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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Sutent® / Sunitinib malate

PROTOCOL NO.: A6181094

PROTOCOL TITLE: A Phase 3 Study of SU011248 in Combination With Paclitaxel Versus Bevacizumab With Paclitaxel in the First-Line Advanced Disease Setting in Patients Having Breast Cancer

Study Centers: The study was conducted at 108 centers globally, 98 in the United States, 3 in Germany, 3 in Italy, and 4 in Spain.

Study Initiation and Final Completion Dates:

Study Initiation Date: 01 November 2006 (first subject first visit)

Primary Completion Date: 01 June 2009 (final data collection date for primary outcome measure)

Final Completion Date: 30 August 2011(last subject last visit)

This study was terminated early for futility at the first interim analysis.

Phase of Development: Phase 3

Study Objectives: Primary Objective: To compare the progression-free survival (PFS) for subjects having locally recurrent or metastatic breast cancer (BC) who receive sunitinib plus paclitaxel versus (vs) bevacizumab plus paclitaxel

Secondary Objectives:

- To compare the safety of sunitinib plus paclitaxel vs bevacizumab plus paclitaxel in this subject population
- To compare measures of duration of tumor control and overall survival
- To assess patient reported outcomes (PRO) of health-related quality of life (QoL) and disease-related symptoms
- To assess measurement and valuation of health status
- To explore the relationship between specific biomarkers and cancer- and treatment-related outcomes

METHODS

Study Design: This was a multicenter, randomized, open-label, Phase 3 clinical study comparing the efficacy and safety of comparing the efficacy and safety of paclitaxel in combination with sunitinib vs paclitaxel in combination with bevacizumab in subjects with advanced breast cancer (locally recurrent or metastatic) in the first-line treatment setting. Subjects who were not candidates for curative intent treatments were eligible for this study.

Subjects were to continue treatment on study until objective disease progression was documented according to Response Evaluation Criteria in Solid Tumors (RECIST) or withdrawal from the study for other reasons. Subjects discontinuing treatment with paclitaxel prior to disease progression were to continue treatment with sunitinib or bevacizumab as assigned at randomization. Subjects could continue treatment as assigned at randomization beyond the time of RECIST-defined progression at the discretion of the investigator, if the subject was perceived to be experiencing clinical benefit. Overall survival was to be assessed for 5 years from randomization.

The study was designed to have 2 interim analyses and a final analysis based on the primary endpoint of PFS. An external independent Data Monitoring Committee (DMC) was convened to periodically review accumulating safety data and planned interim analyses. The study was stopped early due to futility after the first interim analysis as determined by the DMC based on PFS as reported by investigator response. Further enrollment in the study was stopped at the first interim analysis when 27% of the PFS events were available for analysis and the planned second interim and final analyses were not performed. Subjects who were judged by the Investigator as receiving clinical benefit could continue treatment on study if they chose to remain on the study. Data collected on these subjects included additional exposure and safety data since the data cutoff date of 01 June 2009.

Table 1 presents a schedule of study events.

Table 1. Schedule of Events

Parameters	Screening	Each Treatment Cycle[a]				Post-Treatment		
Treatment and Safety Procedures[b]	≤28 Days Prior to Rand	Day 1 (±2 Days)	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 22 (-2/+1 Day)	End of Treatment[c]	Post Treatment[d]	Follow-up[e]
Baseline documentation								
Informed consent	X							
Medical/oncologic history	X							
Physical examination[f]	X	X[g]				X	X	
Baseline signs/symptoms		X[h]						
Vital signs[i]/weight	X	X[g]	X	X		X		
Clinical laboratory tests								
Hematology	X	X[g]	X	X	X[j]	X	X	
Serum chemistry	X	X[g]		X[j]		X	X	
Thyroid testing	X[k]							
Urine protein: creatinine ratio (UPCR)	X	X[g, l]						
Pregnancy[m]	X							
12-lead ECG[n]	X			X[h, k]		X		
MUGA scan or echocardiography	X	X[o]				X		
Randomization								
Randomization	X							
Treatments								
Premedication[p]		X	X	X				
Paclitaxel[q]		X	X	X				
Bevacizumab[r]		X		X				
Sunitinib[s]		X→	→	→	→			
Study drug compliance[t]		X				X		
Other clinical assessments								
EORTC QLQ-C30 and BR23[u]		X[v]				X		
EQ-5D[u]		X[l]				X		
AEs[w]		X→	→	→	→	→	→X	
Concomitant medications[x]	X→	→	→	→	→	→	→X	
Efficacy assessments								
Tumor assessment[y]	X	X[z]				X		X
Bone scan	X	X[aa]				X[aa]		X[z]
Survival follow-up								X[bb]

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Treatment and Safety Procedures[b]	≤28 Days Prior to Rand	Day 1 (±2 Days)	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 22 (-2/+1 Day)	End of Treatment[c]	Post Treatment[d]	Follow-up[e]
Special laboratory assessments								
Soluble proteins[cc]		X[dd]	X[h]	X[h]				

AE = Adverse events; BR-23 = EORTC QLQ breast cancer module; CRF = case report form; CT = computed tomography; ECG = electrocardiograms; ECOG = eastern cooperative oncology group; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = EuroQol 5-dimensional; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multigated acquisition scans; PRO = patient-reported outcomes; Rand = randomization

a. Each cycle was 4 weeks long. Subjects who discontinued treatment with paclitaxel and continued on bevacizumab or sunitinib could have reduced clinic visits, returning to clinic as required for bevacizumab treatment or at 4-week intervals.
b. All assessments performed before treatment on the day indicated, except as indicated below.
c. Assessments did not need to be completed if they had been performed within 4 weeks of study withdrawal (8 weeks for tumor assessments).
d. 28 days after termination; all assessments were as necessary to follow-up AEs. Serious and sunitinib-related AEs ongoing at the post-treatment visit were followed until resolution or determined to be chronic or stable.
e. Subjects who discontinued for reasons other than disease progression continued to undergo tumor assessments every 8 weeks until progression. After progression, survival status was determined every 2 months until death or for 5 years.
f. Examination of major body systems; includes ECOG performance status and weight. Height was recorded at screening only.
g. Cycle 1, Day 1 assessments not required if acceptable screening assessments performed within 7 days before dosing.
h. Cycle 1 only.
i. Temperature, blood pressure, pulse, and respiration rate.
j. Cycles 1 to 3 only.
k. At the indicated time point and as clinically indicated thereafter.
l. Odd-numbered cycles only (eg, Cycles 1, 3, 5, etc.).
m. For women of child-bearing potential only.
n. Three consecutive 12-lead ECGs, performed at least 2 minutes apart, to determine mean corrected QT (QTcF; Fridericia's correction) interval. Triplicate ECG was also to be performed 2 weeks after any sunitinib dose escalation; or sunitinib dose reduction due to QTc interval prolongation, significant electrolyte changes, vomiting, diarrhea, or additional of a potent CYP3A4 inhibitor; and as clinically indicated.
o. Screening (and Cycle 2 Day 1 for subjects with previous anthracycline exposure), every 3 months for all subjects, and as clinically indicated thereafter.
p. Pretreatment for paclitaxel infusions, with oral or IV corticosteroids, diphenhydramine or equivalent histamine H1 antagonists, and cimetidine or equivalent histamine H2 antagonists, according to standard of care.
q. Starting dose of 90 mg/m^2, as a 1-hour infusion. Could be reduced to 65 mg/m^2 based on tolerability; re-escalation to 80 or 90 mg/m^2 upon recovery was permitted.
r. 10 mg/kg; infusion duration according to standard of care.
s. Starting dose of 25 mg daily. After Cycle 1, escalation to 37.5 mg daily was permitted in the absence of complicated neutropenia and if all 3 Cycle 1 paclitaxel doses were successfully administered at 90 mg/m^2, at the Investigator's discretion.

