median BM Value (95% CI)	N	Greater Than or Equal to Median BM Value (95% CI)		
VEGFR3 Baseline[a] pg/mL	26405.00	26	32.4 (20.29, 52.86)	26	13.9 (7.43, 26.57)	0.0145	2.4130 (1.1623, 5.0092)
C1D15:C1D1	0.80	21	17.9 (10.57, 42.29)	21	32.4 (17.57, 52.86)	0.1380	0.5537 (0.2503, 1.2247)
C2D1:C1D1	0.83	20	13.7 (10.57, 24.00)	21	32.4 (17.57, 42.29)	0.0084	0.3475 (0.1532, 0.7882)
C3D1:C1D1	0.74	20	24.0 (12.14, 35.71)	20	32.4 (20.29, 66.29)	0.0677	0.4768 (0.2111, 1.0770)
C4D1:C1D1	0.71	16	26.1 (13.86, 36.00)	16	32.4 (20.29, NA)	0.2074	0.5518 (0.2161, 1.4090)
C5D1:C1D1	0.71	13	25.0 (17.86, 35.71)	14	42.3 (20.29, 66.29)	0.0131	0.2512 (0.0777, 0.8127)
C7D1:C1D1	0.72	9	-	9	-	-	-
C9D1:C1D1	0.61	6	-	6	-	-	-
C11D1:C1D1	0.71	5	-	6	-	-	-

Assuming proportional hazards, a hazard ratio >1 indicates a reduction in hazard rate in favor of less than median; a hazard ratio <1 indicates a reduction in hazard rate in favor of greater than or equal to Median.
The survival analyses were not produced when the sample size was small in any input group (N<10).
Only BM evaluable subjects with soluble protein baseline data >0 are shown.
BM = biomarker; C = cycle; CI = confidence interval; D = day; N = number of participants analyzed; NA = not applicable; PFS = progression-free survival; SKIT = soluble v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.
a. Baseline is Cycle 1 Day 1 result.

Table 17. Comparison of Levels of CEC Biomarkers at Baseline, and of Ratios to Baseline at Each Timepoint, After Stratification by CR/PR vs SD/PD: Bevacizumab

Variable	CR or PR			PD or SD			p-Value[a]
	Mean	Median	n	Mean	Median	n	Wilcoxon Rank Sum Test
Total CEC Baseline[b] (cells/mL)	16817.00	5552.00	13	16552.42	4446.00	19	0.8491
C1D15:C1D1	0.90	0.36	11	6	2.11	14	0.0511
C2D1:C1D1	12.63	0.96	11	13.3	3.07	12	0.2203
C3D1:C1D1	15.58	1.02	12	6.1	2.06	13	0.6480
C4D1:C1D1	2.84	1.55	11	6.5	2.62	12	0.1993
C5D1:C1D1	5.94	1.23	11	6.95	2.54	8	0.1899
C7D1:C1D1	6.17	1.88	9	5.78	6.05	4	-
C9D1:C1D1	10.13	6.92	7	-	-	-	-
C11D1:C1D1	11.38	7.53	5	1.3	1.3	1	-
pVEGFR2+ Baseline[b] (FIU)	2056684	2059533.5	16	1374872	1354859	21	0.0428
C1D15:C1D1	1.61	0.92	15	1.34	0.79	17	0.6807
C2D1:C1D1	1.27	0.81	14	2.18	1.23	16	0.1743
C3D1:C1D1	1.40	0.47	15	1.12	0.93	14	0.3345
C4D1:C1D1	1.07	0.73	14	1.65	1.04	14	0.4549
C5D1:C1D1	0.94	0.67	13	1.69	1.41	9	0.1395
C7D1:C1D1	1.37	0.56	11	1.2	1.18	4	-
C9D1:C1D1	1.02	1.23	9	2.86	2.86	2	-
C11D1:C1D1	1.04	0.95	8	2.52	2.52	1	-
VEGFR2+ Baseline[b] (FIU)	1918479.44	1817455.00	16	1880784.33	1382393.00	21	0.2009
C1D15:C1D1	1.00	0.66	15	1.36	0.59	17	0.9105
C2D1:C1D1	0.94	0.70	14	1.03	0.78	16	0.7574
C3D1:C1D1	0.90	0.49	15	1.04	0.8	14	0.5043
C4D1:C1D1	0.84	0.60	14	0.84	0.65	14	0.9456
C5D1:C1D1	0.85	0.90	12	0.78	0.69	9	0.8608
C7D1:C1D1	0.70	0.68	11	1.01	1.00	4	-
C9D1:C1D1	0.65	0.58	9	2.14	2.14	2	-
C11D1:C1D1	0.79	0.78	8	0.69	0.69	1	-
pPDGFRB+ Baseline[b] (FIU)	1697064.13	1633161.50	16	1430029.10	1349248.00	21	0.2224
C1D15:C1D1	1.37	0.62	15	1.92	0.76	17	0.6269
C2D1:C1D1	1.13	1.15	14	2.33	1.42	16	0.1743
C3D1:C1D1	1.04	0.74	15	1.25	0.98	14	0.1671
C4D1:C1D1	0.89	0.71	14	1.73	1.20	14	0.2516
C5D1:C1D1	0.94	0.64	13	3.68	0.66	9	0.4707
C7D1:C1D1	2.57	0.55	11	1.68	0.89	4	-
C9D1:C1D1	1.37	1.19	9	2.12	2.12	2	-
C11D1:C1D1	2.07	1.70	8	1.89	1.89	1	-
PDGFRB+ Baseline[b] (FIU)	2767538.13	2390408.00	16	3823320.29	2289152.00	21	0.8670
C1D15:C1D1	0.93	0.72	15	1.51	0.54	17	0.3718
C2D1:C1D1	0.61	0.55	14	0.73	0.48	16	0.8529
C3D1:C1D1	0.65	0.54	15	1.06	0.56	14	0.6503
C4D1:C1D1	0.69	0.55	14	1.02	0.60	14	0.8377
C5D1:C1D1	0.55	0.58	13	0.80	0.41	9	1.0000
C7D1:C1D1	0.62	0.42	11	0.51	0.53	4	-
C9D1:C1D1	0.60	0.50	9	3.43	3.43	2	-
C11D1:C1D1	1.06	0.77	8	1.03	1.03	1	-

