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

PROTOCOL NO.: A6181064

PROTOCOL TITLE: A Randomised, Phase 3 Study of Docetaxel in Combination With Sunitinib Versus Docetaxel in the First-Line Treatment of Advanced Breast Cancer Patients

Study Centers: A total of 127 centers took part in the study and enrolled subjects; 12 each in Germany and Italy, 10 in Spain, 9 in France, 8 in the United Kingdom (UK), 7 in the Russian Federation, 5 in Australia, 4 each in Austria, Canada, the Czech Republic, Hungary, Portugal, Romania, Slovakia, and Ukraine, 3 each in Argentina, Belgium, Ireland, Poland, Netherlands, the Republic of Korea, Sweden, Turkey, and the United States (US), 2 each in Colombia and Finland, and 1 in Panama.

Study Initiation Date and Final Completion Date: 27 February 2007 to 15 July 2011.

Primary Completion Date: 01 February 2010.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To demonstrate that the combination of docetaxel with sunitinib was superior to docetaxel in prolonging progression-free survival (PFS) in subjects with advanced breast cancer (ABC).

Secondary Objectives:

- To compare the clinical benefit in subjects treated with the 2 regimens;
- To compare the safety of the 2 regimens;
- To compare the patient reported outcomes (PROs) of subjects treated with the 2 regimens.

METHODS:

Study Design: This study was a multinational, multicenter, randomized, open-label, Phase 3 clinical trial comparing the efficacy and safety of docetaxel in combination with sunitinib versus docetaxel in subjects with ABC. Eligible subjects had human epidermal growth factor-2 (HER-2) negative disease and were candidates for receiving docetaxel as first-line treatment for their advanced disease. In order to avoid inclusion of subjects who were

refractory or resistant to taxanes, subjects who had received a taxane as a component of their adjuvant regimen could enter the study only if ≥12 months had elapsed since completion of their adjuvant chemotherapy. Subjects were required to have not received treatment other than hormonal therapies for advanced disease and to not have been candidates for curative therapies. Subjects were required to have measurable disease as per Response Evaluation Criteria in Solid Tumors or bone-only disease as their only site of disease. Subjects that had bone-only disease who were hormone receptor-positive were required to have had disease progression during or after hormone therapy to be eligible.

Subjects were randomly assigned (1:1) to either docetaxel/sunitinib or docetaxel. The randomization was stratified according to the following known prognostic factors: number of metastatic sites ≤2 versus >2 sites), estrogen receptor (ER) status (negative versus positive/unknown), and disease-free interval from prior adjuvant treatment (≤12 months versus >12 months).

An external, independent central radiological laboratory reviewed all tumor assessments performed during the study for determination of tumor response and progression dates. An external independent Data Monitoring Committee periodically reviewed accumulating safety data and planned interim analyses. The study was designed to have 2 interim analyses and a final analysis based on the primary endpoint of PFS.

The schedule of activities during the study is provided in Table 1 and Table 2.

Table 1. Schedule of Activities

Treatment and Safety Procedures[b]	Screening	Treatment Period[a]								
		Cycle 1				Additional Cycles		Post-Treatment		
	≤21 Days	Day 1	Day 2	Day 7 (±3 days)	Day 15 (±2 days)	Day 1 (±2 days)	Day 2	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	X	
Baseline signs/symptoms		X								
Clinical laboratory tests										
Hematology	X	X[g]		X	X	X		X	X	
Serum chemistry	X	X[g]				X		X	X	
Thyroid function and pregnancy[h]	X									
Urinalysis[i]	X					(X)		X	(X)	
12-lead ECG[j]	X				X			X		
MUGA scan or echocardiography	X					(X)		X		
Treatments										
Premedication[k]		→X→				→X→				
Docetaxel[l]		X				X				
Sunitinib[m]			X→	→	→X		X→			
Other clinical assessments										
Compliance[n]					X	X		X		
Adverse events[o]		X→	→	→	→	→	→	→	→X	
Concomitant medications[p]	X→	→	→	→	→	→	→	→	→X	

Table 1. Schedule of Activities

( ) indicates an optional procedure or assessment.
ECG = electrocardiogram; MUGA = Multigated acquisition (scan).

a. Each cycle was 3 weeks long, with docetaxel administration on Day 1 and sunitinib administration on Days 2-15. Cycles could have been delayed up to 2 weeks to allow recovery from toxicity.
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 3 weeks of study withdrawal (6 weeks for tumor assessments).
d. 28 days after termination; all assessments were as necessary to follow-up adverse events. Serious and sunitinib-related adverse events 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 6 weeks until progression. After progression survival status was determined every 2 months.
f. Examination of major body systems; including Eastern Cooperative Oncology Group (ECOG) performance status, vital signs (temperature, blood pressure, pulse, and respiration rate), and weight. Height at screening only.
g. Day 1 assessments not required if acceptable screening assessments performed within 7 days before dosing.
h. Thyroid-stimulating hormone (TSH) repeated as clinically indicated. Pregnancy for women of child-bearing potential; repeated as required by local guidelines.
i. Urinalysis was to be performed by dipstick at baseline, Cycle 3 Day 1, at the end of each study treatment and as clinically indicated. If ≥2+ proteinuria was indicated, then follow-up was performed with a quantitative urine protein analysis according to local standard practices.
j. Three consecutive 12-lead ECGs, performed at least 2 minutes apart, to determine mean corrected-QT (Fridericia's [cube root] correction; QTcF) interval. Triplicate ECG was also performed as clinically indicated throughout the study.
k. Premedication for docetaxel, oral dexamethasone 8 mg twice daily, or equipotent doses of oral prednisone or prednisolone or methylprednisolone, given for 3 days starting 1 day before docetaxel administration.
l. 75 mg/m2 (Arm A: docetaxel/sunitinib) or 100 mg/m2 (Arm B: docetaxel), as a 1-hour infusion.
m. Administered daily on Days 2 to 15 of each cycle at a starting dose of 37.5 mg (Arm A: docetaxel/sunitinib only). Docetaxel was administered by study site research staff and the administration was recorded (both arms).
n. Bottles and any unused capsules were returned to the clinic on Day 15 of Cycle 1 and Day 1 of Cycles ≥3.
o. Adverse events 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." Serious adverse events were reported from the time of informed consent.
p. Concomitant medications and treatments were recorded from 28 days before Day 1 to 28 days after the last dose of study treatment.

Table 2. Schedule of Activities–Other Study Procedures

Other Procedures[b]	Screening	Treatment Period[a]					Post-Treatment		
		First 3-Week Cycle				Every 6 Weeks After Randomization (±7 days)			
	≤21 Days	Day 1	Day 2	Day 7	Day 13 - 15		End of Treatment[c]	Post Treatment[d]	Follow-up[e]
Tumor imaging[f]	X					X	X[g]	X	X
Bone scan[h]	X					X	X	X	X
PRO assessments[i]		X				X	X		
Survival follow-up									X

BR23 = EORTC Quality of Life Questionnaire breast cancer module; CT = computed tomography; DNA = deoxyribonucleic acid; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D = European Quality of Life 5-dimensional; FDG-PET = fluorodeoxyglucose positron-emission tomography; MRI = magnetic resonance imaging; PRO = patient-reported outcomes.

a. Each cycle was 3 weeks long, with docetaxel administration on Day 1 and sunitinib administration on Days 2-15. Cycles could have been delayed up to 2 weeks to allow recovery from toxicity.
b. Tumor assessments, bone scans, and PRO assessments were performed every 6 weeks after randomization, regardless of dosing delays or interruptions.
c. Assessments did not need to be completed if they had been performed within 3 weeks of study withdrawal (6 weeks for tumor assessments).
d. 28 days after termination; all assessments were as necessary to follow-up adverse events. Serious and sunitinib-related adverse events 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 6 weeks until progression. After progression survival status was determined every 2 months.
f. CT or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis and photographs of superficial metastases. Brain CT or MRI at screening and at any time of suspected brain metastasis.
g. Bottles and any unused capsules were returned to the clinic on Day 15 of Cycle 1 and Day 1 of Cycles ≥3.
h. Bone scan required every 12 weeks for bone-only disease subjects unless bone lesions identified at screening and followed for response, in which case every 6 weeks. If bone lesions were followed for response, lesions identified on bone scan were further assessed by X-ray, CT, or MRI.
i. EORTC QLQ-C30, BR23, and EQ-5D. These assessments were to be the first assessments performed at the indicated visits and scheduled to coincide with tumor assessments.

Number of Subjects (Planned and Analyzed): A total sample size of approximately 550 subjects (275 in each treatment arm) was planned for the study.

A total of 593 subjects were randomized of which 296 subjects received sunitinib + docetaxel and 297 subjects received docetaxel alone. One versus 4 subjects on the sunitinib + docetaxel versus docetaxel, respectively, were randomized but did not receive any study treatment. Thus 295 subjects received sunitinib + docetaxel and 293 subjects received docetaxel.

Of 593 subjects; 62 were randomized in Russian Federation, 59 in Ukraine, 56 in France, 54 in Spain, 40 in Italy, 35 in Germany, 32 in Austria, 27 in Sweden, 25 in the Republic of Korea, 24 in the UK, 19 in Australia, 18 in Portugal, 15 each in Czech republic and Turkey, 14 in Belgium; 13 in Canada; 11 each in Ireland, Poland, and Slovakia, 10 in Panama, 9 in Hungary, 8 in Romania, 7 in Argentina, 6 each in Colombia and the Netherlands, and 3 each in Finland and the US.

Diagnosis and Main Criteria for Inclusion: Female subjects aged 18 years and older diagnosed with breast cancer with evidence of unresectable locally recurrent or metastatic disease and HER-2 negative tumors were included in the study. Subjects for whom docetaxel was contraindicated and subjects with clinical presentation of inflammatory carcinoma with no other measurable disease were excluded from the study.