Table 1. Schedule of Events

Parameters	Screening	Each Treatment Cycle[a]				Post-Treatment		
Treatment and Safety Procedures[b]	≤28 Days Prior to Rand	Day 1 (±2 Days)	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 22 (-2/+1 Day)	End of Treatment[c]	Post Treatment[d]	Follow-up[e]

t. The sunitinib bottle and any unused capsules were returned to the clinic for drug accountability. Paclitaxel and bevacizumab were administered by site staff and the administration recorded in subject records.

u. PRO assessments were to be the first assessments performed at the indicated visits and scheduled to coincide with tumor assessments.

v. Cycles 1 to 7 and odd-numbered cycles thereafter.

w. AEs were recorded from Day 1 until 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. Serious AEs were reported from the time of informed consent.

x. Concomitant medications and treatments were recorded from 28 days before Day 1 to 28 days after the last dose of study treatment.

y. Computed tomography (CT) or MRI of chest, abdomen, and pelvis and clinical evaluation of superficial disease. Brain CT or MRI at screening and at any time of suspected brain metastasis.

z. Tumor assessments were performed every 8 weeks (56 calendar days) after randomization; eg, Day 1 of Cycle 3 and odd-numbered cycles thereafter; however, the every-8-week schedule was to be maintained regardless of dosing delays or interruptions. Subjects with measurable disease for whom data was to be included in the first interim analysis had an additional assessment at the beginning of Week 12 (calendar Day 84). Lesions assessed by clinical methods were to be photographed during each assessment and their measurements were recorded in the CRF. The allowable window for disease assessments was ± 7 days. If subjects discontinued all study medications without documented disease progression, tumor assessments were to continue to follow the same schedule.

aa. Screening bone scan required within 6 weeks prior to randomization. Post-screening bone scan required only for subjects with bone lesions identified at Baseline according to the Investigator or the core imaging laboratory and at the time of suspected new bone metastasis. If bone lesions were followed, bone scan could be every 16 weeks (112 calendar days) from randomization date (eg, Day 1 of every fourth cycle). For subjects having bone-only metastases at screening (according to the Investigator), an additional bone scan was required at Week 8 to document "flare" response and to set the baseline for subsequent assessment of new lesions. The allowable window for bone scan assessments was ±7 days. If subjects discontinued all study medications without documented disease progression, bone scans were to continue to follow the same schedule.

bb. After discontinuation of study treatment, subjects were contacted to confirm survival status every 2 months until death or for up to 5 years from first study treatment.

cc. At selected sites only, one 10-mL blood sample was collected before dosing on the specified days for 50 subjects in each treatment arm enrolled. An additional 3-mL blood sample could be collected at the same time points in a subset of this group of 100 subjects (selected sites only).

dd. Cycles 1, 2, 3, and 5 only.

Number of Subjects (Planned and Analyzed): A total sample size of approximately 740 subjects (370 in each treatment arm) was planned for this study. As of the data cutoff date (1 June 2009), 485 subjects were randomized and constituted the intent-to-treat (ITT) population used to analyze efficacy (242 subjects were randomized to sunitinib + paclitaxel (Arm A), and 243 subjects were randomized to bevacizumab + paclitaxel (Arm B). As of study completion date (30 August 2011), a total of 488 subjects were randomized of which 477 subjects were treated (235 subjects received sunitinib + paclitaxel and 242 subjects received bevacizumab + paclitaxel) and constituted the as-treated (AT) population used to analyze safety.

Diagnosis and Main Criteria for Inclusion: Subjects with unresectable, locally recurrent, or metastatic BC with measurable disease as per RECIST or bone-only diseases, and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

Exclusion Criteria: Subjects with no prior treatment with cytotoxics in the advanced disease setting, human epidermal growth factor (HER2)/neu positive disease unless trastuzumab was previously received or is contraindicated, and subjects treated with a taxane in the adjuvant setting unless the disease free interval was >12 months after end of treatment.

Study Treatment: Subjects were randomized to treatment with sunitinib + paclitaxel or bevacizumab + paclitaxel. Randomization was stratified based on prior neoadjuvant or adjuvant therapy (yes vs no), hormone receptor status (positive vs negative), and disease free interval ≤24 months vs >24 months.

Treatment on study was administered in 4 week cycles. In both treatment arms, paclitaxel was administered intravenously (IV) at a starting dose of 90 mg/m^2 weekly for 3 weeks followed by a 1 week rest. Bevacizumab was administered by IV infusion at 10 mg/kg every 2 weeks. Sunitinib was administered orally, in a continuous regimen, with a starting dose of 25 mg daily. Sunitinib and paclitaxel dose levels could be modified or treatment could be delayed or discontinued to manage toxicity; bevacizumab treatment could be delayed or discontinued, but the bevacizumab dose could not be reduced.

Efficacy, Pharmacodynamic, Outcomes Research, and Safety Endpoints:

Primary Endpoint**:**

- PFS

Secondary Endpoints:

- Type, incidence, severity, timing, seriousness, and relatedness of adverse events (AEs), laboratory abnormalities
- Objective response rate (ORR)
- Duration of response (DR)
- Overall survival (OS)

- Two- and 3-year survival

- PRO of health-related QoL and disease-related symptoms as measured by European Organization for the Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ-C30) and the BC module (QLQ-BR23)

- Health status measured by the EuroQoL EQ-5D Self-Report Questionnaire (EQ-5D)

- Concentrations of plasma proteins (eg, soluble vascular endothelial growth factor receptor [VEGFR]2 and VEGFR3, VEGF-A, PlGF, soluble kinase Insert Domain for Tyrosine, and possibly soluble platelet-derived growth factor receptor [PDGFR] and PDGF) that may be associated with angiogenesis and tumor proliferation.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead electrocardiograms (ECG), AEs, safety laboratory tests, physical examinations, ECOG performance status, and echocardiogram (ECHO) or multigated acquisition scans (MUGA) to measure left ventricular ejection fraction.

Statistical Methods: The intent-to-treat (ITT) population included all subjects who were randomized with study drug assignment designated according to initial randomization. The ITT population was the primary population for evaluating all efficacy endpoints and subject characteristics. The as-treated (AT) population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. The AT population was the primary population for evaluating treatment administration/compliance and safety.

The primary and secondary analyses of endpoints dependent on disease assessments (PFS, ORR, and DR) were based on assessments of disease response and progression performed by the investigational sites. Time-to-event endpoints between 2 treatment arms were compared with a 1-sided stratified log-rank test and an unstratified log-rank test at the α=0.025 overall significance level. Analyses planned to explore the potential influences of the baseline stratification factors and potential influences of baseline subject characteristics were not performed because of the early termination of enrollment in this study for futility.

Time-to-event endpoints were summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals (CIs) for each median were provided.

The rates of binary endpoints for the 2 treatment arms were compared with a significance level of 0.025 using a 1-sided Pearson χ^2 test and Cochran-Mantel-Haenszel (CMH) test. In addition, point estimates of the rates for each treatment arm and differences of the rates between treatment arms were provided along with the corresponding 2-sided 95% CIs using the exact method based on the F-distribution.

Descriptive statistics were used to summarize all subject characteristics, safety parameters, and soluble protein biomarkers.

Protein Biomarkers: Baseline plasma protein concentrations, and ratios to baseline at the indicated time points, were analyzed and were correlated with clinical outcome. Kaplan-Meier curves were compared within each treatment arm after stratification by < median or ≥ median baseline biomarker levels and by < median or ≥ median ratios to baseline at each time point using the proportional hazards model.

Correlations between soluble proteins and clinical benefit response (CBR): In this analysis, CBR was defined as complete response or partial response or stable disease ≥6 months, while absence of CBR was defined as SD <6 months or PD.

As enrollment in this study was terminated for futility at the first interim analysis, several planned analyses, including sensitivity and supportive efficacy analyses, PRO and health status measurement analyses, were not performed.

RESULTS

Subject Disposition and Demography: As of the data cutoff date (1 June 2009), 485 subjects had been randomized; 242 subjects (50.0%) to sunitinib + paclitaxel (Arm A), and 243 (50.0%) to bevacizumab + paclitaxel (Arm B). Six (2.5%) vs 8 subjects (2.9%) on sunitinib + paclitaxel vs bevacizumab + paclitaxel, respectively, withdrew consent and discontinued the study before receiving their first dose of study medication. Three of the 8 subjects on the bevacizumab + paclitaxel arm were randomized before the data cutoff date but received treatment after the data cutoff date. One subject was randomized to the sunitinib + paclitaxel arm but received bevacizumab + paclitaxel; that subject is counted in the sunitinib + paclitaxel arm in the ITT population and in the bevacizumab + paclitaxel arm in the AT population. Subject disposition is summarized in Table 2.

Table 2. Summary of Subject Disposition

Number (%) of Subjects		Sunitinib + Paclitaxel	Bevacizumab + Paclitaxel
Assigned to study treatment	488	241	247
Treated		235	242
Completed		0	0
Discontinued		235 (97.5)	242 (98.0)
Analyzed for Safety:			
Adverse events		235 (97.5)	242 (98.0)
Laboratory data		233 (96.7)	242 (98.0)
Discontinuations			
Reason for Discontinuation		241 (100.0)	247 (100.0)
Adverse event		1 (0.4)	5 (2.0)
Lost to follow-up		2 (0.8)	1 (0.4)
Objective progression or relapse		111 (46.1)	104 (42.1)
Other		73 (30.3)	107 (43.3)
Protocol violation		0	2 (0.8)
Study terminated by Sponsor		41 (17.0)	13 (5.3)
Subject died		9 (3.7)	8 (3.2)
Subject refused continued treatment for reason other than adverse event		4 (1.7)	7 (2.8)
Biomarker evaluable[a]		27	43

Discontinuations have been attributed to the last study treatment received.
BM = biomarker; n = number of subjects with pre-specified criteria.
a. Evaluable for BM referred to any subject randomized who had at least 1 BM sample taken.

Demographic and baseline characteristics are summarized by treatment arm for the ITT population in Table 3. A total of 488 subjects were enrolled in the study. There was only 1 male subject, who was on the sunitinib + paclitaxel arm.