Table 17. Comparison of Levels of CEC Biomarkers at Baseline, and of Ratios to Baseline at Each Timepoint, After Stratification by CR/PR vs SD/PD: Bevacizumab

Only biomarker evaluable subjects with response data and CEC baseline data >0 are shown.
The Wilcoxon rank sum p-value was not produced when the sample size was small in any input group (N<5).
C = cycle; CEC = circulating endothelial cell; CR = complete response; D = day; N = number of participants analyzed; n = participants evaluated at specific time point for each group; PD = progressive disease; PDGFR = platelet-derived growth factor receptor; pPDGFR = phosphorylated platelet-derived growth factor receptor; PR = partial response; pVEGFR = phosphor vascular endothelial growth factor receptor; SD = stable disease; VEGFR = vascular endothelial growth factor receptor.

a. Two-sided normal approximated p-value.
b. Baseline is Cycle 1 Day 1 result.

Table 18. Comparison of Kaplan-Meier PFS Curves After Stratification by Less Than or Greater Than or Equal to Median Levels of CEC Biomarkers at Baseline, and of Ratios to Baseline at Each Timepoint: Bevacizumab

Variable	Median BM Value	Median PFS (Weeks)				Logrank p-Value	Hazard Ratio (95% CI)
		N	Less Than Median BM Value (95% CI)	N	Greater Than or equal to Median BM Value (95% CI)		
Total CEC Baseline[a] (cells/mL)	5552.00	18	17.9 (11.57, 38.00)	19	24.9 (13.86, 34.43)	0.8789	0.9405 (0.4262, 2.0752)
C1D15:C1D1	1.32	14	26.0 (12.43, 40.86)	15	17.9 (11.57, 38.00)	0.1311	2.0770 (0.7890, 5.4680)
C2D1:C1D1	1.97	14	24.9 (6.43, 34.43)	14	17.9 (7.86, 42.14)	0.6706	0.8168 (0.3202, 2.0833)
C3D1:C1D1	0.97	15	25.1 (12.43, 42.14)	15	26.0 (12.29, 38.00)	0.4317	1.4653 (0.5599, 3.8349)
C4D1:C1D1	1.88	13	24.9 (12.29, 42.43)	14	26.0 (14.00, 42.14)	0.4892	0.7148 (0.2737, 1.8667)
C5D1:C1D1	1.83	11	34.4 (13.86, 48.14)	12	26.0 (14.00, 38.00)	0.2745	1.9727 (0.5724, 6.7985)
C7D1:C1D1	2.06	7	-	7	-	-	-
C9D1:C1D1	6.92	3	-	4	-	-	-
C11D1:C1D1	7.53	3	-	3	-	-	-
pVEGFR2+ Baseline[a] (FIU)	1365452.00	21	17.9 (11.57, 24.86)	21	37.3 (18.29, 42.14)	0.0061	0.3094 (0.1286, 0.7441)
C1D15:C1D1	0.79	18	26.4 (12.29, 37.29)	19	25.1 (12.43, 42.14)	0.9841	1.0084 (0.4405, 2.3086)
C2D1:C1D1	0.96	17	24.9 (6.29, 42.14)	18	18.1 (11.57, 34.43)	0.4074	1.4288 (0.6108, 3.3422)
C3D1:C1D1	0.76	17	26.4 (14.00, 40.86)	17	24.9 (13.86, 42.14)	0.9191	0.9553 (0.3933, 2.3199)
C4D1:C1D1	0.85	16	26.4 (14.00, 48.14)	16	26.0 (12.43, 38.00)	0.3665	1.5135 (0.6100, 3.7552)
C5D1:C1D1	0.71	13	26.4 (17.86, 48.14)	13	38.0 (13.86, 42.14)	0.8432	0.8981 (0.3102, 2.6005)
C7D1:C1D1	0.56	8	-	8	-	-	-
C9D1:C1D1	1.31	5	-	6	-	-	-
C11D1:C1D1	0.97	4	-	5	-	-	-
VEGFR2+ Baseline[a] (FIU)	1502255.00	21	18.1 (6.43, 34.43)	21	26.0 (14.00, 42.43)	0.2939	0.6641 (0.3068, 1.4371)
C1D15:C1D1	0.66	18	25.1 (13.86, 42.43)	19	26.0 (11.86, 38.00)	0.3686	1.4869 (0.6221, 3.5539)
C2D1:C1D1	0.76	17	26.0 (13.86, 48.14)	18	18.3 (11.57, 37.29)	0.3535	1.4938 (0.6355, 3.5115)
C3D1:C1D1	0.84	17	37.3 (13.86, 40.86)	17	25.6 (12.43, 34.43)	0.9054	1.0554 (0.4328, 2.5737)
C4D1:C1D1	0.65	16	34.4 (14.00, 42.43)	16	26.0 (12.43, 38.00)	0.2019	1.8597 (0.7045, 4.9090)
C5D1:C1D1	0.80	12	26.0 (13.86, 38.00)	13	42.1 (17.86, NA)	0.0353	0.2901 (0.0856, 0.9826)
C7D1:C1D1	0.75	8	-	8	-	-	-
C9D1:C1D1	0.58	5	-	6	-	-	-
C11D1:C1D1	0.72	4	-	5	-	-	-
pPDGFRB+ Baseline[a] (FIU)	1475282.50	21	14.0 (7.86, 26.00)	21	34.4 (18.14, 40.86)	0.2930	0.6676 (0.3121, 1.4280)
C1D15:C1D1	0.66	18	34.4 (14.00, 38.00)	19	18.3 (11.86, 40.86)	0.1630	1.8255 (0.7733, 4.3092)
C2D1:C1D1	1.30	17	24.9 (6.43, 40.86)	18	18.1 (11.57, 48.14)	0.9330	1.0372 (0.4430, 2.4286)