Study Treatment: Subjects were randomly assigned (1:1) to either docetaxel/sunitinib (Arm A) or docetaxel (Arm B). Treatment was administered in 3-week cycles. On Arm A, docetaxel was administered intravenously (IV) as a 1-hour infusion once every 3 weeks (on Day 1 of each 3-week cycle) at a starting dose of 75 mg/m^2, and sunitinib was administered orally from Day 2 to Day 15 every 3 weeks (Schedule 2/1) at a starting dose of 37.5 mg. On Arm B, docetaxel was administered IV as a 1-hour infusion once every 3 weeks (on Day 1 of each 3-week cycle) at a starting dose of 100 mg/m^2.

Sequential administration of study treatments was chosen to lower the possibility of any interaction between the 2 drugs and to minimize any overlapping toxicities that might occur between IV administered docetaxel and orally administered sunitinib. Crossover between treatment arms was not permitted.

Central supply or locally obtained commercial supplies of docetaxel was used, in accordance with local regulations. Docetaxel was prepared, dispensed, and administered according to product labeling. Sunitinib L-malate salt was supplied to the clinic pharmacy by the Sponsor as hard gelatin capsules containing either 12.5 mg, or 25 mg or 50 mg equivalents of sunitinib free base, in light-resistant bottles containing 30 capsules.

Efficacy, Outcome Research, and Safety Endpoints:

Primary Efficacy Endpoint: PFS (in months) was the primary efficacy endpoint.

Secondary Efficacy Endpoints:

- Objective response rate (ORR);

- Duration of response (DR);
- Overall survival (OS);

Outcome Research Endpoints: PRO changes in scores for health-related quality of life and disease/treatment-related symptoms as measured by the core questionnaire of the European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire (EORTC QLQ-C30) and the companion breast cancer module (QLQ-BR23), and the EuroQol Group's EQ-5D Self-Report Questionnaire (EQ-5D).

Safety Endpoints: Safety endpoints included type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0), timing, seriousness, and relationship to study therapy of adverse events (AEs); laboratory abnormalities.

Safety Evaluations: Safety evaluations included: assessment of AEs, laboratory assessments (hematology, blood chemistry, thyroid function tests, pregnancy test and urinalysis), and other safety assessments including physical examination, performance status as per Eastern Cooperative Oncology Group (ECOG) performance status scale, vital signs (temperature, blood pressure [BP], heart rate, and respiratory rate after 5 minutes of rest), 12-lead electrocardiogram, and echocardiography or multigated acquisition scan.

Statistical Methods:

Intent-to-Treat (ITT) Population: The ITT population was the primary population for evaluating all efficacy endpoints and subject characteristics, which comprised of all subjects who were randomized, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.

As-Treated (AT) Population: The AT population was the primary population for evaluating safety which comprised of all subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. Secondary analyses of other endpoints could be performed on the AT population.

Time-to-event endpoints between 2 treatment arms were compared with a 2-sided stratified log-rank test and an unstratified log-rank test at α=0.05 overall significance level. Cox-proportional hazard models were planned to explore the potential influences of the baseline stratification factors (prior adjuvant chemotherapy, hormone receptor status, disease free interval, and number of metastatic sites) on time-to-event endpoints. In addition, potential influences of baseline subject characteristics such as age, ethnic origin, and performance status on the endpoints could be evaluated. Additionally for each treatment arm, the median event time and a 2-sided 95% confidence interval (CI) are provided for each level of stratification factors or baseline characteristics.

Time-to-event endpoints were summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% CIs for each median are provided. In addition, some time-to-event endpoints were compared between the 2 treatment arms using a 1-sided unstratified log-rank test with a significance level of 0.025.

The rates of binary endpoints for the 2 treatment arms were compared with a significance level of 0.025 using a 1-sided Cochran-Mantel-Haenszel 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.

RESULTS:

Subject Disposition and Demography: Table 3 summarizes the overall subject disposition of the different subject populations. Two hundred ninety-six versus 297 subjects randomized to sunitinib + docetaxel versus docetaxel, respectively comprised the ITT population. One versus 4 randomized subjects on the sunitinib + docetaxel versus docetaxel, respectively did not receive any study treatment. Two hundred and ninety-five versus 293 subjects on sunitinib + docetaxel versus docetaxel, respectively, comprised the AT population.

The reasons for study discontinuation are summarized in Table 3. Subjects might have discontinued study treatment for reasons other than those summarized in Table 3 but remained on active follow-up.

Table 3. Disposition of Subjects (ITT and AT Populations)

Variable	Sunitinib + Docetaxel (N=296)	Docetaxel (N=297)	Total (N=593)
Randomized/ITT population, N[a]	296	297	593
Randomized/ITT but did not take any drug, n (%)	1 (0.3)	4 (1.3)	5 (0.8)
Received sunitinib and docetaxel, n (%)	295 (99.7)	0	295 (49.7)
Received sunitinib only, n (%)	0	0	0
Received docetaxel only, n (%)	0	293 (98.7)	293 (49.4)
AT population, N[b]	295	293	588
Subjects who discontinued from the study, n (%)	296 (100.0)	297 (100.0)	593 (100.0)
Primary reason for discontinuation from the study, n (%)			
Adverse event	0	0	0
Protocol violation	1 (0.3)	1 (0.3)	2 (0.3)
Lost to follow-up	2 (0.7)	4 (1.3)	6 (1.0)
Subject died	10 (3.4)	4 (1.3)	14 (2.4)
Decision of Sponsor	5 (1.7)	13 (4.4)	18 (3.0)
Withdrawn due to pregnancy	0	0	0
Objective progression or relapse	239 (80.7)	223 (75.1)	462 (77.9)
Global deterioration of health status	0	0	0
Subject refused continued treatment for reason other than AE	2 (0.7)	7 (2.4)	9 (1.5)
Other	37 (12.5)	45 (15.2)	82 (13.8)

AE = adverse event; AT = as-treated; ITT = intent-to-treat; N = number of subjects in each group; n = number of subjects with specified criteria.

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

b. The AT population included all subjects who received at least 1 dose of study treatment with treatment assignments designated according to actual study treatment received.

Demographic and baseline characteristics are summarized by treatment arm for the ITT population in Table 4. All subjects were female. Overall, no major imbalances have been observed between the 2 arms.

The median age was 54.0 and 56.0 years (range: 31.0 to 84.0 years on sunitinib + docetaxel versus 28.0 to 78.0 years on docetaxel). The majority of subjects in both arms were <65 years (84.8% versus 81.8% on sunitinib + docetaxel versus docetaxel).

Table 4. Summary of Demographic and Baseline Characteristics (ITT Population)

Variable	Sunitinib + Docetaxel (N=296)	Docetaxel (N=297)
Age (years)		
Mean (standard deviation)	54.3 (9.74)	55.1 (10.36)
Median	54.0	56.0
Min, Max	31.0, 84.0	28.0, 78.0
Age category, n (%)		
<65	251 (84.8)	243 (81.8)
≥65	45 (15.2)	54 (18.2)
Sex, n (%)		
Female	296 (100.0)	297 (100.0)
Race, n (%)		
White	268 (90.5)	275 (92.6)
Black	2 (0.7)	1 (0.3)
Asian	18 (6.1)	8 (2.7)
Other	8 (2.7)	13 (4.4)
ECOG performance status, n (%)[a]		
0	167 (56.4)	161 (54.2)
1	125 (42.2)	136 (45.8)
≥2	3 (1.0)	0
Missing	1 (0.3)	0

ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; Min = minimum; Max = maximum; N = number of subjects in each treatment group; n = number of subjects with specified criteria.
a. Baseline ECOG performance status score was the last value on or before the first dose date.

Efficacy Results: The primary endpoint of this study was the PFS on sunitinib + docetaxel as compared to that on docetaxel.

In the primary analysis of PFS (independent radiology assessment, ITT population), the median PFS was similar on the 2 treatment arms, being 8.6 months (95% CI: 8.2 to 10.3 months) on sunitinib + docetaxel compared with 8.3 months (95% CI: 7.7 to 9.6 months) on docetaxel, (stratified hazard ratio of 0.9222 [95% CI: 0.7156 to 1.1885]; 1-sided log-rank test p-value = 0.2651). The results were similar in the supportive analyses using the AT population and in both analysis populations when using the Investigators' assessments of PFS and when controlling for stratification factors and for other demographic and known risk factors.

Other efficacy measures included ORR, DR, and OS. Of these, in the independent radiology assessment in the ITT population, there was a statistically significant difference in ORR (51.0% versus 39.1% on sunitinib + docetaxel versus docetaxel, respectively; p-value = 0.0018). One-hundred and nineteen (40.2%) versus 150 subjects (50.5%) had stable disease. The median DR was 7.5 months (95% CI: 6.3 to 9.8 months) versus 7.2 months (95% CI: 5.7 to 9.9 months).

An overview of efficacy results are presented in Table 5.