Table 3. Summary of Subject Demographic Characteristics

Variable		Sunitinib + Paclitaxel (N=241)	Bevacizumab + Paclitaxel (N=247)
Age (years):			
	<18	0	0
	18-44	38 (15.8)	40 (16.2)
	45-64	144 (59.8)	137 (55.5)
	≥65	59 (24.5)	70 (28.3)
	Mean	56.4	57
	SD	11.5	11.9
	Range	27-84	32-92
Race:			
	White	200 (83.0)	214 (86.6)
	Black	25 (10.4)	24 (9.7)
	Asian	6 (2.5)	4 (1.6)
	Other	10 (4.1)	5 (2.0)
Weight (kg):			
	Mean	73.9	77
	SD	16.7	17.6
	Range	41.2-137.5	47.0-140.6
	N	241 (100.0)	245 (99.2)
Height (cm):			
	Mean	162.7	163.2
	SD	7	7.5
	Range	143.0-180.0	128.0-185.0
	N	241 (100.0)	247 (100.0)

N = total number of subjects; SD = standard deviation.

Efficacy, Pharmacodynamic, Outcomes Research Results:

Efficacy Results

On 27 May 2009, the independent DMC reviewed the progress of the study, and results of the first interim analysis using the available data of 451 subjects as of 21 May 2009 were analyzed. There were 137 PFS events based on investigator assessments, resulting in a PFS hazard ratio of 1.73 (95% CI: 1.22 to 2.43) favoring bevacizumab + paclitaxel. The pre-specified futility boundary was a PFS hazard ratio of 1.15. The resulting futility boundary would suggest stopping for futility if the observed upper bound of 90% CI for the hazard ratio was 1.15 or higher. Since the futility boundary had been crossed in this study, the likelihood of observing a significant improvement on sunitinib + paclitaxel as compared with bevacizumab + paclitaxel was extremely low. Therefore, the DMC recommended that the study be closed to further enrollment of subjects due to futility.

As of the cutoff date for efficacy analyses, there were 89 vs 70 observed disease progressions or deaths on sunitinib + paclitaxelvs bevacizumab + paclitaxel, respectively. The median PFS was 7.4 (95% CI: 6.9 to 8.5 months) vs 9.2 months (95% CI: 7.7 to 13.0 months). Results of the primary endpoint are summarized in (Table 4).

Table 4. Summary of Progression-Free Survival (Investigator Assessment; ITT Population)

Variable	Sunitinib + Paclitaxel (N=242)	Bevacizumab + Paclitaxel (N=243)
Progression status (n [%])		
Subjects who had disease progression or died	89 (36.8)	70 (28.8)
Objective progression observed	81 (33.5)	61 (25.1)
New lesion/site	50 (20.7)	32 (13.2)
≥20% increase in target without new lesion/site	27 (11.2)	24 (9.9)
Non-target only	4 (1.7)	5 (2.1)
Death without objective progression	8 (3.3)	9 (3.7)
Progression-free survival (months)		
Quartile (95% CI)		
25%	4.1 (3.2 to 5.5)	5.6 (5.5 to 7.2)
50% (median)	7.4 (6.9 to 8.5)	9.2 (7.7 to 13.0)
75%	11.1 (9.6 to 13.0)	23.5 (13.1 to 23.5)
Range of event time	0.7 to 16.3	1.3 to 23.5
Stratified analysis:		
Hazard ratio[a] (95% CI)	1.6299 (1.1793 to 2.2527)	-
Log-rank test statistic (p-value)[b]	-2.9945 (0.9986)	-
Unstratified analysis:		
Hazard ratio[a] (95% CI)	1.6350 (1.1893 to 2.2479)	-
Log-rank test statistic (p-value)[c]	-3.0661 (0.9989)	-

AE = adverse event; CI = confidence interval; ITT = intent-to-treat; N = total number of subjects; n = subjects with specified criteria; vs = versus

a. Assuming proportional hazards, a hazard ratio greater than 1 indicates a reduction in hazard rate in favor bevacizumab + paclitaxel.

b. Log-rank test statistic and p-value are from a 1-sided log-rank test stratified for prior adjuvant or neo-adjuvant chemotherapy (yes vs no), hormone receptor status (positive vs negative), and disease-free interval (≤24 months vs >24 months). All stratification factors are from the Interactive Voice Randomization System.

c. Log-rank test statistic and p-value are from a 1-sided, unstratified log-rank test.

ORR and DR are summarized in Table 5. ORR was similar on the 2 treatment arms (32.2% vs 32.1% on sunitinib + paclitaxel vs bevacizumab + paclitaxel, respectively), but DR was longer on bevacizumab + paclitaxel (6.3 vs 14.8 months).

Table 5. Summary of Objective Response Rate and Duration of Response (ITT Population)

Variable	Treatment: Sunitinib + Paclitaxel n (%)	Treatment: Bevacizumab + Paclitaxel n (%)	Absolute Treatment Difference %	p-Value[a]
ORR	78 (32.2)	78 (32.1)	0.1	
95% CI[b]	(26.4 to 38.5)	(26.3 to 38.4)	(-8.2 to 8.4)	
Odds ratio (95% CI)		Stratified analysis	1.01 (0.67 to 1.50)	0.5251
		Unstratified analysis	1.01 (0.67 to 1.50)	0.5263
Duration of response (months)[b]	6.3	14.8		
95% CI	(5.6 to 7.9)	(7.4 to 21.7)		
Number of observations[c] (n%)	35 (44.9)	24 (30.8)		

CI = confidence interval; CR = complete response; DR = duration of response; ITT = intent-to-treat; n = subjects with specified criteria; ORR = Objective response rate; PR = partial response.
a. Based on a 1-sided exact test.
b. Median DR and CIs are based on the Kaplan-Meier estimates.
c. Number of subjects who had an observation of confirmed PR or CR and subsequently experienced disease progression or death.

There were 52 vs 32 deaths on sunitinib + paclitaxel vs bevacizumab + paclitaxel, respectively. One hundred ninety vs 211 observations were censored, and the reasons for censoring appeared to be balanced between the 2 treatment arms. The median OS was 17.6 months (95% CI: 16.4 to [upper limit not reached [NR] months) vs NR on sunitinib + paclitaxel vs bevacizumab + paclitaxel, respectively (Table 6).

Table 6. Summary of Overall Survival (ITT Population)

Variable	Sunitinib + Paclitaxel (N=242)	Bevacizumab + Paclitaxel (N=243)
Survival status (n [%])		
Died	52 (21.5)	32 (13.2)
Alive[a]	190 (78.5)	211 (86.8)
Subjects who ended study	84 (34.7)	91 (37.4)
Survival time (months)		
Quartile (95% CI)		
25%	12.5 (9.2 to 15.3)	15.2 (12.7 to NR)
50% (median)	17.6 (16.4 to NR)	(22.1 to NR)
75%	(22.0 to NR)	
Range of event time	1.4 to 23.8	1.3 to 22.1
1-year survival probability (95% CI)	0.768 (0.687 to 0.830)	0.837 (0.760 to 0.891)
2-year survival probability (95% CI)[b]	0.355 (0.209 to 0.503)	0.610 (0.432 to 0.747)
Stratified analysis:		
Hazard ratio[c] (95% CI)	1.8222 (1.1610 to 2.8600)	-
Log-rank test statistic (p-value)[d]	-2.6475 (0.9959)	-
Unstratified analysis:		
Hazard ratio[c] (95% CI)	1.7676 (1.1378 to 2.7461)	-
Log-rank test statistic (p-value)[e]	-2.5701 (0.9949)	-

As treated population up to 30 Aug 2011.
CI = confidence interval; ITT = intent-to-treat; N = total number of subjects; n = subjects with specified

Table 6. Summary of Overall Survival (ITT Population)

criteria.

a. Subjects who were not known to be dead at the time of the data cutoff date for the analysis were censored on the date they were last known to be alive.

b. Three-year survival could not be estimated because of insufficient data.

c. Assuming proportional hazards, a hazard ratio greater than 1 indicates a reduction in hazard rate in favor bevacizumab + paclitaxel.

d. Log-rank test statistic and p-value are from a 1-sided, stratified log-rank test. The stratification factors were prior adjuvant or neo-adjuvant chemotherapy (yes vs no), hormone receptor status (positive vs negative), and disease-free interval from prior adjuvant treatment ≤24 months vs >24 months).

e. Log-rank test statistic and p-value are from a 1-sided, unstratified log-rank test.

Outcome Research Results

QoL and measurement and valuation of health status assessments were not analyzed since enrollment in this study was terminated early for futility at the first interim analysis.

PD Results

In the sunitinib + paclitaxel arm, plasma VEGF-A levels were significantly elevated above baseline at each time point, with median ratio-to-baseline values ranging from 1.43 to 2.18. Sample sizes for analysis of PlGF and PDGF change from baseline were too small to allow meaningful interpretation. Plasma sVEGFR-2 levels were significantly reduced below baseline at time points beyond Cycle 1 Day 8, with median ratio values ranging from 0.60 to 0.86. Plasma sVEGFR-3 levels were significantly reduced below baseline at all-time points with median ratio values ranging from 0.56 to 0.91. Sample sizes for analysis of plasma sPDGFRβ change from baseline were too small to allow meaningful interpretation. sKIT levels were significantly below baseline at all -time points beyond Cycle 1 Day 8, with ratios to baseline ranging from 0.34 to 0.84.