Table 18. Comparison of Kaplan-Meier PFS Curves After Stratification by Less Than or Greater Than or Equal to Median Levels of CEC Biomarkers at Baseline, and of Ratios to Baseline at Each Timepoint: Bevacizumab

Variable	Median BM Value	Median PFS (Weeks)				Logrank p-Value	Hazard Ratio (95% CI)
		N	Less Than Median BM Value (95% CI)	N	Greater Than or equal to Median BM Value (95% CI)		
C3D1:C1D1	0.80	17	37.3 (18.14, 42.43)	17	18.1 (12.43, 34.43)	0.0625	2.3394 (0.9299, 5.8853)
C4D1:C1D1	0.82	16	26.4 (14.00, 40.86)	16	26.0 (12.43, NA)	0.4686	0.7183 (0.2916, 1.7692)
C5D1:C1D1	0.61	13	40.9 (14.00, NA)	13	34.4 (18.14, 42.14)	0.5230	1.4431 (0.4659, 4.4700)
C7D1:C1D1	0.59	8	-	8	-	-	-
C9D1:C1D1	1.30	5	-	6	-	-	-
C11D1:C1D1	1.89	4	-	5	-	-	-
PDGFRB+ Baseline[a] (FIU)	2237507.50	21	24.9 (12.43, 40.86)	21	25.1 (12.29, 38.00)	0.5875	1.2414 (0.5660, 2.7225)
C1D15:C1D1	0.62	18	25.1 (12.29, 38.00)	19	24.9 (12.43, 40.86)	0.7671	1.1354 (0.4902, 2.6302)
C2D1:C1D1	0.54	17	18.3 (12.29, 37.29)	18	24.9 (11.57, 40.86)	0.5960	1.2606 (0.5338, 2.9766)
C3D1:C1D1	0.58	17	18.3 (13.86, 34.43)	17	37.3 (12.43, 48.14)	0.0731	0.4252 (0.1619, 1.1165)
C4D1:C1D1	0.50	16	30.4 (14.00, 42.43)	16	24.9 (12.43, 42.14)	0.4719	1.4040 (0.5529, 3.5652)
C5D1:C1D1	0.52	13	25.1 (14.00, 38.00)	13	37.3 (17.86, 42.14)	0.2180	0.5268 (0.1871, 1.4834)
C7D1:C1D1	0.46	8	-	8	-	-	-
C9D1:C1D1	0.55	5	-	6	-	-	-
C11D1:C1D1	0.83	4	-	5	-	-	-

Only BM evaluable subjects with CEC Baseline data >0 are shown.
Assuming proportional hazards, a hazard ratio >1 indicates a reduction in hazard rate in favor of less than median; a hazard ratio <1 indicates a reduction in hazard rate in favor of greater than or equal to median.
The survival analyses were not produced when the sample size was small in any input group (N<10).
BM = biomarker; C = cycle; CEC = circulating endothelial cell; CI = confidence interval; D = day; N = number of participants analyzed; NA = not applicable; PDGFR = platelet-derived growth factor receptor; PFS = progression-free survival; pPDGFR = phosphorylated platelet-derived growth factor receptor; pVEGFR = phosphor vascular endothelial growth factor receptor; SD = stable disease; VEGFR = vascular endothelial growth factor receptor.
a. Baseline is Cycle 1 Day 1 result.

Safety Results: Overall, the percentage of subjects with AEs (all causality and treatment-related) was similar between the treatment groups (Table 19) with 98.3% of subjects in each group reporting at least 1 AE (all-causality). However, the rate of Grade 3 or 4 AEs was higher for axitinib subjects than those in the bevacizumab group (84.5% and 62.7% of subjects in the axitinib and bevacizumab groups, respectively, experienced Grade 3 or 4 AEs). Similarly, the rate of temporary dose reductions or discontinuations due to AEs was higher among axitinib subjects.