Table 5. Summary of Time-to-Event Endpoints (ITT and AT Populations)

Variable	Number of Events		Hazard Ratio[a]	95% CI of Hazard Ratio[a]	p-Value[a]
	Sunitinib + Docetaxel n (%)	Docetaxel n (%)			
Progression-Free Survival					
Independent radiology assessment					
ITT population, N					
Events, n (%)	147 (49.7)	109 (36.7)	a: 0.9222	0.7156 to 1.1885	0.2651
Median (months)	8.6	8.3	b: 0.9474	0.7385 to 1.2153	0.3355
95% CI	8.2 to 10.3	7.7 to 9.6			
AT population, N					
Events, n (%)	147 (49.8)	109 (37.2)	a: 0.9222	0.7156 to 1.1885	0.2651
Median (months)	8.6	8.3	b: 0.9474	0.7385 to 1.2153	0.3355
95% CI	8.2 to 10.3	7.7 to 9.6			
Investigators' assessment					
ITT population, N					
Events, n (%)	198 (66.9)	162 (54.5)	a: 0.8560	0.6921 to 1.0589	0.0753
Median (months)	8.2	6.9	b: 0.8714	0.7067 to 1.0745	0.0980
95% CI	7.3 to 8.6	6.5 to 7.3			
Overall Survival					
ITT population, N					
Events, n (%)	161 (54.4)	148 (49.8)	a: 1.1539	0.9209 to 1.4458	0.8933
Median (months)	26.0	28.9	b: 1.1425	0.9139 to 1.4283	0.8792
95% CI	22.5 to 32.1	25.5 to 33.4			
Duration of Response					
Independent radiology assessment					
ITT population, N					
Events, n (%)	79 (52.3)	43 (37.1)			
Median (months)	7.5	7.2			
95% CI	6.3 to 9.8	5.7 to 9.9			
Investigators' assessment					
ITT population, N					
Events, n (%)	112 (71.8)	72 (55.4)			
Median (months)	6.9	5.8			
95% CI	5.8 to 7.1	5.0 to 7.0			

AT = as-treated; CI = confidence interval; ITT = intent-to-treat; N = total number of subjects in the evaluable population; n = number of subjects with specified criteria.

a. Hazard ratios, CIs, and p-values in row "a" were from a stratified log-rank test; those in row "b" were from an unstratified log-rank test.

Progression-Free Survival: The primary and secondary analyses of PFS was conducted in the ITT population and the AT population respectively. There was no significant between-groups difference in PFS. PFS based on the central radiology assessment is summarized for the ITT and AT population in Table 6 and Investigators' assessment in Table 7.

Discordance between the central radiology and Investigators' assessments of progression was 42.2% and the censoring discrepancy rate was 28.3%. Investigators recorded PFS earlier than the central radiology lab more frequently in the docetaxel arm than in the sunitinib + docetaxel arm (49.4% versus 42.9 %). This discrepancy may help explain the reason for a shorter median PFS in the docetaxel arm (6.9 months) by Investigators' assessment when compared to independent radiology assessment (8.3 months). Nevertheless, the results from both assessments are consistent and the addition of sunitinib to docetaxel treatment did not result in a significant increase in PFS using either assessment.

Table 6. Summary of Analyses of Progression-Free Survival (Independent Radiology Assessment; ITT and AT Populations)

Variable	Sunitinib + Docetaxel N=296	Docetaxel N=297
ITT Population, N		
Subjects who had disease progression or died, n (%)	147 (49.7)	109 (36.7)
Objective progression observed, n (%)	130 (43.9)	104 (35.0)
Death without objective progression, n (%)	17 (5.7)	5 (1.7)
Subjects with censored endpoints, n (%)	149 (50.3)	188 (63.3)
PFS (months)		
Quartile (95% CI)		
25%	6.2 (5.5, 6.9)	5.1 (4.4, 5.9)
50% (Median)	8.6 (8.2, 10.3)	8.3 (7.7, 9.6)
75%	15.1 (13.2, NA)	NA (11.3, NA)
Range of event time	0.9 – 17.5	0.9 – 15.3
Stratified analysis		
Hazard ratio (sunitinib + docetaxel versus docetaxel)[a]	0.9222	
95% CI for hazard ratio	(0.7156, 1.1885)	
Log-rank test (p-value)[b]	0.6278 (0.2651)	
Unstratified analysis		
Hazard ratio (sunitinib + docetaxel versus docetaxel)[a]	0.9474	
95% CI for hazard ratio	(0.7385, 1.2153)	
Log-rank test (p-value)c	0.4248 (0.3355)	
AT Population, N		
Subjects who had disease progression or died, n (%)	147 (48.8)	109 (37.2)
Objective progression observed, n (%)	130 (44.1)	104 (35.5)
Death without objective progression, n (%)	17 (5.8)	5 (1.7)
Subjects with censored endpoints, n (%)	148 (50.2)	184 (62.8)
PFS (months)		
Quartile (95% CI)		
25%	6.2 (5.5, 6.9)	5.1 (4.4, 5.9)
50% (median)	8.6 (8.2, 10.3)	8.3 (7.7, 9.6)
75%	15.1 (13.2, NA)	NA (11.3, NA)
Range of event time	0.9 to 17.5	0.9 to 15.3
Stratified analysis		
Hazard ratio (sunitinib+docetaxel versus docetaxel)[a]	0.9222	
95% CI for hazard ratio	(0.7156, 1.1885)	
Log-rank test (p-value)[b]	0.6278 (0.2651)	
Unstratified analysis		
Hazard ratio (sunitinib+docetaxel versus docetaxel)[a]	0.9474	
95% CI for hazard ratio	(0.7385, 1.2153)	
Log-rank test (p-value)[c]	0.4248 (0.3355)	

NA = not available; the statistic could not be calculated.
AT = as-treated; CI = confidence interval; HR = hazard ratio; N = number of subjects; n = number of subjects with specified criteria; NA = not available; PFS = progression-free disease.

a. Assuming proportional hazards, a HR less than 1 indicates a reduction in hazard rate in favor of sunitinib + docetaxel.

b. Log-rank test statistic and p-value were from a 1-sided log-rank test stratified for the number of metastatic sites/organs (≤ 2 versus >2), estrogen receptor status (negative versus positive/unknown), and disease-free interval from prior adjuvant treatment (≤12 months versus >12 months). All stratification factors were from the interactive voice randomization system.

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

Table 7. Summary of Analyses of Progression-Free Survival (Investigators' Assessment; ITT Population)

Variable	Sunitinib + Docetaxel (N=296)	Docetaxel (N=297)
Progression status, n (%)		
Subjects who had disease progression or died	198 (66.9)	162 (54.5)
Objective progression observed	189 (63.9)	157 (52.9)
Death without objective progression	9 (3.0)	5 (1.7)
Subjects with censored endpoints	98 (33.1)	135 (45.5)
PFS (months)		
Quartile (95% confidence interval)		
25%	5.2 (4.4, 5.7)	4.3 (4.1, 5.1)
50% (median)	8.2 (7.3, 8.6)	6.9 (6.5, 7.3)
75%	11.3 (10.8, 12.3)	10.9 (8.5, 12.4)
Range of event time	0.7, 18.2	1.1, 20.3
Stratified analysis:		
HR (sunitinib + docetaxel versus docetaxel)[a]	0.8560	
(95% CI)	(0.6921, 1.0589)	
Log-rank test statistic (p-value)[b]	1.4371 (0.0753)	
Unstratified analysis:		
HR (sunitinib + docetaxel versus docetaxel)[a]	0.8714	
(95% CI)	(0.7067, 1.0745)	
Log-rank test statistic (p-value)[c]	1.2933 (0.0980)	

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; ITT = intent-to-treat

a. Assuming proportional hazards, a HR less than 1 indicates a reduction in hazard rate in favor of sunitinib + docetaxel.

b. Log-rank test statistic and p-value were from a 1-sided log-rank test stratified for the number of metastatic sites/organs (≤2 versus >2), estrogen receptor status (negative versus positive/unknown), and disease-free interval from prior adjuvant treatment (≤12 months versus >12 months). All stratification factors were from the Interactive Voice Randomization System.

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

The results of Cox proportional hazard analysis using the independent radiology assessment for the ITT population is summarized in Table 8.

Table 8. Multivariate Model for Progression-Free Survival From a Cox Proportional Hazard Analysis (ITT Population; Independent Radiology Assessment)

Model	Hazard Ratio	95% CI for Hazard Ratio	p-Value[a]
Treatment (sunitinib + docetaxel versus docetaxel)	0.907	0.704 to 1.167	0.4472
Metastatic sites/organs (≤2 versus >2)	0.735	0.572 to 0.945	0.0162
Disease-free interval (≤12 versus >12 months)	1.524	1.182 to 1.966	0.0012
Triple negative receptor status (yes versus no)	1.961	1.487 to 2.586	<0.001
Prior anthracycline (yes versus no)	1.603	1.155 to 2.226	0.0048

CI = confidence interval; ITT = intent-to-treat.

a. From a 2-sided Wald chi-square test.

Objective Response Rate: ORR is summarized by the central radiology assessment and by Investigators' assessment for the ITT population in Table 9.

ORR was stratified by the baseline factors number of metastatic sites (≤2 versus >2), hormone receptor status (ER negative versus positive/unknown), disease-free interval (≤12 months versus >12 months), baseline ECOG performance status (0 versus ≥1), age at baseline (<65 versus ≥65 years), ethnic origin (White versus Non-White), triple negative

status (yes versus no), prior anthracycline use (yes versus no), and prior adjuvant/neoadjuvant taxane use (yes versus no).

Table 9. Summary of Analyses of Objective Response Rate (ITT Population)

Variable	Sunitinib + Docetaxel (N=296)	Docetaxel (N=297)
Independent Radiology Assessment		
Confirmed overall response, n (%)		
Complete response	0 (0.0)	0 (0.0)
Partial response	151 (51.0)	116 (39.1)
Stable disease	119 (40.2)	150 (50.5)
Progressive disease	12 (4.1)	14 (4.7)
Not evaluable	14 (4.7)	17 (5.7)
ORR (CR + PR), n (%)	151 (51.0)	116 (39.1)
(95% exact CI of ORR)	(45.2, 56.8)	(33.5, 44.9)
Treatment difference and 95% exact CI (%)	12.0 (4.0, 19.9)	
Stratified analysis		
Odds ratio (95% exact CI)	1.65 (1.17, 2.33)	
Exact 1-sided p-value	0.0018	
Unstratified analysis		
Odds ratio (95% exact CI)	1.62 (1.16, 2.28)	
Exact 1-sided p-value	0.0022	
Investigators' Assessment		
Best overall response, n (%)		
Complete response	7 (2.4)	5 (1.7)
Partial response	149 (50.3)	125 (42.1)
Stable disease	112 (37.8)	129 (43.4)
Progressive disease	16 (5.4)	22 (7.4)
Not evaluable	12 (4.1)	16 (5.4)
ORR (CR + PR), n (%)	156 (52.7)	130 (43.8)
(95% exact CI of ORR)	(46.8, 58.5)	(38.0, 49.6)
Treatment difference and 95% exact CI (%)	8.9 (0.9, 16.9)	
Stratified analysis		
Odds ratio (95% exact CI)	1.44 (1.03, 2.02)	
Exact 1-sided p-value	0.0172	
Unstratified analysis		
Odds ratio (95% exact CI)	1.43 (1.02 to 2.00)	
Exact 1-sided p-value	0.0181	

CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria; ORR = overall response rate; PR = partial response.