- Comparison of Kaplan-Meier PFS Curves After Stratification by Median Baseline Soluble Protein Concentration or by Median Ratio to Baseline at Each Time Point:

In the sunitinib + paclitaxel arm, subjects with ≥ median baseline sVEGFR-2 concentrations had longer PFS (median PFS =55.0 weeks) than those with relatively lower baseline sVEGFR-2 concentrations (median PFS=20.3 weeks, log-rank p=0.0477). No significant differences in PFS were seen when subjects were stratified by median baseline concentrations of the other proteins analyzed. When subjects were stratified by the median ratio-to-baseline at each time point, no significant and consistent differences were seen for any of the proteins analyzed.

In the bevacizumab + paclitaxel arm, results for the analysis of PFS after stratification by median soluble protein levels at baseline and by median ratios to baseline showed no significant differences were seen for any of the soluble proteins analyzed at any time point, either at baseline or on treatment.

- Correlations Between Soluble Proteins and Clinical Benefit Response:

Subjects experiencing a CBR had significantly lower baseline VEGF-A concentrations than those who did not, with median VEGF-A levels of 36.4 pg/mL and 63.2 pg/mL, respectively (p=0.0356). Subjects having a CBR also had significantly lower baseline levels of sKIT than those who did not, with median sKIT concentrations of 24,657 pg/mL and 49,052 pg/mL, respectively (p=0.0335). Subjects having a CBR had significantly lower sVEGFR-3 ratios to baseline at Cycle 1, Day 15 than those without a CBR (p=0.0424), with a trend in the same direction at Cycle 1, Day 8. No other significant differences were seen in this analysis.

In the bevacizumab + paclitaxel arm, no significant differences were seen for analysis of baseline plasma protein levels by response status. Subjects experiencing a CBR had significantly higher sVEGFR-2 ratio-to-baseline values at Cycle 1 Day 15 (p=0.0145) and Cycle 3 Day 1 (p=0.0287). No other significant differences in ratio-to-baseline values were seen in this analysis.

Safety Results: An overall summary of AEs is provided in Table 7.

Table 7. Overall Summary of Adverse Events (As-Treated Population)

Variable	Sunitinib + Paclitaxel (N=235) n (%)	Bevacizumab + Paclitaxel (N=242) n (%)
Subjects with ≥1 AE	233 (99.1)	242 (100.0)
Subjects with ≥1 SAE	89 (37.9)	85 (35.1)
Subjects with ≥1 treatment-related AE[a]	229 (97.4)	235 (97.1)
Related to sunitinib	220 (93.6)	0
Related to paclitaxel	227 (96.6)	234 (96.7)
Related to bevacizumab	0	207 (85.5)
Subjects with ≥1 treatment-related SAEs[a]	53 (22.6)	35 (14.5)
Related to sunitinib	49 (20.9)	0
Related to paclitaxel	38 (16.2)	18 (7.4)
Related to bevacizumab	0	30 (12.4)
Subjects for whom study drug was discontinued permanently	68 (28.9)	99 (40.9)
Sunitinib permanently discontinued	55 (23.4)	0
Paclitaxel permanently discontinued	57 (24.3)	85 (35.1)
Bevacizumab permanently discontinued	0	74 (30.6)
Subjects who died	72 (30.6)	61 (25.2)
On-study deaths[b]	11 (4.7)	9 (3.7)
Follow-up deaths[c]	61 (26.0)	52 (21.5)

SAE and AE are not separated out in this table.
AE = adverse event; N/n = number of subjects; SAE = serious adverse event.
a. Includes AEs with causality indicated as "Yes/Unknown".
b. Deaths that occurred after the first dose date, but within 28 days after the last dose date.
c. Deaths that occurred more than 28 days after the last dose date.

Treatment emergent adverse event (TEAE) with frequency rate ≥5 are summarized in Table 8. The most commonly reported AEs in sunitinib + paclitaxel arm included neutropenia, fatigue, diarrhea, nausea, and alopecia. For bevacizumab + paclitaxel arm, the

most commonly reported AEs included fatigue, alopecia, peripheral neuropathy, nausea, and diarrhea.

Table 8. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5

System organ class MedDRA Preferred term	Sunitinib + Paclitaxel n (%)	Bevacizumab + Paclitaxel n (%)
Number (%) of subjects: evaluable for AEs	**235**	**242**
Number (%) of subjects: with AEs	232 (98.7)	239 (98.8)
Blood and lymphatic system disorders	196 (83.4)	144 (59.5)
Anaemia	104 (44.3)	65 (26.9)
Leukopenia	63 (26.8)	55 (22.7)
Lymphopenia	17 (7.2)	13 (5.4)
Neutropenia	170 (72.3)	98 (40.5)
Thrombocytopenia	56 (23.8)	15 (6.2)
Cardiac disorders	20 (8.5)	29 (12.0)
Tachycardia	8 (3.4)	12 (5.0)
Eye disorders	50 (21.3)	47 (19.4)
Lacrimation increased	14 (6.0)	14 (5.8)
Vision blurred	15 (6.4)	9 (3.7)
Gastrointestinal disorders	206 (87.7)	193 (79.8)
Abdominal pain	34 (14.5)	36 (14.9)
Abdominal pain upper	21 (8.9)	7 (2.9)
Constipation	69 (29.4)	92 (38.0)
Diarrhoea	145 (61.7)	109 (45.0)
Dry mouth	15 (6.4)	12 (5.0)
Dyspepsia	41 (17.4)	31 (12.8)
Gastrooesophageal reflux disease	28 (11.9)	12 (5.0)
Haemorrhoids	14 (6.0)	10 (4.1)
Nausea	118 (50.2)	113 (46.7)
Oral pain	21 (8.9)	8 (3.3)
Stomatitis	44 (18.7)	23 (9.5)
Vomiting	67 (28.5)	58 (24.0)
General disorders and administration site conditions	195 (83.0)	200 (82.6)
Asthenia	29 (12.3)	21 (8.7)
Chest pain	12 (5.1)	10 (4.1)
Chills	13 (5.5)	17 (7.0)
Fatigue	148 (63.0)	156 (64.5)
Mucosal inflammation	50 (21.3)	52 (21.5)
Oedema peripheral	39 (16.6)	33 (13.6)
Pain	25 (10.6)	17 (7.0)
Pyrexia	43 (18.3)	40 (16.5)
Infections and infestations	110 (46.8)	149 (61.6)
Sinusitis	18 (7.7)	21 (8.7)

Table 8. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5

System organ class MedDRA Preferred term	Sunitinib + Paclitaxel n (%)	Bevacizumab + Paclitaxel n (%)
Upper respiratory tract infection	20 (8.5)	45 (18.6)
Urinary tract infection	31 (13.2)	43 (17.8)
Investigations	108 (46.0)	98 (40.5)
Alanine aminotransferase increased	29 (12.3)	12 (5.0)
Aspartate aminotransferase increased	26 (11.1)	16 (6.6)
Blood alkaline phosphatase increased	21 (8.9)	11 (4.5)
Haemoglobin decreased	12 (5.1)	15 (6.2)
Weight decreased	32 (13.6)	30 (12.4)
Metabolism and nutrition disorders	125 (53.2)	121 (50.0)
Decreased appetite	71 (30.2)	62 (25.6)
Dehydration	31 (13.2)	22 (9.1)
Hyperglycaemia	26 (11.1)	30 (12.4)
Hypoalbuminaemia	15 (6.4)	13 (5.4)
Hypocalcaemia	15 (6.4)	7 (2.9)
Hypokalaemia	39 (16.6)	27 (11.2)
Hypomagnesaemia	17 (7.2)	19 (7.9)
Hyponatraemia	17 (7.2)	9 (3.7)
Musculoskeletal and connective tissue disorders	121 (51.5)	159 (65.7)
Arthralgia	45 (19.1)	64 (26.4)
Back pain	39 (16.6)	39 (16.1)
Bone pain	30 (12.8)	26 (10.7)
Muscle spasms	14 (6.0)	15 (6.2)
Muscular weakness	9 (3.8)	17 (7.0)
Musculoskeletal chest pain	12 (5.1)	21 (8.7)
Musculoskeletal pain	16 (6.8)	23 (9.5)
Myalgia	26 (11.1)	42 (17.4)
Pain in extremity	27 (11.5)	54 (22.3)
Nervous system disorders	175 (74.5)	201 (83.1)
Dizziness	24 (10.2)	51 (21.1)
Dysgeusia	62 (26.4)	53 (21.9)
Headache	56 (23.8)	67 (27.7)
Neuropathy peripheral	93 (39.6)	116 (47.9)
Paraesthesia	16 (6.8)	18 (7.4)
Peripheral sensory neuropathy	21 (8.9)	32 (13.2)
Psychiatric disorders	95 (40.4)	99 (40.9)
Anxiety	31 (13.2)	23 (9.5)
Depression	19 (8.1)	23 (9.5)