Table 19. Summary of Treatment-Emergent Adverse Events (All Causality and Treatment Related)

	Number (%) of Subjects			
	Axitinib		Bevacizumab	
	All Causality	Treatment Related	All Causality	Treatment Related
Subjects evaluable for adverse events	58	58	59	59
Number of adverse events	744	403	645	346
Subjects with adverse events	57 (98.3)	55 (94.8)	58 (98.3)	54 (91.5)
Subjects with serious adverse events	31 (53.4)	16 (27.6)	19 (32.2)	14 (23.7)
Subjects with Grade 3 or 4 adverse events	49 (84.5)	41 (70.7)	37 (62.7)	28 (47.5)
Subjects with Grade 5 adverse events	14 (24.1)	3 (5.2)	6 (10.2)	2 (3.4)
Subjects who discontinued treatment due to adverse events	19 (32.8)	11 (19.0)	16 (27.1)	19 (15.3)
Subjects with dose reduced due to adverse events	16 (27.6)	13 (22.4)	2 (3.4)	1 (1.7)
Subjects with temporary discontinuation due to adverse events	32 (55.2)	28 (48.3)	23 (39.0)	21 (35.6)

AE and SAE results are not separated out. Included data up to 28 days after last dose of study drug.
Except for the number of adverse events subjects are counted only once per treatment in each row.
Grades: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening or disabling, 5 = Death
MedDRA (v14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; v = version.

Treatment-emergent non serious AEs (all causalities) experienced by ≥5% of subjects are presented in Table 20.

Table 20. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For ≥5% of Subjects

System Organ Class and MedDRA (v15.1) Preferred Term	Axitinib (N=58) n (%)	Bevacizumab (N=59) n (%)
With adverse events	54 (93.1)	58 (98.3)
Blood and lymphatic system disorders	25 (43.1)	24 (40.7)
Anaemia	12 (20.7)	15 (25.4)
Leukopenia	7 (12.1)	5 (8.5)
Neutropenia	18 (31.0)	15 (25.4)
Thrombocytopenia	12 (20.7)	11 (18.6)
Endocrine disorders	9 (15.5)	2 (3.4)
Hypothyroidism	9 (15.5)	2 (3.4)
Gastrointestinal disorders	41 (70.7)	34 (57.6)
Abdominal pain	6 (10.3)	3 (5.1)
Abdominal pain upper	3 (5.2)	4 (6.8)
Constipation	16 (27.6)	17 (28.8)
Diarrhoea	27 (46.6)	20 (33.9)
Dyspepsia	8 (13.8)	2 (3.4)
Nausea	21 (36.2)	19 (32.2)
Stomatitis	8 (13.8)	6 (10.2)
Vomiting	14 (24.1)	11 (18.6)
General disorders and administration site conditions	39 (67.2)	35 (59.3)
Asthenia	17 (29.3)	6 (10.2)
Chest pain	8 (13.8)	3 (5.1)
Fatigue	20 (34.5)	22 (37.3)
Malaise	3 (5.2)	0
Mucosal inflammation	5 (8.6)	3 (5.1)
Oedema peripheral	2 (3.4)	6 (10.2)
Pain	6 (10.3)	6 (10.2)
Pyrexia	6 (10.3)	9 (15.3)
Hepatobiliary disorders	0	3 (5.1)
Hyperbilirubinaemia	0	3 (5.1)
Infections and infestations	10 (17.2)	14 (23.7)
Lower respiratory tract infection	4 (6.9)	6 (10.2)
Nasopharyngitis	0	3 (5.1)
Respiratory tract infection	2 (3.4)	4 (6.8)
Upper respiratory tract infection	0	3 (5.1)
Urinary tract infection	4 (6.9)	3 (5.1)
Investigations	10 (17.2)	6 (10.2)
Weight decreased	10 (17.2)	6 (10.2)
Metabolism and nutrition disorders	30 (51.7)	17 (28.8)
Decreased appetite	25 (43.1)	12 (20.3)
Dehydration	3 (5.2)	1 (1.7)
Hyperglycaemia	2 (3.4)	3 (5.1)
Hypokalaemia	3 (5.2)	3 (5.1)
Hyponatraemia	4 (6.9)	3 (5.1)
Musculoskeletal and connective tissue disorders	23 (39.7)	34 (57.6)
Arthralgia	13 (22.4)	11 (18.6)
Back pain	10 (17.2)	5 (8.5)
Bone pain	5 (8.6)	7 (11.9)
Musculoskeletal chest pain	4 (6.9)	1 (1.7)
Musculoskeletal pain	3 (5.2)	4 (6.8)
Myalgia	7 (12.1)	7 (11.9)

Table 20. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For ≥5% of Subjects

System Organ Class and MedDRA (v15.1) Preferred Term	Axitinib (N=58) n (%)	Bevacizumab (N=59) n (%)
Neck pain	4 (6.9)	1 (1.7)
Pain in extremity	4 (6.9)	10 (16.9)
Nervous system disorders	31 (53.4)	33 (55.9)
Dizziness	5 (8.6)	4 (6.8)
Dysgeusia	4 (6.9)	6 (10.2)
Headache	11 (19.0)	4 (6.8)
Lethargy	4 (6.9)	5 (8.5)
Neuropathy peripheral	15 (25.9)	15 (25.4)
Neurotoxicity	2 (3.4)	5 (8.5)
Paraesthesia	6 (10.3)	8 (13.6)
Peripheral sensory neuropathy	3 (5.2)	1 (1.7)
Polyneuropathy	3 (5.2)	2 (3.4)
Syncope	3 (5.2)	0
Psychiatric disorders	16 (27.6)	14 (23.7)
Anxiety	4 (6.9)	4 (6.8)
Depression	4 (6.9)	2 (3.4)
Insomnia	10 (17.2)	8 (13.6)
Renal and urinary disorders	6 (10.3)	6 (10.2)
Proteinuria	6 (10.3)	6 (10.2)
Respiratory, thoracic and mediastinal disorders	27 (46.6)	31 (52.5)
Cough	9 (15.5)	9 (15.3)
Dysphonia	7 (12.1)	8 (13.6)
Dyspnoea	17 (29.3)	15 (25.4)
Epistaxis	8 (13.8)	10 (16.9)
Haemoptysis	3 (5.2)	6 (10.2)
Oropharyngeal pain	3 (5.2)	3 (5.1)
Skin and subcutaneous tissue disorders	27 (46.6)	28 (47.5)
Alopecia	21 (36.2)	27 (45.8)
Palmar-plantar erythrodysaesthesia syndrome	3 (5.2)	1 (1.7)
Pruritus	2 (3.4)	3 (5.1)
Rash	6 (10.3)	6 (10.2)
Rash pruritic	0	3 (5.1)
Vascular disorders	29 (50.0)	25 (42.4)
Hypertension	24 (41.4)	25 (42.4)
Hypotension	6 (10.3)	1 (1.7)

Subjects were only counted once per treatment for each row. Data up to 28 days were included after last dose of study drug.
MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; v = version.

