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

PROTOCOL NO.: A6181107

PROTOCOL TITLE: Phase 3 Randomized, Multicenter Study of Sunitinib Malate (SU-011248) or Capecitabine in Subjects with Advanced Breast Cancer Who Failed Both a Taxane and an Anthracycline Chemotherapy Regimen or Failed With a Taxane and for Whom Further Anthracycline Therapy is not Indicated

Study Centers: A total of 119 centers in Asia (Hong Kong [4]; Taiwan [7]; Singapore [2]; Japan [11]; Korea [5]; India [4]; and Philippines [4]), Europe (Germany [13]; Italy [4]; United Kingdom [4]; France [7]; Spain [15]; Bulgaria [2]; and Turkey [2]), Africa (South Africa [1]), North America (Canada [4]); South America (Brazil [6]; Argentina [7]; Colombia [3]; Mexico [6]; and Peru [2]), and Australia (6) participated and randomized subjects in this study.

Study Initiation, Primary Completion, and Final Completion Dates:

Study Initiation Date: 23 November 2006

Primary Completion Date: 10 July 2009

Final Completion Date: 15 June 2011

This study was terminated early due to futility.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To compare the progression-free survival (PFS) of subjects with advanced breast cancer (ABC) receiving sunitinib malate at a starting dose of 37.5 mg orally once daily (OD) with that of capecitabine at a dose of 1250 or 1000 (in subjects older than 65 years) mg/m^2 twice a day for 2 consecutive weeks, followed by a 1-week rest period and given as 3-week cycles.

Secondary Objectives

To assess

- Time to tumor progression (TTP);

- Overall response (OR);
- Duration of response (DR);
- Time to tumor response (TTR);
- Overall survival (OS);
- Patient reported outcomes (PROs);
- Safety;

of sunitinib malate at a starting dose of 37.5 mg orally OD and of capecitabine at a dose of 1250 or 1000 (in subjects older than 65 years) mg/m^2 twice a day (BID) for 2 consecutive weeks, followed by a 1-week rest period and given as 3-week cycles.

METHODS

Study Design:

This study was terminated early due to futility.

This was a multinational, multicenter, randomized, open-label, Phase 3 clinical trial comparing the efficacy and safety of sunitinib versus (vs) capecitabine administered as monotherapy in subjects with ABC either as a first-, second-, or third-line therapy in the metastatic disease setting.

A total of 700 subjects with ABC whose tumors were either refractory to (a) the combination of a taxane and an anthracycline chemotherapy regimen or failed with the combination of a taxane and an anthracycline chemotherapy regimen, or (b) single-agent taxane in subjects for whom anthracycline therapy was not indicated were planned to be enrolled in this trial. Failure was defined as progressive disease (PD) while on treatment, with or without an initial response, or relapse following treatment with a taxane and an anthracycline.

Subjects were randomized 1:1 to sunitinib 37.5 mg continuous daily dosing (CDD) or capecitabine 1250 or 1000 (in subjects older than 65 years) mg/m^2 BID (Days 1-14) every 3 weeks.

Subjects should have continued treatment until either disease progression was documented according to Response Evaluation Criteria in Solid Tumors (RECIST) or unacceptable toxicity occurred.

Enrollment in this trial was terminated early due to futility determined by the independent data monitoring committee at the first interim analysis. Before and after study termination due to futility, and at the discretion of the investigator, subjects who were still experiencing clinical benefit from sunitinib treatment (regardless of progression status and with permission from the Sponsor) were allowed to continue treatment with sunitinib in an open-label continuation study after they completed the primary study. Additionally, at the discretion of

the investigator, subjects who had disease progression during treatment with capecitabine were also allowed to enter an open-label continuation study to receive treatment with sunitinib (except for subjects in Japan where study was not available).

Following study termination due to futility, subjects who received capecitabine and experienced PD did not enter the open-label continuation study to receive sunitinib. Instead, these subjects were treated at the discretion of the investigator. A summary of the schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