Table 8. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5

System organ class MedDRA Preferred term	Sunitinib + Paclitaxel n (%)	Bevacizumab + Paclitaxel n (%)
Insomnia	50 (21.3)	48 (19.8)
Respiratory, thoracic and mediastinal disorders	142 (60.4)	179 (74.0)
Cough	46 (19.6)	72 (29.8)
Dysphonia	7 (3.0)	20 (8.3)
Dyspnoea	55 (23.4)	63 (26.0)
Epistaxis	69 (29.4)	100 (41.3)
Nasal congestion	12 (5.1)	18 (7.4)
Oropharyngeal pain	21 (8.9)	32 (13.2)
Rhinorrhoea	1 (0.4)	16 (6.6)
Sinus congestion	9 (3.8)	13 (5.4)
Skin and subcutaneous tissue disorders	184 (78.3)	193 (79.8)
Alopecia	116 (49.4)	142 (58.7)
Dry skin	25 (10.6)	9 (3.7)
Erythema	14 (6.0)	10 (4.1)
Nail disorder	12 (5.1)	50 (20.7)
Palmar-plantar erythrodysaesthesia syndrome	29 (12.3)	4 (1.7)
Pruritus	18 (7.7)	21 (8.7)
Rash	66 (28.1)	60 (24.8)
Vascular disorders	92 (39.1)	117 (48.3)
Flushing	15 (6.4)	12 (5.0)
Hot flush	20 (8.5)	20 (8.3)
Hypertension	52 (22.1)	77 (31.8)
Hypotension	15 (6.4)	9 (3.7)
Lymphoedema	7 (3.0)	14 (5.8)

Subjects were only counted once per treatment for each row.
MedDRA (version 14.0) coding dictionary applied.
Includes data up to 9999 days after last dose of study drug.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subject with AEs.

A summary of treatment-related AEs by treatment, MedDRA system organ class, and preferred term is summarized in Table 9.

Table 9. Summary of Treatment-Related Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (As-Treated Population) for Events Having a Frequency Rate ≥5

System Organ Class Preferred Term	Sunitinib + Paclitaxel (N=235) Number (%) of Subjects	Bevacizumab + Paclitaxel (N=242) Number (%) of Subjects	Total (N=477) Number (%) of Subjects
Any treatment-related AEs	229 (97.4)	235 (97.1)	464 (97.3)
Blood and lymphatic system disorders	193 (82.1)	139 (57.4)	332 (69.6)
Anaemia	99 (42.1)	59 (24.4)	158 (33.1)
Febrile neutropenia	14 (6.0)	7 (2.9)	21 (4.4)
Leukopenia	62 (26.4)	55 (22.7)	117 (24.5)
Lymphopenia	17 (7.2)	13 (5.4)	30 (6.3)
Neutropenia	168 (71.5)	99 (40.9)	267 (56.0)
Thrombocytopenia	55 (23.4)	13 (5.4)	68 (14.3)
Eye disorders	27 (11.5)	29 (12.0)	56 (11.7)
Lacrimation increased	10 (4.3)	12 (5.0)	22 (4.6)
Gastrointestinal disorders	197 (83.8)	158 (65.3)	355 (74.4)
Abdominal pain	19 (8.1)	14 (5.8)	33 (6.9)
Constipation	38 (16.2)	46 (19.0)	84 (17.6)
Diarrhoea	133 (56.6)	81 (33.5)	214 (44.9)
Dyspepsia	32 (13.6)	15 (6.2)	47 (9.9)
Gastrooesophageal reflux disease	20 (8.5)	6 (2.5)	26 (5.5)
Nausea	106 (45.1)	91 (37.6)	197 (41.3)
Oral pain	21 (8.9)	8 (3.3)	29 (6.1)
Stomatitis	43 (18.3)	22 (9.1)	65 (13.6)
Vomiting	47 (20.0)	39 (16.1)	86 (18.0)
General disorders and administration site conditions	172 (73.2)	169 (69.8)	341 (71.5)
Asthenia	26 (11.1)	15 (6.2)	41 (8.6)
Fatigue	133 (56.6)	135 (55.8)	268 (56.2)
Mucosal inflammation	49 (20.9)	52 (21.5)	101 (21.2)
Oedema peripheral	16 (6.8)	14 (5.8)	30 (6.3)
Pyrexia	19 (8.1)	11 (4.5)	30 (6.3)
Investigations	78 (33.2)	63 (26.0)	141 (29.6)
Alanine aminotransferase increased	22 (9.4)	6 (2.5)	28 (5.9)
Aspartate aminotransferase increased	18 (7.7)	9 (3.7)	27 (5.7)
Haemoglobin decreased	10 (4.3)	14 (5.8)	24 (5.0)
Weight decreased	18 (7.7)	18 (7.4)	36 (7.5)
Metabolism and nutrition disorders	96 (40.9)	64 (26.4)	160 (33.5)
Decreased appetite	59 (25.1)	44 (18.2)	103 (21.6)
Dehydration	20 (8.5)	15 (6.2)	35 (7.3)
Hypokalaemia	20 (8.5)	7 (2.9)	27 (5.7)
Musculoskeletal and connective tissue disorders	61 (26.0)	86 (35.5)	147 (30.8)
Arthralgia	23 (9.8)	32 (13.2)	55 (11.5)
Myalgia	22 (9.4)	32 (13.2)	54 (11.3)
Pain in extremity	15 (6.4)	24 (9.9)	39 (8.2)

Table 9. Summary of Treatment-Related Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (As-Treated Population) for Events Having a Frequency Rate ≥5

System Organ Class Preferred Term	Sunitinib + Paclitaxel (N=235) Number (%) of Subjects	Bevacizumab + Paclitaxel (N=242) Number (%) of Subjects	Total (N=477) Number (%) of Subjects
Nervous system disorders	156 (66.4)	186 (76.9)	342 (71.7)
Dizziness	11 (4.7)	19 (7.9)	30 (6.3)
Dysgeusia	59 (25.1)	53 (21.9)	112 (23.5)
Headache	23 (9.8)	38 (15.7)	61 (12.8)
Neuropathy peripheral	87 (37.0)	116 (47.9)	203 (42.6)
Paraesthesia	14 (6.0)	18 (7.4)	32 (6.7)
Peripheral sensory neuropathy	21 (8.9)	32 (13.2)	53 (11.1)
Psychiatric disorders	22 (9.4)	18 (7.4)	40 (8.4)
Insomnia	15 (6.4)	10 (4.1)	25 (5.2)
Renal and urinary disorders	13 (5.5)	21 (8.7)	34 (7.1)
Proteinuria	6 (2.6)	16 (6.6)	22 (4.6)
Respiratory, thoracic and mediastinal disorders	90 (38.3)	109 (45.0)	199 (41.7)
Dyspnoea	24 (10.2)	21 (8.7)	45 (9.4)
Epistaxis	55 (23.4)	84 (34.7)	139 (29.1)
Skin and subcutaneous tissue disorders	170 (72.3)	175 (72.3)	345 (72.3)
Alopecia	116 (49.4)	142 (58.7)	258 (54.1)
Dry skin	21 (8.9)	5 (2.1)	26 (5.5)
Nail disorder	12 (5.1)	50 (20.7)	62 (13.0)
Palmar-plantar erythrodysaesthesia syndrome	29 (12.3)	3 (1.2)	32 (6.7)
Pruritus	14 (6.0)	14 (5.8)	28 (5.9)
Rash	57 (24.3)	42 (17.4)	99 (20.8)
Vascular disorders	62 (26.4)	91 (37.6)	153 (32.1)
Hot flush	13 (5.5)	10 (4.1)	23 (4.8)
Hypertension	37 (15.7)	68 (28.1)	105 (22.0)

AEs and SAEs are not separated out in this table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SAEs = serious adverse events.

A summary of serious AEs (SAEs) is provided in Table 10.