Treatment related treatment-emergent AEs experienced by ≥5% of subjects are presented in Table 21.

Table 21. Treatment-Emergent Adverse Events (Treatment-Related) by System Organ Class and Preferred Term For ≥5% Subjects - As Treated Population

System Organ Class and MedDRA (v14.1) Preferred Term	Axitinib (N=58) n (%)	Bevacizumab (N=59) n (%)
Subjects with adverse events	55 (94.8)	54 (91.5)
Blood and lymphatic system disorders	23 (39.7)	24 (40.7)
Anaemia	9 (15.5)	13 (22.0)
Leukopenia	5 (8.6)	4 (6.8)
Neutropenia	17 (29.3)	16 (27.1)
Thrombocytopenia	10 (17.2)	10 (16.9)
Endocrine disorders	9 (15.5)	0
Hypothyroidism	9 (15.5)	0
Gastrointestinal disorders	34 (58.6)	28 (47.5)
Constipation	6 (10.3)	10 (16.9)
Diarrhoea	16 (27.6)	10 (16.9)
Dyspepsia	6 (10.3)	1 (1.7)
Nausea	18 (31.0)	17 (28.8)
Stomatitis	6 (10.3)	6 (10.2)
Vomiting	10 (17.2)	11 (18.6)
General disorders and administration site conditions	32 (55.2)	21 (35.6)
Asthenia	13 (22.4)	5 (8.5)
Fatigue	18 (31.0)	17 (28.8)
Mucosal inflammation	6 (10.3)	3 (5.1)
Pyrexia	3 (5.2)	3 (5.1)
Infections and infestations	8 (13.8)	5 (8.5)
Lower respiratory tract infection	1 (1.7)	3 (5.1)
Urinary tract infection	3 (5.2)	0
Investigations	8 (13.8)	6 (10.2)
Weight decreased	4 (6.9)	2 (3.4)
Metabolism and nutrition disorders	21 (36.2)	13 (22.0)
Decreased appetite	17 (29.3)	10 (16.9)
Dehydration	4 (6.9)	1 (1.7)
Musculoskeletal and connective tissue disorders	11 (19.0)	19 (32.2)
Arthralgia	7 (12.1)	6 (10.2)
Bone pain	0	3 (5.1)
Myalgia	5 (8.6)	7 (11.9)
Pain in extremity	0	4 (6.8)
Nervous system disorders	31 (53.4)	34 (57.6)
Dizziness	2 (3.4)	3 (5.1)
Dysgeusia	4 (6.9)	6 (10.2)
Headache	3 (5.2)	2 (3.4)
Lethargy	3 (5.2)	5 (8.5)
Neuropathy peripheral	15 (25.9)	15 (25.4)
Neurotoxicity	2 (3.4)	5 (8.5)
Paraesthesia	6 (10.3)	8 (13.6)
Polyneuropathy	3 (5.2)	2 (3.4)
Psychiatric disorders	4 (6.9)	2 (3.4)
Insomnia	3 (5.2)	0
Renal and urinary disorders	9 (15.5)	6 (10.2)
Proteinuria	5 (8.6)	4 (6.8)
Respiratory, thoracic and mediastinal disorders	15 (25.9)	13 (22.0)
Dysphonia	4 (6.9)	2 (3.4)
Epistaxis	6 (10.3)	7 (11.9)

Table 21. Treatment-Emergent Adverse Events (Treatment-Related) by System Organ Class and Preferred Term For ≥5% Subjects - As Treated Population

System Organ Class and MedDRA (v14.1) Preferred Term	Axitinib (N=58) n (%)	Bevacizumab (N=59) n (%)
Haemoptysis	3 (5.2)	4 (6.8)
Skin and subcutaneous tissue disorders	31 (53.4)	29 (49.2)
Alopecia	21 (36.2)	27 (45.8)
Palmar-plantar erythrodysaesthesia syndrome	3 (5.2)	1 (1.7)
Rash	5 (8.6)	2 (3.4)
Vascular disorders	26 (44.8)	22 (37.3)
Hypertension	21 (36.2)	21 (35.6)
Hypotension	3 (5.2)	0

AE and SAE results are not separated out. Subjects were only counted once per treatment for each row. Data up to 28 days were included after last dose of study drug. MedDRA (v14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; SAE = serious adverse event; v = version.

Treatment-emergent serious adverse events (SAEs) (all causalities) are presented in Table 22.