Duration of Response: Table 10 summarizes the DR for the independent radiology results. The median DR was 7.5 (95% CI: 6.3 to 9.8 months) versus 7.2 (95% CI: 5.7 to 9.9 months). The results were comparable when based on the Investigators' assessment (Table 5).

Table 10. Summary of Duration of Response (Independent Radiology Assessment; ITT Populations)

Variable	Sunitinib + Docetaxel N=296	Docetaxel N=297
Number of responders	151	116
Subjects who had disease progression or died, n (%)	79 (52.3)	43 (37.1)
Subjects with censored endpoints, n (%)	72 (47.7)	73 (62.9)
DR (months)		
Quartile (95% CI)		
25%	5.2 (4.3, 5.6)	4.4 (4.0, 5.6)
50% (Median)	7.5 (6.3, 9.8)	7.2 (5.7, 9.9)
75%	13.9 (10.9, NA)	NA (9.9, NA)

NA = not available; the statistic could not be calculated.
CI = confidence interval; DR = duration of response; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria; NA = not applicable.

Overall Survival: OS is summarized for the ITT population in Table 11.

Table 11. Summary of Overall Survival (ITT Population)

Variable	Sunitinib + Docetaxel (N=296)	Docetaxel (N=297)
Survival status, n (%)		
Died	161 (54.4)	148 (49.8)
Still alive[a]	135 (45.6)	149 (50.2)
Survival time (months)		
Quartile (95% CI)		
25%	13.5 (12.7, 16.1)	15.5 (13.6, 18.7)
50% (Median)	26.0 (22.5, 32.1)	28.9 (25.5, 33.4)
75%	40.2 (38.4, NA)	NA
Range of event time	0.9 to 40.2	3.7 to 36.0
Stratified analysis		
HR (sunitinib + docetaxel versus docetaxel)[b]	1.1539	
(95% CI for HR)	(0.9209, 1.4458)	
Log-rank test (p-value)[c]	-1.2445 (0.8933)	
Unstratified analysis		
HR (sunitinib + docetaxel versus docetaxel)	1.1425	
(95% CI for HR)	(0.9139, 1.4283)	
Log-rank test (p-value)[d]	-1.1711 (0.8792)	
1-Year survival probability (95% CI)	0.806 (0.754 to 0.848)	0.843 (0.794 to 0.881)
2-Year survival probability (95% CI)	0.543 (0.481 to 0.601)	0.579 (0.516 to 0.636)

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; N = number of subjects in each group; n = number of subjects with specified criteria; NA = not applicable; the median and/or 95% CI could not be calculated; OS = overall survival.

a. Subjects who were not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
b. Assuming proportional hazards, a HR greater than 1 indicates a reduction in hazard rate in favor of docetaxel.
c. Log-rank test statistic and p-value were from a 1-sided log-rank test stratified for the number of metastatic sites/organs (≤2 versus >2), estrogen receptor status (negative versus positive/unknown), and disease-free interval from prior adjuvant treatment (≤12 months versus >12 months). All stratification factors were from the Interactive Voice Randomization System (IVRS).
d. Log-rank test statistic and p-value were from a 1-sided, unstratified log-rank test.

Patient Reported Outcome: PRO assessments were not analyzed because the study did not meet its primary endpoint.

Safety Results: The overall adverse experience is summarized by treatment arm in Table 12.

Table 12. Overall Adverse Event Experience (As-Treated Population)

Variable	Sunitinib + Docetaxel (N=295) n (%)	Docetaxel (N=293) n (%)
Subjects with at least 1 adverse event	293 (99.3)	292 (99.7)
Subjects with at least 1 serious adverse event	112 (38.0)	79 (27.0)
Subjects with at least 1 treatment-related adverse event[a]	289 (98.0)	291 (99.3)
Subjects with at least 1 treatment-related serious adverse event[a]	75 (25.4)	58 (19.8)
Related to sunitinib	54 (18.3)	0
Related to docetaxel	65 (22.0)	58 (19.8)
Related to sunitinib and docetaxel	44 (14.9)	0
Subjects for whom study drug was discontinued permanently	115 (39.0)	61 (20.8)
Sunitinib permanently discontinued	82 (27.8)	0
Docetaxel permanently discontinued	87 (29.5)	61 (20.8)
Subjects who died	161 (54.6)	148 (50.5)
On-study deaths[b]	12 (4.1)	4 (1.4)
Follow-up deaths[c]	149 (50.5)	144 (49.1)

Adverse events and serious adverse events are not separated out.
N = number of subjects in each treatment group; n = number of subjects with adverse event.
a. Treatment-related included adverse eventss with causality.
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 Events (TEAEs, All Causalities): The most common TEAEs (those occurring in ≥5% total subjects) are summarized in Table 13. The most common TEAEs in the sunitinib + docetaxel arm were alopecia, diarrhea, neutropenia, and fatigue. The most common AEs in the docetaxel arm were alopecia, neutropenia, and nausea.

Table 13. Treatment-Emergent Adverse Events-All Causalities Reported in ≥5% of Subjects (As-Treated Population)

System Organ Class MedDRA (v14.0) Preferred Term	Sunitinib/Docetaxel n (%)	Docetaxel n (%)
Number (%) of subjects evaluable for adverse events	295	293
Number (%) of subjects with adverse events	290 (98.3)	291 (99.3)
Blood and lymphatic system disorders	207 (70.2)	186 (63.5)
Anaemia	67 (22.7)	50 (17.1)
Febrile neutropenia	29 (9.8)	22 (7.5)
Leukopenia	77 (26.1)	83 (28.3)
Neutropenia	165 (55.9)	144 (49.1)
Thrombocytopenia	45 (15.3)	5 (1.7)
Cardiac disorders	21 (7.1)	12 (4.1)
Tachycardia	21 (7.1)	12 (4.1)
Endocrine disorders	17 (5.8)	2 (0.7)
Hypothyroidism	17 (5.8)	2 (0.7)
Eye disorders	87 (29.5)	65 (22.2)
Conjunctivitis	20 (6.8)	16 (5.5)
Eyelid oedema	16 (5.4)	2 (0.7)
Lacrimation increased	69 (23.4)	50 (17.1)
Gastrointestinal disorders	237 (80.3)	207 (70.6)
Abdominal pain	36 (12.2)	25 (8.5)
Abdominal pain upper	22 (7.5)	14 (4.8)
Constipation	57 (19.3)	51 (17.4)
Diarrhoea	177 (60.0)	111 (37.9)
Dry mouth	33 (11.2)	19 (6.5)
Dyspepsia	70 (23.7)	24 (8.2)
Gastritis	18 (6.1)	10 (3.4)
Gingivitis	16 (5.4)	2 (0.7)
Nausea	119 (40.3)	114 (38.9)
Stomatitis	96 (32.5)	75 (25.6)
Vomiting	59 (20.0)	65 (22.2)
General disorders and administration site conditions	249 (84.4)	222 (75.8)
Asthenia	99 (33.6)	88 (30.0)
Chest pain	15 (5.1)	11 (3.8)
Face oedema	37 (12.5)	12 (4.1)
Fatigue	127 (43.1)	101 (34.5)
Mucosal inflammation	82 (27.8)	59 (20.1)
Oedema	32 (10.8)	16 (5.5)
Oedema peripheral	67 (22.7)	93 (31.7)
Pain	15 (5.1)	12 (4.1)
Pyrexia	56 (19.0)	48 (16.4)
Infections and infestations	46 (15.6)	40 (13.7)
Cystitis	6 (2.0)	16 (5.5)
Infection	16 (5.4)	9 (3.1)
Nasopharyngitis	28 (9.5)	18 (6.1)
Investigations	57 (19.3)	31 (10.6)
Alanine aminotransferase increased	21 (7.1)	10 (3.4)
Aspartate aminotransferase increased	20 (6.8)	10 (3.4)
Haemoglobin decreased	18 (6.1)	7 (2.4)
Weight decreased	21 (7.1)	13 (4.4)
Metabolism and nutrition disorders	101 (34.2)	84 (28.7)
Decreased appetite	94 (31.9)	71 (24.2)
Hyperglycaemia	13 (4.4)	20 (6.8)
Musculoskeletal and connective tissue disorders	145 (49.2)	163 (55.6)
Arthralgia	45 (15.3)	65 (22.2)
Back pain	27 (9.2)	31 (10.6)
Bone pain	35 (11.9)	38 (13.0)
Musculoskeletal pain	26 (8.8)	29 (9.9)
Myalgia	53 (18.0)	72 (24.6)

Table 13. Treatment-Emergent Adverse Events-All Causalities Reported in ≥5% of Subjects (As-Treated Population)