Protocol Activities and Forms to be Completed	Screening	Treatment With Sunitinib or Capecitabine[a]			Post-Treatment		
	≤28 Days Prior to Treatment On-Study	Cycle 1		Subsequent Cycles	End of Tx or Withdrawal[b]	28 Days Post Treatment	Follow-Up[c]
		Day 1[d] –1/+0	Day 15 -3/+3	Day 1 –3/+3	+3 Days	+ 7 Days	-14/+14 Days
Baseline Documentation							
Informed consent[e]	X						
Medical/oncology history[f]	X						
Baseline signs and symptoms		X					
Physical examination[g]	X	(X)		X (every 2 cycles C3, C5)	X		
Vital signs	X	(X)	X	X			
Laboratory studies							
Hematology[h]	X	(X)	X	X	X		
Blood chemistry[h]	X	(X)	X	X	X		
Thyroid-stimulating hormone[h]	X	(X)		X (every 2 cycles, C3, C5)	X		
Pregnancy test	X						
Urinalysis[i]	X			X (Cycle 3)	X		
12-Lead electrocardiogram[j]	X		X				
2-D ECHO or MUGA[k]	X			X (Cycle 2, then every 4 cycles, C6, C10)	X		
Study randomization[l]	X						
Sunitinib[m]		→		→			
Capecitabine[n]		→		→			
Tumor imaging[o]							
CT or MRI of chest, abdomen, Pelvis	X			X (every 6 weeks from randomization)	X		(X)
Nuclear bone scan	X			X (every 12 weeks from randomization)	(X)		(X)
Brain CT or MRI	(X)			(X)	(X)		(X)
Other clinical assessments							
Adverse events[p]	X	X	X	X	X	X	X
EORTC QLQ-C30 & BR23[q]		X		X	X		
Sunitinib compliance[r]				X	X		
Concomitant treatments[s]	X	X	X	X	X	X	

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		Day 1[d] –1/+0	Day 15 -3/+3	Day 1 –3/+3	+3 Days	+ 7 Days	-14/+14 Days
Poststudy survival[t]							X
PK of sunitinib[u]		X	X	X			
Subject summary CRF page[v]						X	
Systemic therapy/response for Primary diagnosis						X	X

2-D = 2-dimensional; ( ) if applicable; AE = adverse event; BID = twice daily; C = Cycle; CRF = Case Report Form; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire & the breast cancer module; IVRS = Interactive Voice Response System; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PD = progressive disease; PK = pharmacokinetics; TSH = thyroid-stimulating hormone; Tx = treatment.

a. Treatment: All assessments should have been performed prior to dosing with sunitinib or capecitabine unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. The term "month" is taken to mean a 28-day period.

b. End of Study Treatment (until disease progression or toxicity)/Withdrawal: these assessments were obtained if not completed during the previous 2 weeks on study (during the last 6 weeks on study for radiological tumor assessments).

c. Follow-up: Subjects who discontinued from the trial for reasons other than disease progression or death were required to have efficacy assessments (tumor imaging/scans) performed until PD, death, or a subsequent anticancer therapy.

d. Cycle 1 Day 1: Hematology, blood chemistry, thyroid-stimulating hormone, and physical examination not required if acceptable Screening assessment was performed within 7 days prior to randomization.

e. Informed Consent: Must have been obtained prior to undergoing any trial specific procedure and may have occurred prior to the 28-day Screening period.

f. Medical/Oncology History and Demographics: To include information on prior regimens, including dosing and duration of administration, plus description of best response observed and treatment failure.

g. Physical Examination: Examination of major body systems every 2 cycles (or 6 weeks) starting at Cycle 1. ECOG performance status was to be performed at Screening, Cycle 3, every 2 cycles, ie, C5, C7, and at end of treatment.

h. Hematology, Blood Chemistry: TSH should have been performed at Screening, then on Day 1 of every 2 cycles, ie, C3, C5, and at end of treatment.

i. Urinalysis: Dipstick protein urinalysis at Screening, Day 1 of Cycle 3, as clinically indicated, and at the end of study treatment with only dipstick urine protein results captured on the CRF. If the results of the dipstick test indicated ≥2+ proteinuria, then follow-up should have been performed with a quantitative urine protein analysis according to local standard practices with data captured on the AE CRF if AE criteria were met.

j. A 12-lead ECG was performed to determine the QTc interval. The ECGs should have been time matched (+/-3 hour). If the QTc interval was prolonged (>470 msec), the ECG should have been repeated and if still prolonged, they should have been reread by a cardiologist at the site for confirmation. ECGs should have been repeated as clinically indicated to include 2 weeks following intrasubject sunitinib dose adjustments.

k. MUGA or ECHO: Either must be performed at Screening, on Day 1 of Cycle 2, every 4 cycles (3 months), at end of treatment, and as clinically indicated. If a sunitinib-associated cardiac event was observed, then a MUGO or ECHO should have been repeated within 4-6 weeks.