Table 22. Treatment-Emergent Serious Adverse Events (All Causalities)

System Organ Class and MedDRA (v15.1) Preferred Term	Axitinib (N=58) n (%)	Bevacizumab (N=59) n (%)
Subjects with adverse events	31 (53.4)	19 (32.2)
Blood and lymphatic system disorders	4 (6.9)	5 (8.5)
Anaemia	1 (1.7)	0
Febrile neutropenia	0	1 (1.7)
Leukopenia	1 (1.7)	1 (1.7)
Neutropenia	1 (1.7)	2 (3.4)
Pancytopenia	1 (1.7)	0
Thrombocytopenia	1 (1.7)	1 (1.7)
Cardiac disorders	6 (10.3)	2 (3.4)
Acute myocardial infarction	1 (1.7)	0
Atrial fibrillation	1 (1.7)	1 (1.7)
Cardiac arrest	1 (1.7)	0
Myocardial infarction	2 (3.4)	0
Pericardial effusion	1 (1.7)	0
Supraventricular tachycardia	1 (1.7)	0
Tachycardia	0	1 (1.7)
Endocrine disorders	1 (1.7)	0
Inappropriate antidiuretic hormone secretion	1 (1.7)	0
Gastrointestinal disorders	2 (3.4)	4 (6.8)
Anal fissure	0	1 (1.7)
Diarrhoea	1 (1.7)	0
Oesophagitis	0	2 (3.4)
Vomiting	1 (1.7)	1 (1.7)
General disorders and administration site conditions	13 (22.4)	7 (11.9)
Asthenia	3 (5.2)	0
Chest pain	0	1 (1.7)
Chills	0	1 (1.7)
Death	1 (1.7)	0
Disease progression	7 (12.1)	3 (5.1)
Fatigue	1 (1.7)	2 (3.4)
General physical health deterioration	0	1 (1.7)
Mucosal inflammation	1 (1.7)	0
Pain	1 (1.7)	0
Pyrexia	1 (1.7)	0
Immune system disorders	1 (1.7)	0
Anaphylactic reaction	1 (1.7)	0
Infections and infestations	7 (12.1)	5 (8.5)
Device related infection	1 (1.7)	0
Diverticulitis	1 (1.7)	1 (1.7)
Endocarditis bacterial	0	1 (1.7)
Febrile infection	1 (1.7)	0
Lower respiratory tract infection	0	2 (3.4)
Neutropenic sepsis	1 (1.7)	0
Pneumonia	1 (1.7)	1 (1.7)
Sepsis	2 (3.4)	0
Staphylococcal infection	1 (1.7)	0
Urinary tract infection	1 (1.7)	0
Investigations	1 (1.7)	0
Alanine aminotransferase increased	1 (1.7)	0
Aspartate aminotransferase increased	1 (1.7)	0
Blood alkaline phosphatase increased	1 (1.7)	0

Table 22. Treatment-Emergent Serious Adverse Events (All Causalities)

System Organ Class and MedDRA (v15.1) Preferred Term	Axitinib (N=58) n (%)	Bevacizumab (N=59) n (%)
Metabolism and nutrition disorders	4 (6.9)	1 (1.7)
Decreased appetite	0	1 (1.7)
Dehydration	4 (6.9)	0
Hyperkalaemia	0	1 (1.7)
Musculoskeletal and connective tissue disorders	0	1 (1.7)
Arthralgia	0	1 (1.7)
Myalgia	0	1 (1.7)
Nervous system disorders	2 (3.4)	2 (3.4)
Cerebral infarction	1 (1.7)	0
Headache	0	1 (1.7)
Loss of consciousness	0	1 (1.7)
Meningeal disorder	1 (1.7)	0
Psychiatric disorders	2 (3.4)	2 (3.4)
Anxiety	0	1 (1.7)
Confusional state	1 (1.7)	1 (1.7)
Hallucination	0	1 (1.7)
Mental status changes	1 (1.7)	0
Renal and urinary disorders	1 (1.7)	1 (1.7)
Renal failure acute	1 (1.7)	1 (1.7)
Respiratory, thoracic and mediastinal disorders	6 (10.3)	4 (6.8)
Chronic obstructive pulmonary disease	0	1 (1.7)
Dyspnoea	1 (1.7)	1 (1.7)
Haemoptysis	1 (1.7)	1 (1.7)
Pneumonia aspiration	1 (1.7)	0
Pneumothorax	1 (1.7)	0
Pulmonary embolism	1 (1.7)	1 (1.7)
Respiratory distress	1 (1.7)	0
Vascular disorders	2 (3.4)	2 (3.4)
Deep vein thrombosis	0	1 (1.7)
Hypertension	1 (1.7)	0
Hypotension	1 (1.7)	0
Peripheral ischaemia	0	1 (1.7)

Subjects were only counted once per treatment for each row. Data up to 28 days were included after last dose of study drug.
MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; v = version.

Treatment related treatment-emergent SAEs are presented in Table 23.

Table 23. Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Treatment Related) - As Treated Population