System Organ Class MedDRA (v14.0) Preferred Term	Sunitinib/Docetaxel n (%)	Docetaxel n (%)
Pain in extremity	40 (13.6)	36 (12.3)
Nervous system disorders	152 (51.5)	173 (59.0)
Dizziness	18 (6.1)	15 (5.1)
Dysgeusia	89 (30.2)	68 (23.2)
Headache	48 (16.3)	38 (13.0)
Neuropathy peripheral	41 (13.9)	50 (17.1)
Paraesthesia	22 (7.5)	27 (9.2)
Peripheral sensory neuropathy	46 (15.6)	54 (18.4)
Psychiatric disorders	29 (9.8)	24 (8.2)
Insomnia	29 (9.8)	24 (8.2)
Respiratory, thoracic and mediastinal disorders	134 (45.4)	88 (30.0)
Cough	45 (15.3)	27 (9.2)
Dyspnoea	63 (21.4)	54 (18.4)
Epistaxis	71 (24.1)	16 (5.5)
Oropharyngeal pain	22 (7.5)	10 (3.4)
Pleural effusion	20 (6.8)	16 (5.5)
Skin and subcutaneous tissue disorders	234 (79.3)	224 (76.5)
Alopecia	178 (60.3)	188 (64.2)
Dry skin	28 (9.5)	15 (5.1)
Erythema	28 (9.5)	18 (6.1)
Nail disorder	44 (14.9)	61 (20.8)
Onycholysis	6 (2.0)	17 (5.8)
Palmar-plantar erythrodysaesthesia syndrome	124 (42.0)	26 (8.9)
Pruritus	17 (5.8)	31 (10.6)
Rash	49 (16.6)	50 (17.1)
Skin toxicity	15 (5.1)	6 (2.0)
Vascular disorders	60 (20.3)	40 (13.7)
Flushing	14 (4.7)	18 (6.1)
Hypertension	36 (12.2)	3 (1.0)
Lymphoedema	14 (4.7)	19 (6.5)

Subjects were only counted once per treatment for each row.
Excluded events that occurred prior to dosing or after subjects crossed over from Standard of Care to sunitinib.
MedDRA (v14.0) coding dictionary was applied.
MedDRA (v14.0) = Medical Dictionary for Regulatory Activities (version 14.0); n = number of subjects with adverse events.

Treatment-Related TEAEs: The most common treatment-related TEAEs (those occurring in ≥5% total subjects) are summarized in Table 14. The most common treatment-related TEAEs in the sunitinib + docetaxel arm were alopecia (60.3%), neutropenia (55.9%), diarrhea (55.6%), palmar-plantar erythrodysesthesia (41.7%), and fatigue (40.0%). The most common treatment-related TEAEs in the docetaxel arm were alopecia (64.2%), neutropenia (49.1%), diarrhea (35.8%), nausea (36.9%), and fatigue (32.8%).

Table 14. Treatment-Emergent Treatment-Related Adverse Events Reported in ≥5% of Subjects (As-Treated Population)

Preferred Term	Sunitinib + Docetaxel (N=295) n (%)	Docetaxel (N=293) n (%)
Any treatment-related adverse event	289 (98.0)	291 (99.3)
Alopecia	178 (60.3)	188 (64.2)
Neutropenia	165 (55.9)	144 (49.1)
Diarrhoea	164 (55.6)	105 (35.8)
Palmar-plantar erythrodysesthesia	123 (41.7)	25 (8.5)
Fatigue	118 (40.0)	96 (32.8)
Nausea	102 (34.6)	108 (36.9)
Stomatitis	96 (32.5)	74 (25.3)
Dysgeusia	89 (30.2)	66 (22.5)
Asthenia	87 (29.5)	82 (28.0)
Decreased appetite	85 (28.8)	68 (23.2)
Leukopenia	76 (25.8)	83 (28.3)
Mucosal inflammation	82 (27.8)	58 (19.8)
Lacrimation increased	68 (23.1)	48 (16.4)
Epistaxis	63 (21.4)	14 (4.8)
Anaemia	59 (20.0)	48 (16.4)
Dyspepsia	59 (20.0)	19 (6.5)
Myalgia	52 (17.6)	66 (22.5)
Oedema peripheral	50 (16.9)	75 (25.6)
Rash	46 (15.6)	44 (15.0)
Peripheral sensory neuropathy	45 (15.3)	53 (18.1)
Nail disorder	44 (14.9)	61 (20.8)
Vomiting	44 (14.9)	58 (19.8)
Thrombocytopenia	43 (14.6)	4 (1.4)
Neuropathy peripheral	41 (13.9)	49 (16.7)
Face edema	34 (11.5)	11 (3.8)
Constipation	33 (11.2)	35 (11.9)
Dry mouth	30 (10.2)	19 (6.5)
Hypertension	30 (10.2)	1 (0.3)
Arthralgia	29 (9.8)	51 (17.4)
Dyspnea	29 (9.8)	27 (9.2)
Febrile neutropenia	29 (9.8)	22 (7.5)
Dry skin	28 (9.5)	14 (4.8)
Pyrexia	27 (9.2)	32 (10.9)
Edema	27 (9.2)	13 (4.4)
Pain in extremity	26 (8.8)	26 (8.9)
Abdominal pain	26 (8.8)	17 (5.8)
Headache	20 (6.8)	20 (6.8)
Erythema	20 (6.8)	16 (5.5)
Paraesthesia	19 (6.4)	27 (9.2)
Conjunctivitis	16 (5.4)	16 (5.5)
Pruritus	15 (5.1)	27 (9.2)
Bone pain	9 (3.1)	21 (7.2)

Adverse events and serious adverse events are not separated out.
N = number of subjects in each treatment group; n = number of subjects with adverse events.

Severity of AEs as per CTCAE Criteria: Fourteen (4.7%) versus 4 (1.4%) subjects on sunitinib + docetaxel versus docetaxel, respectively, experienced AEs with a maximum severity of Grade 5, 124 (42.0%) versus 139 (47.4%) subjects Grade 4, and 121 (41.0%) subjects versus 86 (29.4%) subjects experienced AEs with a maximum severity of Grade 3. Adverse events of Grade ≥3 experienced by ≥5% subjects on sunitinib + docetaxel included febrile neutropenia, neutropenia, leucopenia, diarrhea, asthenia, fatigue, and palmar-plantar

erythrodysesthesia. The Grade ≥3 AEs experienced by ≥5% total subjects on docetaxel were febrile neutropenia, neutropenia, leucopenia, asthenia, and fatigue.

Treatment-Emergent Serious Adverse Events (SAEs, All Causality): Table 15 presents treatment emergent SAEs (all causality) reported during the study. SAEs were more common on sunitinib + docetaxel than on docetaxel (38.0% versus 27.0%). The most common SAEs in both the treatment groups were febrile neutropenia and neutropenia.

Table 15. Summary of Serious Adverse Events–All Causality (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)		Total (N=588)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any serious adverse events	112 (38.0)	241	79 (27.0)	154	191 (32.5)	395
Blood and lymphatic system disorders	36 (12.2)	47	32 (10.9)	42	68 (11.6)	89
Anaemia	4 (1.4)	4	2 (0.7)	2	6 (1.0)	6
Febrile neutropenia	20 (6.8)	22	13 (4.4)	15	33 (5.6)	37
Leukopenia	5 (1.7)	6	7 (2.4)	7	12 (2.0)	13
Lymphatic disorder	1 (0.3)	1	0	0	1 (0.2)	1
Neutropenia	11 (3.7)	13	16 (5.5)	18	27 (4.6)	31
Thrombocytopenia	1 (0.3)	1	0	0	1 (0.2)	1
Cardiac disorders	7 (2.4)	7	2 (0.7)	3	9 (1.5)	10
Angina pectoris	0	0	1 (0.3)	2	1 (0.2)	2
Atrial fibrillation	1 (0.3)	1	0	0	1 (0.2)	1
Atrioventricular block	1 (0.3)	1	0	0	1 (0.2)	1
Cardiac arrest	1 (0.3)	1	0	0	1 (0.2)	1
Cardiac disorder	1 (0.3)	1	0	0	1 (0.2)	1
Cardiac failure	1 (0.3)	1	0	0	1 (0.2)	1
Myocardial infarction	0	0	1 (0.3)	1	1 (0.2)	1
Myocardial ischaemia	1 (0.3)	1	0	0	1 (0.2)	1
Pericardial effusion	1 (0.3)	1	0	0	1 (0.2)	1
Ear and labyrinth disorders	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Vertigo	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Eye disorders	2 (0.7)	2	0	0	2 (0.3)	2
Conjunctivitis	1 (0.3)	1	0	0	1 (0.2)	1
Visual impairment	1 (0.3)	1	0	0	1 (0.2)	1
Gastrointestinal disorders	18 (6.1)	23	13 (4.4)	20	31 (5.3)	43
Abdominal pain	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Anal fistula	0	0	1 (0.3)	1	1 (0.2)	1
Cheilitis	1 (0.3)	1	0	0	1 (0.2)	1
Diarrhoea	6 (2.0)	6	2 (0.7)	4	8 (1.4)	10
Diverticular perforation	0	0	1 (0.3)	1	1 (0.2)	1
Dysphagia	1 (0.3)	1	0	0	1 (0.2)	1
Nausea	2 (0.7)	2	6 (2.0)	6	8 (1.4)	8
Oesophagitis ulcerative	1 (0.3)	1	0	0	1 (0.2)	1
Pancreatitis	1 (0.3)	1	0	0	1 (0.2)	1
Periproctitis	2 (0.7)	2	0	0	2 (0.3)	2
Pneumoperitoneum	1 (0.3)	1	0	0	1 (0.2)	1
Stomatitis	3 (1.0)	3	2 (0.7)	3	5 (0.9)	6
Vomiting	4 (1.4)	4	4 (1.4)	4	8 (1.4)	8
General disorders and administration site conditions	29 (9.8)	35	16 (5.5)	21	45 (7.7)	56
Adverse drug reaction	1 (0.3)	1	0	0	1 (0.2)	1
Asthenia	4 (1.4)	4	1 (0.3)	1	5 (0.9)	5
Chest pain	1 (0.3)	1	0	0	1 (0.2)	1
Death	1 (0.3)	1	0	0	1 (0.2)	1
Device dislocation	1 (0.3)	1	0	0	1 (0.2)	1
Disease progression	6 (2.0)	6	4 (1.4)	4	10 (1.7)	10
Fatigue	2 (0.7)	2	1 (0.3)	1	3 (0.5)	3
General physical health deterioration	5 (1.7)	5	4 (1.4)	5	9 (1.5)	10
Impaired healing	1 (0.3)	1	0	0	1 (0.2)	1
Mucosal inflammation	2 (0.7)	2	1 (0.3)	1	3 (0.5)	3
Oedema peripheral	0	0	1 (0.3)	1	1 (0.2)	1
Pain	0	0	2 (0.7)	2	2 (0.3)	2
Pyrexia	10 (3.4)	11	5 (1.7)	6	15 (2.6)	17
Hepatobiliary disorders	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Cholestasis	1 (0.3)	1	0	0	1 (0.2)	1
Jaundice	0	0	1 (0.3)	1	1 (0.2)	1