Table 10. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Paclitaxel (N=235) Number (%) of Subjects	Bevacizumab + Paclitaxel (N=242) Number (%) of Subjects	Total (N=477) Number (%) of Subjects
Any SAEs	89 (37.9)	85 (35.1)	174 (36.5)
Blood and lymphatic system disorders	21 (8.9)	5 (2.1)	26 (5.5)
Anaemia	3 (1.3)	1 (0.4)	4 (0.8)
Febrile neutropenia	12 (5.1)	3 (1.2)	15 (3.1)
Leukopenia	1 (0.4)	0 (0.0)	1 (0.2)
Neutropenia	6 (2.6)	2 (0.8)	8 (1.7)
Pancytopenia	2 (0.9)	0 (0.0)	2 (0.4)
Thrombocytopenia	2 (0.9)	0 (0.0)	2 (0.4)
Cardiac disorders	5 (2.1)	4 (1.7)	9 (1.9)
Atrial fibrillation	1 (0.4)	2 (0.8)	3 (0.6)
Cardiac failure congestive	1 (0.4)	1 (0.4)	2 (0.4)
Cardiogenic shock	1 (0.4)	0 (0.0)	1 (0.2)
Cardiovascular disorder	0 (0.0)	1 (0.4)	1 (0.2)
Myocardial infarction	1 (0.4)	0 (0.0)	1 (0.2)
Myocardial ischaemia	1 (0.4)	0 (0.0)	1 (0.2)
Supraventricular extrasystoles	1 (0.4)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	22 (9.4)	14 (5.8)	36 (7.5)
Abdominal pain	3 (1.3)	4 (1.7)	7 (1.5)
Abdominal pain lower	0 (0.0)	2 (0.8)	2 (0.4)
Abdominal pain upper	1 (0.4)	0 (0.0)	1 (0.2)
Ascites	1 (0.4)	0 (0.0)	1 (0.2)
Colitis ulcerative	1 (0.4)	0 (0.0)	1 (0.2)
Constipation	1 (0.4)	2 (0.8)	3 (0.6)
Diarrhoea	9 (3.8)	3 (1.2)	12 (2.5)
Diverticular perforation	1 (0.4)	0 (0.0)	1 (0.2)
Duodenitis	1 (0.4)	0 (0.0)	1 (0.2)
Gastric ulcer	1 (0.4)	0 (0.0)	1 (0.2)
Gastritis	1 (0.4)	0 (0.0)	1 (0.2)
Haematemesis	1 (0.4)	0 (0.0)	1 (0.2)
Haematochezia	0 (0.0)	1 (0.4)	1 (0.2)
Ileus	1 (0.4)	0 (0.0)	1 (0.2)
Intestinal ischaemia	0 (0.0)	1 (0.4)	1 (0.2)
Intestinal obstruction	1 (0.4)	0 (0.0)	1 (0.2)
Intestinal perforation	0 (0.0)	1 (0.4)	1 (0.2)
Lower gastrointestinal haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)
Nausea	7 (3.0)	0 (0.0)	7 (1.5)
Oesophageal perforation	1 (0.4)	0 (0.0)	1 (0.2)
Oesophagitis	0 (0.0)	1 (0.4)	1 (0.2)
Pancreatitis	0 (0.0)	2 (0.8)	2 (0.4)
Rectal haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)
Small intestinal obstruction	1 (0.4)	0 (0.0)	1 (0.2)
Stomatitis	1 (0.4)	0 (0.0)	1 (0.2)
Vomiting	9 (3.8)	1 (0.4)	10 (2.1)
General disorders and administration site conditions	24 (10.2)	19 (7.9)	43 (9.0)
Asthenia	3 (1.3)	2 (0.8)	5 (1.0)

Table 10. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Paclitaxel (N=235) Number (%) of Subjects	Bevacizumab + Paclitaxel (N=242) Number (%) of Subjects	Total (N=477) Number (%) of Subjects
Chest pain	2 (0.9)	0 (0.0)	2 (0.4)
Disease progression	7 (3.0)	7 (2.9)	14 (2.9)
Fatigue	2 (0.9)	2 (0.8)	4 (0.8)
General physical health deterioration	4 (1.7)	2 (0.8)	6 (1.3)
Generalised oedema	1 (0.4)	0 (0.0)	1 (0.2)
Malaise	0 (0.0)	1 (0.4)	1 (0.2)
Mucosal inflammation	1 (0.4)	1 (0.4)	2 (0.4)
Non-cardiac chest pain	2 (0.9)	0 (0.0)	2 (0.4)
Oedema peripheral	0 (0.0)	1 (0.4)	1 (0.2)
Pain	1 (0.4)	1 (0.4)	2 (0.4)
Pyrexia	4 (1.7)	5 (2.1)	9 (1.9)
Hepatobiliary disorders	5 (2.1)	1 (0.4)	6 (1.3)
Cholecystitis	3 (1.3)	0 (0.0)	3 (0.6)
Hepatic cirrhosis	0 (0.0)	1 (0.4)	1 (0.2)
Hyperbilirubinaemia	1 (0.4)	0 (0.0)	1 (0.2)
Jaundice cholestatic	1 (0.4)	0 (0.0)	1 (0.2)
Immune system disorders	1 (0.4)	0 (0.0)	1 (0.2)
Drug hypersensitivity	1 (0.4)	0 (0.0)	1 (0.2)
Infections and infestations	23 (9.8)	29 (12.0)	52 (10.9)
Abscess	0 (0.0)	1 (0.4)	1 (0.2)
Appendicitis	0 (0.0)	2 (0.8)	2 (0.4)
Bacteraemia	1 (0.4)	0 (0.0)	1 (0.2)
Breast infection	1 (0.4)	1 (0.4)	2 (0.4)
Bronchitis	0 (0.0)	2 (0.8)	2 (0.4)
Catheter site infection	0 (0.0)	1 (0.4)	1 (0.2)
Cellulitis	1 (0.4)	2 (0.8)	3 (0.6)
Device related infection	3 (1.3)	0 (0.0)	3 (0.6)
Device related sepsis	1 (0.4)	0 (0.0)	1 (0.2)
Diverticulitis	0 (0.0)	1 (0.4)	1 (0.2)
Escherichia bacteraemia	1 (0.4)	0 (0.0)	1 (0.2)
Gastroenteritis	1 (0.4)	1 (0.4)	2 (0.4)
Gastrointestinal viral infection	0 (0.0)	1 (0.4)	1 (0.2)
Groin infection	1 (0.4)	0 (0.0)	1 (0.2)
Hepatitis A	1 (0.4)	0 (0.0)	1 (0.2)
Infection	0 (0.0)	2 (0.8)	2 (0.4)
Neutropenic sepsis	2 (0.9)	0 (0.0)	2 (0.4)
Pneumonia	3 (1.3)	4 (1.7)	7 (1.5)
Pneumonia fungal	0 (0.0)	1 (0.4)	1 (0.2)
Pneumonia klebsiella	0 (0.0)	1 (0.4)	1 (0.2)
Pneumonia primary atypical	1 (0.4)	0 (0.0)	1 (0.2)
Post procedural infection	0 (0.0)	1 (0.4)	1 (0.2)
Sepsis	2 (0.9)	3 (1.2)	5 (1.0)
Septic shock	0 (0.0)	1 (0.4)	1 (0.2)
Sinusitis	1 (0.4)	0 (0.0)	1 (0.2)
Skin infection	0 (0.0)	1 (0.4)	1 (0.2)
Staphylococcal sepsis	0 (0.0)	2 (0.8)	2 (0.4)
Streptococcal bacteraemia	1 (0.4)	0 (0.0)	1 (0.2)

Table 10. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Paclitaxel (N=235) Number (%) of Subjects	Bevacizumab + Paclitaxel (N=242) Number (%) of Subjects	Total (N=477) Number (%) of Subjects
Upper respiratory tract infection	0 (0.0)	2 (0.8)	2 (0.4)
Urinary tract infection	3 (1.3)	5 (2.1)	8 (1.7)
Urosepsis	0 (0.0)	1 (0.4)	1 (0.2)
Viral diarrhoea	1 (0.4)	0 (0.0)	1 (0.2)
Wound infection	0 (0.0)	1 (0.4)	1 (0.2)
Injury, poisoning and procedural complications	3 (1.3)	6 (2.5)	9 (1.9)
Femur fracture	0 (0.0)	1 (0.4)	1 (0.2)
Hip fracture	1 (0.4)	1 (0.4)	2 (0.4)
Humerus fracture	1 (0.4)	1 (0.4)	2 (0.4)
Joint sprain	0 (0.0)	1 (0.4)	1 (0.2)
Lumbar vertebral fracture	1 (0.4)	0 (0.0)	1 (0.2)
Meniscus lesion	0 (0.0)	1 (0.4)	1 (0.2)
Post procedural haematoma	0 (0.0)	1 (0.4)	1 (0.2)
Radius fracture	0 (0.0)	1 (0.4)	1 (0.2)
Seroma	1 (0.4)	0 (0.0)	1 (0.2)
Wound dehiscence	1 (0.4)	0 (0.0)	1 (0.2)
Wound necrosis	0 (0.0)	1 (0.4)	1 (0.2)
Investigations	2 (0.9)	3 (1.2)	5 (1.0)
Alanine aminotransferase increased	0 (0.0)	1 (0.4)	1 (0.2)
Ammonia increased	0 (0.0)	1 (0.4)	1 (0.2)
Aspartate aminotransferase increased	0 (0.0)	1 (0.4)	1 (0.2)
Blood magnesium decreased	0 (0.0)	1 (0.4)	1 (0.2)
Blood pressure increased	1 (0.4)	0 (0.0)	1 (0.2)
Ejection fraction decreased	1 (0.4)	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	21 (8.9)	13 (5.4)	34 (7.1)
Decreased appetite	0 (0.0)	1 (0.4)	1 (0.2)
Dehydration	15 (6.4)	12 (5.0)	27 (5.7)
Electrolyte imbalance	1 (0.4)	0 (0.0)	1 (0.2)
Failure to thrive	2 (0.9)	0 (0.0)	2 (0.4)
Hypocalcaemia	1 (0.4)	2 (0.8)	3 (0.6)
Hypoglycaemia	2 (0.9)	0 (0.0)	2 (0.4)
Hypokalaemia	3 (1.3)	1 (0.4)	4 (0.8)
Hyponatraemia	1 (0.4)	0 (0.0)	1 (0.2)
Hypovolaemia	1 (0.4)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (1.7)	5 (2.1)	9 (1.9)
Arthralgia	1 (0.4)	0 (0.0)	1 (0.2)
Back pain	0 (0.0)	1 (0.4)	1 (0.2)
Bone pain	0 (0.0)	1 (0.4)	1 (0.2)
Bursitis	0 (0.0)	1 (0.4)	1 (0.2)
Muscular weakness	1 (0.4)	1 (0.4)	2 (0.4)
Musculoskeletal chest pain	1 (0.4)	0 (0.0)	1 (0.2)
Myalgia	1 (0.4)	0 (0.0)	1 (0.2)