System Organ Class and MedDRA (v14.1) Preferred Term	Axitinib (N=58) n (%)	Bevacizumab (N=59) n (%)
Any serious adverse events	16 (27.6)	14 (23.7)
Blood and lymphatic system disorders	3 (5.2)	5 (8.5)
Anaemia	1 (1.7)	0
Febrile neutropenia	0	1 (1.7)
Leukopenia	1 (1.7)	1 (1.7)
Neutropenia	1 (1.7)	2 (3.4)
Thrombocytopenia	1 (1.7)	1 (1.7)
Cardiac disorders	1 (1.7)	0
Cardiac arrest	1 (1.7)	0
Gastrointestinal disorders	2 (3.4)	3 (5.1)
Diarrhoea	1 (1.7)	0
Oesophagitis	0	2 (3.4)
Vomiting	1 (1.7)	1 (1.7)
General disorders and administration site conditions	4 (6.9)	3 (5.1)
Asthenia	1 (1.7)	0
Death	1 (1.7)	0
Fatigue	1 (1.7)	2 (3.4)
Mucosal inflammation	1 (1.7)	0
General physical health deterioration	0	1 (1.7)
Immune system disorders	1 (1.7)	0
Anaphylactic reaction	1 (1.7)	0
Infections and infestations	2 (3.4)	2 (3.4)
Diverticulitis	1 (1.7)	0
Lower respiratory tract infection	0	2 (3.4)
Urinary tract infection	1 (1.7)	0
Neutropenic sepsis	1 (1.7)	0
Metabolism and nutrition disorders	3 (5.2)	1 (1.7)
Dehydration	3 (5.2)	0
Decreased appetite	0	1 (1.7)
Musculoskeletal and connective tissue disorders	0	1 (1.7)
Arthralgia	0	1 (1.7)
Myalgia	0	1 (1.7)
Nervous system disorders	1 (1.7)	2 (3.4)
Cerebral infarction	1 (1.7)	0
Headache	0	1 (1.7)
Loss of consciousness	0	1 (1.7)
Psychiatric disorders	1 (1.7)	1 (1.7)
Confusional state	0	1 (1.7)
Hallucination	0	1 (1.7)
Mental status changes	1 (1.7)	0
Respiratory, thoracic and mediastinal disorders	4 (6.9)	2 (3.4)
Haemoptysis	1 (1.7)	1 (1.7)
Pneumothorax	1 (1.7)	0
Pulmonary embolism	1 (1.7)	1 (1.7)
Respiratory distress	1 (1.7)	0
Vascular disorders	2 (3.4)	1 (1.7)
Hypertension	1 (1.7)	0
Hypotension	1 (1.7)	0
Deep vein thrombosis	0	1 (1.7)

MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; v = version.

All deaths are summarized in Table 24.

Table 24. Deaths During Study Treatment and Follow-Up - Full Analysis Population

Variable	Axitinib N=58 n (%)	Bevacizumab N=60 n (%)
Subjects who died	45 (77.6)	46 (76.7)
Subjects who died on-study[a]	9 (15.5)	5 (8.3)[b]
Disease under study	6 (10.3)	4 (6.7)[b]
Study treatment toxicity	0	2 (3.3)
Death could be associated to the disease under study or possibly related to bevacizumab	0	1 (1.7)
Most probably. Not possible to specify which one of drugs.	0	1 (1.7)
Unknown	0	0
Other	3 (5.2)	0
Myocardial infarction	1 (1.7)	0
Sepsis	1 (1.7)	0
Serious adverse event - respiratory distress	1 (1.7)	0
Subjects who died during follow-up[c]	36 (62.1)	41 (68.3)
Disease under study	32 (55.2)	36 (60.0)
Study treatment toxicity	0	0
Unknown	3 (5.2)	2 (3.3)
Other	1 (1.7)	3 (5.0)
Disease progression	1 (1.7)	0
Metastatic lung cancer	0	1 (1.7)
Pneumothorax	0	1 (1.7)
Serious adverse event - bacterial endocarditis	0	1 (1.7)

N = number of subjects; n = number of subject reported with death.

a. On-study deaths were those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.

b. For 1 subject in bevacizumab group, 2 reasons for death have been included (ie. each reason was counted in both disease under study and study treatment toxicity in on study death section of the table).

c. Follow-up deaths were those that occurred >28 days after the last dose of study drug.

Discontinuations: There were 24 (41.4%) axitinib subjects and 18 (30.5%) bevacizumab subjects who permanently discontinued from treatment due to AEs during the study.

Reasons for permanent axitinib treatment discontinuations occurring in more than a single subject included hemoptysis (n=3), disease progression (n=5), sepsis (n=2), and myocardial infarction (n=2). AEs leading to treatment discontinuation were still present at end of study in 4 subjects and were fatal in 10 subjects (Table 25). Reasons for permanent bevacizumab treatment discontinuations occurring in more than a single subject included disease progression (n=4) and hemoptysis (n=3). AEs leading to treatment discontinuation were still present at end of study in 1 subject and were fatal in 5 subjects (Table 26).

Table 25. Permanent Discontinuations From Axitinib Treatment Due to Adverse Events

Serial Number	MedDRA Preferred Term	Maximum CTCAE Grade	SAE (Y/N)	Outcome	Causality
1	Intestinal ischemia	2	N	Resolved	Axitinib/bevacizumab
2	Sepsis	5	Y	Death	Disease under study
3	Hypertension	2	Y	Resolved	Axitinib/bevacizumab
4	Hemoptysis	2	N	Resolved	Other
5	Sepsis	5	Y	Death	Disease under study
6	Cachexia	3	N	Still present at end of study	Disease under study
7	Respiratory distress	5	Y	Death	Axitinib/bevacizumab /paclitaxel/carboplatin
8	Pneumothorax	4	Y	Unknown	Axitinib/bevacizumab
9	Peripheral neuropathy	2	N	Still present at end of study	Paclitaxel/carboplatin
10	Anaphylaxis	4	Y	Resolved	Paclitaxel
11	Confusional state	4	Y	Still present at end of study	Other
12	Mental status changes	3	Y	Resolved	Axitinib/bevacizumab
13	Disease progression	5	Y	Death	Disease under study
14	Myocardial infarction	4	Y	Resolved	Other illness
15	Disease progression	5	Y	Death	Disease under study
16	Vomiting	3	Y	Resolved	Paclitaxel/carboplatin
17	Myocardial infarction	5	Y	Death	Other illness-myocardial infarction
18	Disease progression	5	Y	Death	Disease under study
19	Disease progression	5	Y	Death	Disease under study
20	Diarrhea	3	N	Resolved	Axitinib/bevacizumab
21	Palmar-plantar erythrodysaesthesia syndrome	2	N	Resolved	Axitinib/bevacizumab
22	Hemoptysis	1	N	Resolved	Axitinib/bevacizumab
23	Hemoptysis	4	Y	Still Present (at time of death)	Axitinib/bevacizumab
	Cardiac arrest	5	Y	Death	Axitinib/bevacizumab
24	Disease progression	5	Y	Death	Disease under study

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = no; SAE = serious adverse event; Y = yes.