Table 15. Summary of Serious Adverse Events–All Causality (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)		Total (N=588)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Immune system disorders	1 (0.3)	1	0	0	1 (0.2)	1
Hypersensitivity	1 (0.3)	1	0	0	1 (0.2)	1
Infections and infestations	29 (9.8)	39	23 (7.8)	31	52 (8.8)	70
Anal abscess	1 (0.3)	1	0	0	1 (0.2)	1
Bronchitis	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Catheter site infection	2 (0.7)	2	1 (0.3)	1	3 (0.5)	3
Cellulitis	1 (0.3)	1	0	0	1 (0.2)	1
Clostridial infection	0	0	1 (0.3)	2	1 (0.2)	2
Cystitis	0	0	3 (1.0)	3	3 (0.5)	3
Device related infection	2 (0.7)	2	0	0	2 (0.3)	2
Diverticulitis	0	0	1 (0.3)	1	1 (0.2)	1
Erysipelas	1 (0.3)	2	1 (0.3)	1	2 (0.3)	3
Gastroenteritis viral	0	0	1 (0.3)	1	1 (0.2)	1
Groin infection	1 (0.3)	1	0	0	1 (0.2)	1
Haematoma infection	1 (0.3)	1	0	0	1 (0.2)	1
Infection	2 (0.7)	2	3 (1.0)	3	5 (0.9)	5
Localised infection	0	0	1 (0.3)	2	1 (0.2)	2
Lung infection	1 (0.3)	1	0	0	1 (0.2)	1
Nasopharyngitis	0	0	1 (0.3)	1	1 (0.2)	1
Necrotising fasciitis	1 (0.3)	1	0	0	1 (0.2)	1
Neutropenic infection	3 (1.0)	3	3 (1.0)	3	6 (1.0)	6
Neutropenic sepsis	3 (1.0)	3	3 (1.0)	3	6 (1.0)	6
Osteomyelitis	1 (0.3)	1	0	0	1 (0.2)	1
Paronychia	0	0	1 (0.3)	1	1 (0.2)	1
Peridiverticular abscess	0	0	1 (0.3)	1	1 (0.2)	1
Pneumocystis jiroveci pneumonia	1 (0.3)	1	0	0	1 (0.2)	1
Pneumonia	2 (0.7)	2	5 (1.7)	5	7 (1.2)	7
Pneumonia primary atypical	1 (0.3)	1	0	0	1 (0.2)	1
Pyelonephritis	1 (0.3)	1	0	0	1 (0.2)	1
Rectal abscess	1 (0.3)	1	0	0	1 (0.2)	1
Respiratory tract infection	1 (0.3)	1	0	0	1 (0.2)	1
Sepsis	1 (0.3)	1	0	0	1 (0.2)	1
Septic shock	2 (0.7)	3	1 (0.3)	1	3 (0.5)	4
Sinusitis	1 (0.3)	1	0	0	1 (0.2)	1
Streptococcal bacteraemia	1 (0.3)	1	0	0	1 (0.2)	1
Subcutaneous abscess	2 (0.7)	2	0	0	2 (0.3)	2
Tooth abscess	1 (0.3)	1	0	0	1 (0.2)	1
Urinary tract infection	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Injury, poisoning and procedural complications	4 (1.4)	6	2 (0.7)	3	6 (1.0)	9
Contusion	2 (0.7)	2	0	0	2 (0.3)	2
Fall	2 (0.7)	2	1 (0.3)	1	3 (0.5)	3
Femur fracture	0	0	1 (0.3)	1	1 (0.2)	1
Overdose	1 (0.3)	1	0	0	1 (0.2)	1
Periorbital haematoma	1 (0.3)	1	0	0	1 (0.2)	1
Upper limb fracture	0	0	1 (0.3)	1	1 (0.2)	1
Investigations	2 (0.7)	6	1 (0.3)	1	3 (0.5)	7
Alanine aminotransferase increased	1 (0.3)	1	0	0	1 (0.2)	1
Aspartate aminotransferase increased	1 (0.3)	1	0	0	1 (0.2)	1
Blood alkaline phosphatase increased	1 (0.3)	1	0	0	1 (0.2)	1
Blood bilirubin increased	1 (0.3)	1	0	0	1 (0.2)	1
Blood culture positive	0	0	1 (0.3)	1	1 (0.2)	1
Blood thyroid stimulating hormone increased	1 (0.3)	1	0	0	1 (0.2)	1
Gamma-glutamyltransferase increased	1 (0.3)	1	0	0	1 (0.2)	1

Table 15. Summary of Serious Adverse Events–All Causality (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)		Total (N=588)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Metabolism and nutrition disorders	5 (1.7)	5	7 (2.4)	8	12 (2.0)	13
Decreased appetite	2 (0.7)	2	0	0	2 (0.3)	2
Dehydration	3 (1.0)	3	1 (0.3)	1	4 (0.7)	4
Electrolyte imbalance	0	0	1 (0.3)	1	1 (0.2)	1
Fluid retention	0	0	2 (0.7)	2	2 (0.3)	2
Hypocalcaemia	0	0	2 (0.7)	2	2 (0.3)	2
Hypoglycaemia	0	0	1 (0.3)	1	1 (0.2)	1
Malnutrition	0	0	1 (0.3)	1	1 (0.2)	1
Musculoskeletal and connective tissue disorders	3 (1.0)	5	5 (1.7)	6	8 (1.4)	11
Arthralgia	1 (0.3)	1	0	0	1 (0.2)	1
Back pain	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Bone disorder	0	0	1 (0.3)	1	1 (0.2)	1
Bone pain	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Muscular weakness	1 (0.3)	1	0	0	1 (0.2)	1
Musculoskeletal pain	0	0	1 (0.3)	1	1 (0.2)	1
Myalgia	1 (0.3)	1	2 (0.7)	2	3 (0.5)	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	3	0	0	3 (0.5)	3
Endometrial sarcoma	1 (0.3)	1	0	0	1 (0.2)	1
Metastatic pain	1 (0.3)	1	0	0	1 (0.2)	1
Tumour haemorrhage	1 (0.3)	1	0	0	1 (0.2)	1
Nervous system disorders	7 (2.4)	9	3 (1.0)	4	10 (1.7)	13
Cognitive disorder	1 (0.3)	1	0	0	1 (0.2)	1
Convulsion	1 (0.3)	1	0	0	1 (0.2)	1
Epilepsy	1 (0.3)	1	0	0	1 (0.2)	1
Headache	1 (0.3)	1	0	0	1 (0.2)	1
Peripheral motor neuropathy	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Peripheral sensory neuropathy	0	0	1 (0.3)	1	1 (0.2)	1
Presyncope	0	0	1 (0.3)	1	1 (0.2)	1
Psychomotor skills impaired	1 (0.3)	1	0	0	1 (0.2)	1
Somnolence	1 (0.3)	1	0	0	1 (0.2)	1
Syncope	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Tremor	1 (0.3)	1	0	0	1 (0.2)	1
Psychiatric disorders	2 (0.7)	2	2 (0.7)	2	4 (0.7)	4
Anxiety	1 (0.3)	1	0	0	1 (0.2)	1
Confusional state	1 (0.3)	1	0	0	1 (0.2)	1
Depression	0	0	1 (0.3)	1	1 (0.2)	1
Suicide attempt	0	0	1 (0.3)	1	1 (0.2)	1
Renal and urinary disorders	3 (1.0)	3	0	0	3 (0.5)	3
Cystitis haemorrhagic	1 (0.3)	1	0	0	1 (0.2)	1
Renal failure acute	1 (0.3)	1	0	0	1 (0.2)	1
Renal impairment	1 (0.3)	1	0	0	1 (0.2)	1
Reproductive system and breast disorders	2 (0.7)	2	0	0	2 (0.3)	2
Metrorrhagia	1 (0.3)	1	0	0	1 (0.2)	1
Vaginal haemorrhage	1 (0.3)	1	0	0	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders	21 (7.1)	23	8 (2.7)	8	29 (4.9)	31
Cough	1 (0.3)	1	0	0	1 (0.2)	1
Dyspnoea	6 (2.0)	6	5 (1.7)	5	11 (1.9)	11
Epistaxis	1 (0.3)	1	0	0	1 (0.2)	1
Haemoptysis	1 (0.3)	1	0	0	1 (0.2)	1
Hydropneumothorax	1 (0.3)	1	0	0	1 (0.2)	1
Pleural effusion	5 (1.7)	5	3 (1.0)	3	8 (1.4)	8
Pleuritic pain	1 (0.3)	1	0	0	1 (0.2)	1