Table 1. Schedule of Activities

Protocol Activities and Forms to be Completed	Screening	Treatment With Sunitinib or Capecitabine[a]			Post-Treatment		
	≤28 Days Prior to Treatment On-Study	Cycle 1		Subsequent Cycles	End of Tx or Withdrawal[b]	28 Days Post Treatment	Follow-Up[c]
		Day 1[d] –1/+0	Day 15 -3/+3	Day 1 –3/+3	+3 Days	+ 7 Days	-14/+14 Days

l. Study Randomization: Subject number and randomization were obtained from the IVRS system.
m. Study Treatment: Treatment started on Day 1 after completing all predose assessments. Day 1 of study treatment (first dose of study drug) must have occurred either on date of randomization or within 48 hours from subject randomization. Subjects received sunitinib capsules at a starting dose of 37.5 mg daily. The sunitinib dose may have been adjusted according to individual subject tolerance.
n. The starting dose of capecitabine was 1250 mg/m2 administered orally BID (morning and evening; equivalent to 2500 mg/m2 total daily dose) for 2 weeks followed by a 1-week off-treatment period given as 3-week cycles. For subjects >65 years old, the starting dose of capecitabine was 2000 mg/m2 total daily dose for 2 weeks followed by a 1-week off-treatment period given as 3-week cycles. Doses of capecitabine omitted for toxicity were not replaced or restored; instead the subject should have resumed the planned treatment cycles.
o. Tumor Imaging: CT or MRI scan at Screening to include chest, abdomen and pelvis, and a nuclear bone scan. Brain scans were only performed if symptoms suggested brain metastases. Subsequent scans may have only included areas of known or suspected tumors. Additional scans should have been performed whenever disease progression was suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the time of withdrawal from the study (if >6 weeks since last assessment). Bone scans for subjects with known bone metastases were performed at 12-week intervals. Assessments were performed at Screening and at 6-week intervals (42 calendar days) from date of randomization during the study. Assessments should have been fixed according to the calendar from the date of randomization regardless of treatment delays. The allowable window for disease assessments was +/-7 days except for Screening.
p. Adverse Events: Subjects must have been followed for AEs from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. Serious AEs should have been monitored and reported from the time that the subject provided informed consent.
q. EORTC QLQ-C30 and BR23: Subjects completed the questionnaires at the clinic prior to dosing with any study medications and other clinical activities. The assessment schedule purposefully provided for Patient-Reported Outcomes assessment coincident with each disease assessment every 6 weeks except for the first 12 weeks when the questionnaires were administered every 3 weeks. If questionnaires were not available in the subject's native language, these were not required.
r. Sunitinib Compliance: The study drug medication bottle(s) including any unused capsules were returned to the clinic for drug accountability. Compliance for capecitabine was also measured (For centers in Japan only).
s. Concomitant Medications and Treatments: Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment until 28 days after last treatment.
t. Poststudy Survival Status: After discontinuation of study, Poststudy survival status was collected by telephone contact or clinic visit every 2 months for up to 3 years after the last subject was randomized.
u. The PK of sunitinib were performed in approximately 15 Japanese subjects (For centers in Japan only).
v. Subject Summary page was found in the End of Study Visit in the CRF. For subjects entering the continuation study, this page was completed on the day informed consent was signed for participation in those other studies.

Number of Subjects (Planned and Analyzed):

A total of 700 subjects were planned to be enrolled in this study. Overall, 482 (238 in sunitinib treatment group and 244 in capecitabine treatment group) subjects were enrolled in this study, 70 in Japan, 52 in France, 46 in Germany, 44 in Spain, 33 in Taiwan, 30 in Brazil, 27 in Argentina, 25 in Mexico, 23 in Korea, 22 in Australia, 19 in Singapore, 15 in Hong Kong, 15 in Italy, 12 in Canada, 12 in United Kingdom, 9 in Colombia, 8 in Philippines, 6 in India, 5 in Peru, 4 in Turkey, 3 in Bulgaria, and 2 in South Africa.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were females, 18 years of age or older, with histologically or cytologically proven diagnosis of advanced (metastatic or locally-recurrent) breast adenocarcinoma that was not amenable to surgery, radiation, or combined modality therapy with curative intent and who received prior treatment with an anthracycline and a taxane either concurrently or sequentially in the neoadjuvant, adjuvant and/or advanced disease treatment setting; however, no more than 2 chemotherapy regimens in the advanced setting were allowed.