Table 26. Permanent Discontinuations From Bevacizumab Treatment Due to Adverse Events

Serial Number	MedDRA Preferred Term	Maximum CTCAE Grade	SAE (Y/N)	Outcome	Causality
1	Disease Progression	3	N	Resolved	Disease under study
2	Disease Progression	5	Y	Death	Disease under study
3	Chronic obstructive pulmonary disease	2	Y	Resolved	Disease under study
4	Neutropenia	4	Y	Resolved	Paclitaxel/carboplatin
5	Loss of consciousness	4	Y	Resolved	Paclitaxel/carboplatin
6	General physical health deterioration	5	Y	Death	Axitinib/bevacizumab/paclitaxel/ carboplatin
7	Endocarditis bacterial	5	Y	Death	Other
8	Hemoptysis	2	N	Resolved	Axitinib/bevacizumab
9	Hemoptysis	1	N	Still present	Axitinib/bevacizumab/paclitaxel/ carboplatin
10	Drug hypersensitivity	2	N	Resolved	Paclitaxel
11	Headache	2	N	Resolved	Other
12	Lower respiratory tract infection	2	Y	Resolved	Disease under study
13	Disease progression	5	Y	Death	Disease under study
14	Pulmonary embolism	2	Y	Resolved	Axitinib/bevacizumab
15	Disease progression	5	Y	Death	Disease under study
16	Diverticulitis	3	Y	Resolved	Other illness
17	Hemoptysis	1	N	Resolved	Axitinib/bevacizumab
18	Esophagitis	3	Y	Resolved	Axitinib/bevacizumab/paclitaxel/ carboplatin

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = no; SAE = serious adverse event; Y = yes.

Overall, 32 (55.2%) axitinib subjects and 23 (39.0%) bevacizumab subjects temporarily discontinued from the treatment due to AEs. The most frequently reported reasons for temporary discontinuations from treatment in the axitinib and bevacizumab groups, respectively, were hypertension (10 [17.2%] vs 3 [5.1%]), thrombocytopenia (1 [1.7%] vs 6 [10.2%]), neutropenia (2 [3.4%] vs 5 [8.5%]), and fatigue (3 [5.2%] vs 2 [3.4%]).

Dose reductions due to AEs were observed more frequently in axitinib subjects than among those in the bevacizumab group (16 [27.6%] subjects vs 2 [3.4%] subjects, respectively. The most frequently reported AEs resulting in dose reductions among axitinib subjects were hypertension (4 [6.9%]), diarrhea (3 [5.2%]), and fatigue (3 [5.2%]). The only AE that resulted in dose reduction among bevacizumab subjects was weight decreased (2 [3.4%]).

There were no ECGs considered abnormal and clinically significant

Thyroid function was summarized by subjects who had thyroid stimulating hormone (TSH) levels ≥5 μIU/mL but <10 μIU/mL and those who had TSH levels ≥10 μIU/mL, by treatment cycle. Fewer than 10% of subjects in either treatment group had TSH values in either cutoff during any treatment cycle.

BP elevations were commonly observed in both treatment groups as early as the first treatment cycle. As a result, the use of hypertension medications during the study was necessary for the majority of subjects in both groups. Shifts of ≥3 CTCAE grades for hematology parameters were observed most frequently for absolute neutrophils in both treatment groups. Few subjects in either group had shifts of ≥3 CTCAE Grades in clinical chemistry values.

CONCLUSIONS:

- When stratified by gender and prior adjuvant therapy, the difference in PFS, OS, and ORR between the 2 treatment groups was not statistically significant.

- The median DR (95% CI) for the axitinib and bevacizumab groups was 4.4 months (4.2, 6.7 months) and 7.0 months (4.8, 8.3 months), respectively.

- Axitinib, in combination with paclitaxel and carboplatin, has a lower tolerability profile than that of the bevacizumab treatment regimen, based on the higher incidence of temporary treatment discontinuations and dose reductions due to AEs, in particular the AE of hypertension.

- The most frequently reported Grade 3 or 4 AEs in the axitinib group were hypertension and neutropenia.

- Based on mean change scores from Baseline for the EORTC QLQ-C30 and LC-13 within the first 11 cycles (in which there were at least 10 subjects):

    - Global QoL scores were similar between groups;

- In the axitinib group, clinically meaningful and statistically significant worsening was seen for social functioning, role functioning and physical functioning. In the bevacizumab group, emotional functioning showed clinically meaningful and statistically significant improvement;

- Both treatment groups reported statistically significant and clinically meaningful improvements in insomnia and chest pain as well as statistically significant and clinically meaningful worsening in peripheral neuropathy and alopecia;

- Statistically significant and clinically meaningful improvements were also reported for arm/shoulder pain in the axitinib group and for constipation and cough in the bevacizumab group;

- Statistically significant and clinically meaningful worsening was reported for sore mouth only in the axitinib group.