Table 15. Summary of Serious Adverse Events–All Causality (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)		Total (N=588)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Pneumothorax	2 (0.7)	2	0	0	2 (0.3)	2
Productive cough	1 (0.3)	1	0	0	1 (0.2)	1
Pulmonary embolism	3 (1.0)	3	0	0	3 (0.5)	3
Respiratory failure	1 (0.3)	1	0	0	1 (0.2)	1
Skin and subcutaneous tissue disorders	8 (2.7)	11	1 (0.3)	1	9 (1.5)	12
Erythema	1 (0.3)	1	0 (0.0)	0	1 (0.2)	1
Palmar-plantar erythrodysaesthesia syndrome	4 (1.4)	4	1 (0.3)	1	5 (0.9)	5
Rash	1 (0.3)	2	0	0	1 (0.2)	2
Skin disorder	1 (0.3)	1	0	0	1 (0.2)	1
Skin toxicity	2 (0.7)	2	0	0	2 (0.3)	2
Skin ulcer	1 (0.3)	1	0	0	1 (0.2)	1
Vascular disorders	10 (3.4)	10	2 (0.7)	2	12 (2.0)	12
Circulatory collapse	2 (0.7)	2	0 (0.0)	0	2 (0.3)	2
Deep vein thrombosis	1 (0.3)	1	1 (0.3)	1	2 (0.3)	2
Embolism	1 (0.3)	1	0	0	1 (0.2)	1
Hypotension	4 (1.4)	4	0	0	4 (0.7)	4
Hypovolaemic shock	1 (0.3)	1	0	0	1 (0.2)	1
Jugular vein thrombosis	0	0	1 (0.3)	1	1 (0.2)	1
Venous thrombosis limb	1 (0.3)	1	0 (0.0)	0	1 (0.2)	1

N = number of subjects in each treatment group; n = number.

Treatment-Emergent Treatment-Related SAEs: Table 16 presents treatment-related SAEs reported during the study. The treatment-related SAEs that were experienced by ≥2% of subjects on sunitinib + docetaxel were febrile neutropenia, neutropenia, and pyrexia. The treatment-related SAEs that were experienced by ≥2% subjects on docetaxel were neutropenia, febrile neutropenia, leucopenia, nausea, and pyrexia.

Table 16. Summary of Treatment-Related Serious Adverse Events (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any serious adverse event	75 (25.4)	131	58 (19.8)	101
Blood and lymphatic system disorders	34 (11.5)	44	32 (10.9)	41
Anaemia	3 (1.0)	3	1 (0.3)	1
Febrile neutropenia	20 (6.8)	22	13 (4.4)	15
Leukopenia	5 (1.7)	6	7 (2.4)	7
Neutropenia	11 (3.7)	13	16 (5.5)	18
Cardiac disorders	4 (1.4)	4	0	0
Atrioventricular block	1 (0.3)	1	0	0
Cardiac disorder	1 (0.3)	1	0	0
Cardiac failure	1 (0.3)	1	0	0
Myocardial ischemia	1 (0.3)	1	0	0
Gastrointestinal disorders	12 (4.1)	17	12 (4.1)	18
Abdominal pain	1 (0.3)	1	0	0
Anal fistula	0	0	1 (0.3)	1
Cheilitis	1 (0.3)	1	0	0
Diarrhoea	5 (1.7)	5	2 (0.7)	4
Dysphagia	1 (0.3)	1	0	0
Nausea	1 (0.3)	1	6 (2.0)	6
Esophagitis ulcerative	1 (0.3)	1	0	0
Pneumoperitoneum	1 (0.3)	1	0	0
Stomatitis	3 (1.0)	3	2 (0.7)	3
Vomiting	3 (1.0)	3	4 (1.4)	4
General disorders and administration site condition	11 (3.7)	13	11 (3.8)	14
Asthenia	1 (0.3)	1	1 (0.3)	1
Death	1 (0.3)	1	0	0
Fatigue	1 (0.3)	1	1 (0.3)	1
General physical health deterioration	2 (0.7)	2	3 (1.0)	4
Mucosal inflammation	2 (0.7)	2	1 (0.3)	1
Edema peripheral	0	0	1 (0.3)	1
Pyrexia	6 (2.0)	6	5 (1.7)	6
Infections and infestations	19 (6.4)	21	14 (4.8)	18
Catheter site infection	1 (0.3)	1	0	0
Cellulitis	1 (0.3)	1	0	0
Clostridial infection	0	0	1 (0.3)	1
Cystitis	0	0	3 (1.0)	3
Device-related infection	1 (0.3)	1	0	0
Erysipelas	1 (0.3)	2	1 (0.3)	1
Gastroenteritis viral	0	0	1 (0.3)	1
Hematoma infection	1 (0.3)	1	0	0
Infection	2 (0.7)	2	0	0
Localized infection	0	0	1 (0.3)	2
Lung infection	1 (0.3)	1	0	0
Nasopharyngitis	0	0	1 (0.3)	1
Necrotizing fasciitis	1 (0.3)	1	0	0
Neutropenic infection	3 (1.0)	3	3 (1.0)	3
Neutropenic sepsis	3 (1.0)	3	3 (1.0)	3
Osteomyelitis	1 (0.3)	1	0	0
Pneumocystis jiroveci pneumonia	1 (0.3)	1	0	0
Pneumonia	0	0	2 (0.7)	2
Pyelonephritis	1 (0.3)	1	0 (0.0)	0
Septic shock	0	0	1 (0.3)	1
Streptococcal bacteremia	1 (0.3)	1	0	0
Urinary tract infection	1 (0.3)	1	0	0
Investigations	2 (0.7)	6	0	0

Table 16. Summary of Treatment-Related Serious Adverse Events (As-Treated Population)

System Organ Class Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Alanine aminotransferase increased	1 (0.3)	1	0	0
Aspartate aminotransferase increased	1 (0.3)	1	0	0
Blood alkaline phosphatase increased	1 (0.3)	1	0	0
Blood bilirubin increased	1 (0.3)	1	0	0
Blood thyroid stimulating hormone increased	1 (0.3)	1	0	0
Gamma-glutamyltransferase increased	1 (0.3)	1	0	0
Metabolism and nutrition disorders	2 (0.7)	2	3 (1.0)	3
Decreased appetite	1 (0.3)	1	0	0
Dehydration	1 (0.3)	1	0	0
Fluid retention	0	0	2 (0.7)	2
Malnutrition	0	0	1 (0.3)	1
Musculoskeletal and connective tissue disorders	0	0	2 (0.7)	2
Myalgia	0	0	2 (0.7)	2
Neoplasms benign, malignant and unspecified	1 (0.3)	1	0	0
Tumour hemorrhage	1 (0.3)	1	0	0
Nervous system disorders	2 (0.7)	2	1 (0.3)	1
Peripheral motor neuropathy	1 (0.3)	1	0	0
Presyncope	0	0	1 (0.3)	1
Syncope	1 (0.3)	1	0	0
Reproductive system and breast disorders	1 (0.3)	1	0	0
Metrorrhagia	1 (0.3)	1	0	0
Respiratory, thoracic and mediastinal disorders	7 (2.4)	7	2 (0.7)	2
Dyspnea	2 (0.7)	2	1 (0.3)	1
Epistaxis	1 (0.3)	1	0	0
Hemoptysis	1 (0.3)	1	0	0
Pulmonary effusion	0	0	1 (0.3)	1
Pulmonary embolism	2 (0.7)	2	0	0
Respiratory failure	1 (0.3)	1	0	0
Skin and subcutaneous tissue disorders	7 (2.4)	9	1 (0.3)	1
Palmar-plantar erythrodysesthesia syndrome	4 (1.4)	4	1 (0.3)	1
Rash	1 (0.3)	2	0	0
Skin toxicity	2 (0.7)	2	0	0
Skin ulcer	1 (0.3)	1	0	0
Vascular disorders	4 (1.4)	4	1 (0.3)	1
Deep vein thrombosis	1 (0.3)	1	1 (0.3)	1
Hypotension	3 (1.0)	3	0	0

N = number of subjects in each treatment group; n = number.

Permanent Discontinuations Due to AEs: AEs that led to discontinuation of study drug are summarized in Table 17. AEs that led to study drug discontinuation for more than 1% subjects (either drug on either arm) were palmar-plantar erythrodysesthesia syndrome, asthenia, fatigue, general physical health deterioration, diarrhea, disease progression, stomatitis, dyspnea, neuropathy peripheral, edema peripheral, hypersensitivity, peripheral sensory neuropathy, and nail disorder.