Table 10. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Paclitaxel (N=235) Number (%) of Subjects	Bevacizumab + Paclitaxel (N=242) Number (%) of Subjects	Total (N=477) Number (%) of Subjects
Pain in extremity	1 (0.4)	0 (0.0)	1 (0.2)
Pathological fracture	1 (0.4)	1 (0.4)	2 (0.4)
Neoplasms benign, malignant and unspecified	0 (0.0)	2 (0.8)	2 (0.4)
Metastases to meninges	0 (0.0)	1 (0.4)	1 (0.2)
Tumour pain	0 (0.0)	1 (0.4)	1 (0.2)
Nervous system disorders	10 (4.3)	10 (4.1)	20 (4.2)
Cerebellar syndrome	0 (0.0)	1 (0.4)	1 (0.2)
Cerebral infarction	0 (0.0)	1 (0.4)	1 (0.2)
Cerebrovascular accident	2 (0.9)	1 (0.4)	3 (0.6)
Convulsion	1 (0.4)	0 (0.0)	1 (0.2)
Dizziness	1 (0.4)	0 (0.0)	1 (0.2)
Headache	1 (0.4)	2 (0.8)	3 (0.6)
Hydrocephalus	1 (0.4)	0 (0.0)	1 (0.2)
Lacunar infarction	0 (0.0)	1 (0.4)	1 (0.2)
Myelitis transverse	1 (0.4)	0 (0.0)	1 (0.2)
Nerve compression	1 (0.4)	0 (0.0)	1 (0.2)
Subarachnoid haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)
Syncope	3 (1.3)	2 (0.8)	5 (1.0)
Transient ischaemic attack	0 (0.0)	2 (0.8)	2 (0.4)
Psychiatric disorders	0 (0.0)	5 (2.1)	5 (1.0)
Confusional state	0 (0.0)	5 (2.1)	5 (1.0)
Renal and urinary disorders	3 (1.3)	3 (1.2)	6 (1.3)
Nephrotic syndrome	1 (0.4)	1 (0.4)	2 (0.4)
Renal failure acute	2 (0.9)	0 (0.0)	2 (0.4)
Urethral obstruction	0 (0.0)	1 (0.4)	1 (0.2)
Urinary retention	0 (0.0)	1 (0.4)	1 (0.2)
Respiratory, thoracic and mediastina disorders	17 (7.2)	15 (6.2)	32 (6.7)
Acute pulmonary oedema	0 (0.0)	1 (0.4)	1 (0.2)
Acute respiratory failure	1 (0.4)	0 (0.0)	1 (0.2)
Dyspnoea	6 (2.6)	2 (0.8)	8 (1.7)
Epistaxis	1 (0.4)	3 (1.2)	4 (0.8)
Haemoptysis	1 (0.4)	2 (0.8)	3 (0.6)
Pleural effusion	4 (1.7)	1 (0.4)	5 (1.0)
Pneumonitis	1 (0.4)	1 (0.4)	2 (0.4)
Pneumothorax	1 (0.4)	0 (0.0)	1 (0.2)
Pulmonary embolism	4 (1.7)	4 (1.7)	8 (1.7)
Respiratory failure	0 (0.0)	1 (0.4)	1 (0.2)
Stridor	1 (0.4)	0 (0.0)	1 (0.2)
Surgical and medical procedures	0 (0.0)	1 (0.4)	1 (0.2)
Mastectomy	0 (0.0)	1 (0.4)	1 (0.2)
Vascular disorders	5 (2.1)	4 (1.7)	9 (1.9)
Aneurysm	1 (0.4)	0 (0.0)	1 (0.2)
Arterial rupture	1 (0.4)	0 (0.0)	1 (0.2)
Deep vein thrombosis	1 (0.4)	2 (0.8)	3 (0.6)
Hypertension	1 (0.4)	0 (0.0)	1 (0.2)
Hypotension	2 (0.9)	2 (0.8)	4 (0.8)

Table 10. Summary of Serious Adverse Events by Treatment, MedDRA System Organ Class, and Preferred Term (As-Treated Population)

	Sunitinib + Paclitaxel (N=235)	Bevacizumab + Paclitaxel (N=242)	Total (N=477)
System Organ Class Preferred Term	Number (%) of Subjects	Number (%) of Subjects	Number (%) of Subjects

MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects.

Treatment-related SAEs are summarized in Table 11.

Table 11. Summary of Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (As-Treated Population)

	Sunitinib + Paclitaxel (N=235)	Bevacizumab + Paclitaxel (N=242)	Total (477)
System Organ Class Preferred Term	**Number (%) of Subjects**	**Number (%) of Subjects**	**Number (%) of Subjects**
Any Treatment-related SAEs	53 (22.6)	35 (14.5)	88 (18.4)
Blood and lymphatic system disorders	20 (8.5)	5 (2.1)	25 (5.2)
Anaemia	3 (1.3)	1 (0.4)	4 (0.8)
Febrile neutropenia	11 (4.7)	3 (1.2)	14 (2.9)
Leukopenia	1 (0.4)	0 (0.0)	1 (0.2)
Neutropenia	6 (2.6)	2 (0.8)	8 (1.7)
Pancytopenia	2 (0.9)	0 (0.0)	2 (0.4)
Thrombocytopenia	2 (0.9)	0 (0.0)	2 (0.4)
Cardiac disorders	4 (1.7)	2 (0.8)	6 (1.3)
Atrial fibrillation	1 (0.4)	0 (0.0)	1 (0.2)
Cardiac failure congestive	1 (0.4)	1 (0.4)	2 (0.4)
Cardiovascular disorder	0 (0.0)	1 (0.4)	1 (0.2)
Myocardial ischaemia	1 (0.4)	0 (0.0)	1 (0.2)
Supraventricular extrasystoles	1 (0.4)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	15 (6.4)	5 (2.1)	20 (4.2)
Abdominal pain	1 (0.4)	1 (0.4)	2 (0.4)
Colitis ulcerative	1 (0.4)	0 (0.0)	1 (0.2)
Constipation	1 (0.4)	0 (0.0)	1 (0.2)
Diarrhoea	9 (3.8)	1 (0.4)	10 (2.1)
Diverticular perforation	1 (0.4)	0 (0.0)	1 (0.2)
Duodenitis	1 (0.4)	0 (0.0)	1 (0.2)
Gastric ulcer	1 (0.4)	0 (0.0)	1 (0.2)
Gastritis	1 (0.4)	0 (0.0)	1 (0.2)
Haematochezia	0 (0.0)	1 (0.4)	1 (0.2)
Intestinal perforation	0 (0.0)	1 (0.4)	1 (0.2)
Lower gastrointestinal haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)
Nausea	4 (1.7)	0 (0.0)	4 (0.8)
Oesophageal perforation	1 (0.4)	0 (0.0)	1 (0.2)
Pancreatitis	0 (0.0)	1 (0.4)	1 (0.2)
Rectal haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)
Stomatitis	1 (0.4)	0 (0.0)	1 (0.2)
Vomiting	3 (1.3)	0 (0.0)	3 (0.6)
General disorders and administration site conditions	7 (3.0)	5 (2.1)	12 (2.5)
Asthenia	2 (0.9)	2 (0.8)	4 (0.8)
Fatigue	2 (0.9)	0 (0.0)	2 (0.4)
General physical health deterioration	1 (0.4)	0 (0.0)	1 (0.2)
Generalised oedema	1 (0.4)	0 (0.0)	1 (0.2)
Mucosal inflammation	1 (0.4)	1 (0.4)	2 (0.4)
Oedema peripheral	0 (0.0)	1 (0.4)	1 (0.2)
Pyrexia	1 (0.4)	1 (0.4)	2 (0.4)
Hepatobiliary disorders	3 (1.3)	0 (0.0)	3 (0.6)
Cholecystitis	2 (0.9)	0 (0.0)	2 (0.4)
Hyperbilirubinaemia	1 (0.4)	0 (0.0)	1 (0.2)

Table 11. Summary of Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (As-Treated Population)