Table 17. Summary of Adverse Events Leading to Discontinuation of Study Drug (Sunitinib or Docetaxel; As-Treated Population)

Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)
Drug Discontinued	Sunitinib n (%)	Docetaxel n (%)	Docetaxel n (%)
Any adverse events	82 (27.8)	87 (29.5)	61 (20.8)
Palmar-plantar erythrodysesthesia syndrome	11 (3.7)	8 (2.7)	0
Asthenia	5 (1.7)	9 (3.1)	2 (0.7)
Fatigue	6 (2.0)	9 (3.1)	7 (2.4)
General physical health deterioration	3 (1.0)	2 (0.7)	2 (0.7)
Diarrhea	3 (1.0)	1 (0.3)	1 (0.3)
Disease progression	3 (1.0)	1 (0.3)	2 (0.7)
Stomatitis	3 (1.0)	0	0
Dyspnea	2 (0.7)	3 (1.0)	0
Rash	2 (0.7)	2 (0.7)	1 (0.3)
Respiratory failure	2 (0.7)	2 (0.7)	0
Vomiting	2 (0.7)	2 (0.7)	1 (0.3)
Cardiac failure	2 (0.7)	1 (0.3)	0
Pulmonary embolism	2 (0.7)	1 (0.3)	0
Skin ulcer	2 (0.7)	1 (0.3)	0
Ejection fraction decreased	2 (0.7)	0	0
Hypertension	2 (0.7)	0	0
Neutropenia	2 (0.7)	0	0
Neutrophil count decreased	2 (0.7)	0	0
Skin toxicity	2 (0.7)	0	0
Neuropathy peripheral	1 (0.3)	5 (1.7)	6 (2.0)
Erythema	1 (0.3)	2 (0.7)	0
Oedema	1 (0.3)	2 (0.7)	1 (0.3)
Pleural effusion	1 (0.3)	2 (0.7)	1 (0.3)
Anaemia	1 (0.3)	1 (0.3)	1 (0.3)
Blood bilirubin increased	1 (0.3)	1 (0.3)	0
Device related infection	1 (0.3)	1 (0.3)	0
Haematoma infection	1 (0.3)	1 (0.3)	0
Hepatitis	1 (0.3)	1 (0.3)	0
Herpes zoster	1 (0.3)	1 (0.3)	0
Hypovolaemic shock	1 (0.3)	1 (0.3)	0
Infection	1 (0.3)	1 (0.3)	0
Intraocular pressure increased	1 (0.3)	1 (0.3)	0
Pneumonia primary atypical	1 (0.3)	1 (0.3)	0
Polyneuropathy	1 (0.3)	1 (0.3)	1 (0.3)
Syncope	1 (0.3)	1 (0.3)	1 (0.3)
Tracheal disorder	1 (0.3)	1 (0.3)	0
Anorectal cellulitis	1 (0.3)	0	0
Ascites	1 (0.3)	0	0
Bone pain	1 (0.3)	0	1 (0.3)
Cardiotoxicity	1 (0.3)	0	0
Cellulitis	1 (0.3)	0	1 (0.3)
Cheilitis	1 (0.3)	0	0
Convulsion	1 (0.3)	0	0
Cystitis haemorrhagic	1 (0.3)	0	0
Gamma-glutamyltransferase increased	1 (0.3)	0	0
Haemoptysis	1 (0.3)	0	0
Metrorrhagia	1 (0.3)	0	0
Mucous membrane disorder	1 (0.3)	0	0
Multiple gated acquisition scan abnormal	1 (0.3)	0	0
Myocardial ischaemia	1 (0.3)	0	0
Osteomyelitis	1 (0.3)	0	0
Pneumothorax	1 (0.3)	0	0
Psoriasis	1 (0.3)	0	0

Table 17. Summary of Adverse Events Leading to Discontinuation of Study Drug (Sunitinib or Docetaxel; As-Treated Population)

Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)
Drug Discontinued	Sunitinib n (%)	Docetaxel n (%)	Docetaxel n (%)
Renal failure acute	1 (0.3)	0	0
Somnolence	1 (0.3)	0	0
Oedema peripheral	0	5 (1.7)	5 (1.7)
Febrile neutropenia	0	2 (0.7)	0
Fluid retention	0	2 (0.7)	2 (0.7)
Hypersensitivity	0	2 (0.7)	4 (1.4)
Pyrexia	0	2 (0.7)	0
Cardiac disorder	0	1 (0.3)	0
Decreased appetite	0	1 (0.3)	1 (0.3)
Dizziness	0	1 (0.3)	0
Drug hypersensitivity	0	1 (0.3)	0
Face oedema	0	1 (0.3)	0
Generalised oedema	0	1 (0.3)	1 (0.3)
Gingivitis	0	1 (0.3)	0
Lacrimation increased	0	1 (0.3)	0
Leukopenia	0	1 (0.3)	0
Mucosal inflammation	0	1 (0.3)	0
Nail toxicity	0	1 (0.3)	2 (0.7)
Neurotoxicity	0	1 (0.3)	0
Onycholysis	0	1 (0.3)	1 (0.3)
Pancreatitis	0	1 (0.3)	0
Paraesthesia	0	1 (0.3)	1 (0.3)
Peripheral sensory neuropathy	0	1 (0.3)	6 (2.0)
Productive cough	0	1 (0.3)	0
Thrombocytopenia	0	1 (0.3)	0
Weight decreased	0	1 (0.3)	0
Anaphylactic reaction	0	0	1 (0.3)
Back pain	0	0	1 (0.3)
Deep vein thrombosis	0	0	1 (0.3)
Diverticulitis	0	0	1 (0.3)
Myalgia	0	0	1 (0.3)
Nail disorder	0	0	3 (1.0)
Osteonecrosis of jaw	0	0	1 (0.3)
Pain in extremity	0	0	1 (0.3)
Pericardial effusion	0	0	1 (0.3)
Pneumonia	0	0	1 (0.3)
Rash generalised	0	0	1 (0.3)

N = number of subjects in each treatment arm, n = number of subjects with adverse events.

Temporary Discontinuations or Dose Reduction due to AEs: The most common (≥5%) AEs leading to a change in dosing are summarized for each study drug in Table 18. These events included (for ≥5% of subjects on sunitinib + docetaxel) palmar-plantar erythrodysesthesia syndrome, neutropenia, diarrhea, asthenia, fatigue, febrile neutropenia, and leukopenia. The AE occurring in ≥5% of subjects on docetaxel that led to dose delays or reductions was neutropenia.

Table 18. Adverse Events Leading to Dose Interruptions or Changes (Sunitinib) or Dose Delays or Changes (Docetaxel) for ≥5% Total Subjects on either Arm (As-Treated Population)

Preferred Term	Sunitinib + Docetaxel (N=295)		Docetaxel (N=293)
Drug Altered	Sunitinib n (%)	Docetaxel n (%)	Docetaxel n (%)
Any adverse events that led to dose modification or interruption	198 (67.1)	162 (54.9)	139 (47.4)
Palmar-plantar erythrodysesthesia syndrome	52 (17.6)	24 (8.1)	4 (1.4)
Neutropenia	40 (13.6)	42 (14.2)	21 (7.2)
Diarrhoea	30 (10.2)	13 (4.4)	4 (1.4)
Asthenia	23 (7.8)	13 (4.4)	9 (3.1)
Fatigue	18 (6.1)	11 (3.7)	8 (2.7)
Febrile neutropenia	16 (5.4)	12 (4.1)	13 (4.4)
Leukopenia	13 (4.4)	15 (5.1)	5 (1.7)

Interruption or change included actions of study treatment dose stopped temporarily or reduced.
N = number of subjects in each treatment arm, n = number of subjects with adverse events.

Deaths: Table 19 presents a summary of deaths during the study; this summary includes all subjects who died, regardless of how long the death occurred after the last dose of study drug. Twelve (4.1%) versus 4 subjects (1.3%) on sunitinib + docetaxel versus docetaxel, respectively, died on treatment (after the start of study treatment and within 28 days of the last dose of study treatment). Nine (3.0%) deaths versus 4 (1.3%) deaths on treatment were deemed by the Investigators as due to disease progression or to AEs considered related to the underlying disease. Other causes of death in the sunitinib + docetaxel arm were cardiac failure, hypovolemic shock, and unknown. Cardiac failure and the unknown cause of death were assessed as related to sunitinib and docetaxel.

Table 19. Summary of On-Study Deaths by Cause (ITT Population)

Cause of Death	Sunitinib + Docetaxel N=296 n (%)	Docetaxel N=297 n (%)
Study drug[a]	161 (54.4)	148 (49.8)
Study disease	12 (4.1)	4 (1.3)
Other[b]	1 (0.3)	0 (0.0)
Total	1 (0.3)	0 (0.0)

% = n/N × 100
Deaths that occurred within 28 days after last dose of study drug were defined as on-study deaths.
ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria.
a. If the relationship to study drug was unknown, the event was considered to be related to study drug.
b. Other: Related to neither study drug nor disease.

Other Safety Related Findings: There was a decline over time for absolute neutrophil count (with mean declines from baseline up to 8.1×10^9/L) and platelets (with mean declines from baseline up to 109×10^9/L), which was more pronounced for subjects on sunitinib + docetaxel than on docetaxel.

Results for serum chemistry tests for both sunitinib + docetaxel and docetaxel subjects were highly variable and no clinically significant elevations or declines in chemistry values were seen from baseline to end of study.

Laboratory abnormalities of liver enzymes were more frequently reported in the combination arm (alanine transaminase 60.0% versus 40.4%; aspartate transaminase, 62.1% versus 37.0%).

As expected considering sunitinib safety profile, periodic measurements of BP showed that more subjects in the combination arm experienced hypertension. More subjects in the combination arm also showed a prolongation of corrected-QT interval, Fridericia's (cube root) correction of ≥60 msecs as compared to the baseline value (4.8% versus 2.3% on docetaxel). Overall, only marginal differences were observed between the 2 arms in terms of left ventricular ejection fraction (LVEF) changes from baseline. Also, no difference was observed in terms of clinically relevant LVEF decline, defined as an LVEF decrease of ≥20% and below the lower limit of normal (0.4% versus 0.9%).

Weight increase was reported with a similar frequency in the 2 arms (26.1% versus 26.6% of subjects on sunitinib + docetaxel versus docetaxel, respectively). Weight decrease was reported more frequently in subjects on sunitinib + docetaxel (31.3%) than in subject on docetaxel (21.8%).

CONCLUSIONS:

- Sunitinib + docetaxel was not more effective in increasing PFS than docetaxel in subjects with ABC, with a median PFS of 8.6 versus 8.3 months.

- ORR was statistically higher on sunitinib + docetaxel as compared with docetaxel (51.0% versus 39.1%), but this difference was not associated with improvement on any other outcome variables. The other efficacy endpoints, OS and DR, were not improved with sunitinib.

- The overall frequency of AEs, including SAEs, was higher on sunitinib + docetaxel than on docetaxel. However, the AE and safety profiles of sunitinib combined with docetaxel were consistent with those reported for both agents alone.