	Sunitinib + Paclitaxel (N=235)	Bevacizumab + Paclitaxel (N=242)	Total (477)
System Organ Class Preferred Term	Number (%) of Subjects	Number (%) of Subjects	Number (%) of Subjects
Immune system disorders	1 (0.4)	0 (0.0)	1 (0.2)
Drug hypersensitivity	1 (0.4)	0 (0.0)	1 (0.2)
Infections and infestations	6 (2.6)	7 (2.9)	13 (2.7)
Bronchitis	0 (0.0)	1 (0.4)	1 (0.2)
Catheter site infection	0 (0.0)	1 (0.4)	1 (0.2)
Device related infection	1 (0.4)	0 (0.0)	1 (0.2)
Groin infection	1 (0.4)	0 (0.0)	1 (0.2)
Neutropenic sepsis	2 (0.9)	0 (0.0)	2 (0.4)
Pneumonia	0 (0.0)	2 (0.8)	2 (0.4)
Sepsis	1 (0.4)	2 (0.8)	3 (0.6)
Septic shock	0 (0.0)	1 (0.4)	1 (0.2)
Skin infection	0 (0.0)	1 (0.4)	1 (0.2)
Staphylococcal sepsis	0 (0.0)	1 (0.4)	1 (0.2)
Urinary tract infection	1 (0.4)	1 (0.4)	2 (0.4)
Wound infection	0 (0.0)	1 (0.4)	1 (0.2)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.4)	1 (0.2)
Meniscus lesion	0 (0.0)	1 (0.4)	1 (0.2)
Investigations	2 (0.9)	1 (0.4)	3 (0.6)
Blood magnesium decreased	0 (0.0)	1 (0.4)	1 (0.2)
Blood pressure increased	1 (0.4)	0 (0.0)	1 (0.2)
Ejection fraction decreased	1 (0.4)	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	11 (4.7)	5 (2.1)	16 (3.4)
Decreased appetite	0 (0.0)	1 (0.4)	1 (0.2)
Dehydration	9 (3.8)	5 (2.1)	14 (2.9)
Electrolyte imbalance	1 (0.4)	0 (0.0)	1 (0.2)
Failure to thrive	1 (0.4)	0 (0.0)	1 (0.2)
Hypocalcaemia	0 (0.0)	1 (0.4)	1 (0.2)
Hypokalaemia	2 (0.9)	1 (0.4)	3 (0.6)
Hypovolaemia	1 (0.4)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.4)	1 (0.4)	2 (0.4)
Muscular weakness	0 (0.0)	1 (0.4)	1 (0.2)
Myalgia	1 (0.4)	0 (0.0)	1 (0.2)
Nervous system disorders	3 (1.3)	4 (1.7)	7 (1.5)
Cerebellar syndrome	0 (0.0)	1 (0.4)	1 (0.2)
Cerebral infarction	0 (0.0)	1 (0.4)	1 (0.2)
Cerebrovascular accident	0 (0.0)	1 (0.4)	1 (0.2)
Dizziness	1 (0.4)	0 (0.0)	1 (0.2)
Headache	0 (0.0)	1 (0.4)	1 (0.2)
Myelitis transverse	1 (0.4)	0 (0.0)	1 (0.2)
Syncope	1 (0.4)	0 (0.0)	1 (0.2)
Psychiatric disorders	0 (0.0)	1 (0.4)	1 (0.2)
Confusional state	0 (0.0)	1 (0.4)	1 (0.2)
Renal and urinary disorders	2 (0.9)	0 (0.0)	2 (0.4)
Nephrotic syndrome	1 (0.4)	0 (0.0)	1 (0.2)
Renal failure acute	1 (0.4)	0 (0.0)	1 (0.2)

Table 11. Summary of Treatment-Related Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Paclitaxel (N=235) Number (%) of Subjects	Bevacizumab + Paclitaxel (N=242) Number (%) of Subjects	Total (477) Number (%) of Subjects
Respiratory, thoracic and mediastinal disorders	8 (3.4)	10 (4.1)	18 (3.8)
Acute pulmonary oedema	0 (0.0)	1 (0.4)	1 (0.2)
Acute respiratory failure	1 (0.4)	0 (0.0)	1 (0.2)
Dyspnoea	1 (0.4)	0 (0.0)	1 (0.2)
Epistaxis	1 (0.4)	2 (0.8)	3 (0.6)
Haemoptysis	0 (0.0)	2 (0.8)	2 (0.4)
Pleural effusion	1 (0.4)	0 (0.0)	1 (0.2)
Pneumonitis	1 (0.4)	1 (0.4)	2 (0.4)
Pulmonary embolism	3 (1.3)	4 (1.7)	7 (1.5)
Stridor	1 (0.4)	0 (0.0)	1 (0.2)
Vascular disorders	1 (0.4)	0 (0.0)	1 (0.2)
Hypertension	1 (0.4)	0 (0.0)	1 (0.2)

MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects.

A total of 55 (23.4%) sunitinib + paclitaxel subjects discontinued sunitinib due to an AE. The most common AEs that led to study drug discontinuation of sunitinib for sunitinib + paclitaxel subjects were fatigue (5 subjects), neutropenia (4 subjects), and diarrhea (4 subjects). A total of 57 (24.3%) sunitinib + paclitaxel and 85 (35.1%) bevacizumab + paclitaxel subjects discontinued paclitaxel due to an AE. The most common AEs that led to study drug discontinuation of paclitaxel included peripheral neuropathy (8 subjects), fatigue (6 subjects), and neutropenia (5 subjects) in sunitinib + paclitaxel subjects; and peripheral neuropathy (26 subjects), fatigue (5 subjects), and peripheral sensory neuropathy (5 subjects) in bevacizumab + paclitaxel subjects. A total of 74 subjects in bevacizumab + paclitaxel arm discontinued bevacizumab due to an AE. The most common AEs that led to study drug discontinuation of bevacizumab for bevacizumab + paclitaxel subjects included peripheral neuropathy (9 subjects), deep vein thrombosis (3 subjects), and hypertension (3 subjects).

A total of 150 (63.8%) subjects had an interruption or change in sunitinib dose due to an AE during the study. The most common AEs that led to interruption or changes in sunitinib dose were neutropenia (39 [16.6%] subjects) and diarrhea (31 [13.2%] subjects).

A summary of on-study deaths is provided in. Table 12. A total of 11 (4.6%) sunitinib + paclitaxel and 9 (3.6%) bevacizumab + paclitaxel subjects died on study treatment or within 28 days of their last dose of study medication. The most common reason for death was disease progression (includes disease progression and death due to disease progression (also includes progression of disease).

Table 12. Summary of On-Study Deaths by Treatment (Intent-to-Treat Population)

Variable	Sunitinib + Paclitaxel (N=235) n (%)[a]	Bevacizumab + Paclitaxel (N=242) n (%)[a]	Total (N=477) n (%)[a]
Subjects who died	72 (29.9)	61 (24.7)	133 (27.3)
Subjects who died on-study[b]	11 (4.6)	9 (3.6)	20 (4.1)
Acute pulmonary edema	0	1 (0.4)	1 (0.2)
Cardiogenic shock	1 (0.4)	0	1 (0.2)
Disease progression[c]	7 (3.0)	6 (2.5)	13 (2.7)
Failure to thrive	1 (0.4)	0	1 (0.2)
Global deterioration of health status	2 (0.8)	1 (0.4)	3 (0.6)
Septic shock	0	1 (0.4)	1 (0.2)

N/n=number of subjects.
a. %=(n/N)*100.
b. Deaths that occurred after the first dose date, but within 28 days after the last dose date.
c. Includes death due to disease progression, disease progression, and progression of disease.

ECG: There were 3 sunitinib + paclitaxel and 2 bevacizumab + paclitaxel subjects with a post-baseline QTcF value with a maximum CTCAE Grade 3/4

Vital Signs: The mean changes from baseline to end of treatment were small and not clinically significant in either treatment group.

MUGA Scans and ECHO: There was no evidence of a systematic mean decrease during treatment on either treatment arm.

CONCLUSIONS:

- Sunitinib + paclitaxel was not more effective than bevacizumab + paclitaxel in the first-line treatment of advanced BC, with a median PFS of 7.4 vs 9.2 months, respectively.

- ORR was similar between the treatment arms (32.2% vs 32.1%); however, DR was much shorter in the sunitinib + paclitaxel arm than in the bevacizumab + paclitaxel arm, with a median DR of 6.3 vs 14.8 months, respectively.

- Bevacizumab + paclitaxel appeared to be more tolerable than sunitinib + paclitaxel, primarily due to a notable increase in Grade 3/4 neutropenia on sunitinib + paclitaxel as compared with bevacizumab + paclitaxel, while manageability of AEs appeared to be similar on both treatment arms.

- Administration of both the combination of sunitinib + paclitaxel and bevacizumab + paclitaxel had acceptable safety profiles as there were similar incidences of treatment-related SAEs (22.6% vs 14.5%, respectively), deaths (4.6% vs 3.6%, respectively), and Grade 3-4 AEs (82.1% vs 73.1%, respectively); however, sunitinib + paclitaxel had a lower incidence of discontinuations due to AEs than in bevacizumab + paclitaxel (28.9% vs 40.9%) when administered to subjects with breast cancer in the first-line advanced disease setting.

- In the sunitinib + paclitaxel arm, longer PFS was associated with relatively high (≥ median) baseline plasma sVEGFR-2 concentrations and subjects experiencing a CBR had significantly lower baseline plasma concentrations of VEGF-A and sKIT than those who did not. No associations were observed between either PFS or CBR and baseline protein concentrations in the bevacizumab + paclitaxel arm, and there were no consistent associations between ratio-to-baseline values on study and PFS or CBR in either treatment arm.