Subjects were excluded from the study if they had more than 2 prior regimens of chemotherapy in the advanced/metastatic disease setting and any prior regimen containing capecitabine.

Study Treatment:

Sunitinib: Sunitinib was administered orally from Day 1 at the starting dose of 37.5 mg capsule daily on a CDD. Self-administration of sunitinib capsules took place on an outpatient basis. Capsules were to be taken OD, in the morning, without regard to meals.

Subjects experiencing severe toxicity, including, but not limited to Grade 3 or 4 adverse events (AEs) attributed to sunitinib could have treatment breaks of 1 week or more (but no more than 3 consecutive weeks) inserted into the schedule as needed, and their dose may have been reduced depending on individual tolerability. The dose of 37.5 mg may have been reduced to 25 mg daily, which was the minimum dose acceptable for sunitinib in this study. Intrasubject reescalation of sunitinib back to the previous dose was permitted at the discretion of the investigator and considering the subject clinical status. Subjects not achieving a response by RECIST criteria and experiencing only Grade ≤1 nonhematological or Grade ≤2 hematological toxicity attributed to sunitinib within the first 9 weeks of treatment may have had their dose escalated to 50 mg daily.

Capecitabine: Capecitabine must have been used in compliance with its local prescribing information, which should have been reviewed to ensure that appropriate subjects were enrolled in the study. Capecitabine tablet was administered orally BID within 30 minutes after the end of a meal, from Days 1-14 every 3 weeks. The starting dose was 2500 mg/m^2/day or 2000 mg/m^2 (in subjects older than 65 years). However, this dose may have been reduced at the discretion of the investigator. The total capecitabine dose was calculated using body surface area. The total daily dose was split into equal morning and evening doses, to be given approximately 12 hours apart. Doses of capecitabine omitted for

toxicity were not replaced or restored; instead the subject should have resumed the planned treatment cycles.

The cycle length for both treatment arms (sunitinib and capecitabine) was 3 weeks. The start date of all cycles was fixed based on the date of the first dose of study drug, (ie, Cycle 1, Day 1). A new cycle began every 3 weeks (21 days with no window) regardless of dose interruptions or delays. A dose tracking instrument (Capecitabine Calendar) was supplied to study sites and should have been used to maintain the treatment schedule of capecitabine.

Efficacy, Safety and Outcomes Research Endpoints:

Primary:

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

Secondary:

- TTP: defined as the time from date of randomization to first documentation of objective tumor progression.
- OR: defined as confirmed complete response (CR) or confirmed partial response (PR) according to RECIST criteria. Confirmed responses were those that persist on repeat imaging study ≥4 weeks after initial documentation of response.
- DR: defined as the time from the first documentation of OR (CR or PR) that was subsequently confirmed to the first documentation of tumor progression or death due to any cause.
- TTR: defined as the time from randomization to the first documentation of objective tumor response (CR or PR) that was subsequently confirmed.
- OS: defined as the time from randomization to first documentation of death due to any cause.
- Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities.
- PROs of health related quality of life and disease-related symptoms as measured by EORTC Quality of Life Questionnaire (QLQ-C30) and the breast cancer module (QLQ-BR23).

Safety Evaluations: Safety evaluations included clinical monitoring, AEs, safety laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, performance status, and cardiac function (2-dimensional echocardiogram or multigated acquisition scan). Safety evaluations were done at times indicated in Table 1.

Statistical Methods:

Subject Populations:

The intent-to-treat (ITT) population included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. 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 assignment designated according to actual study treatment received. The AT population was the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefit endpoints may have been assessed in this population as well.

Statistical Methods:

Sample size was determined based on the analysis on the primary endpoint, PFS. The sample size for this study was computed based on the following assumptions:

- The median PFS of subjects receiving single agent capecitabine was 4.2 months.
- The PFS distribution following an exponential distribution and a constant accrual rate of approximately 40 subjects per month.
- While there was no historical data for the median PFS for subjects treated with sunitinib in this study population, it was hypothesized that this median was 33% higher (5.6 months) than that for the subjects treated with capecitabine. The hazard ratio (sunitinib/capecitabine) was assumed to be 0.75.
- A 2-sided type I error of $\alpha = 0.05$.
- Two interim analyses at 33% and 67% of the events.

Based on the above assumptions, a minimal number of 525 events were required to give 90% power to detect the statistical difference in PFS between the 2 treatment groups assuming the hazard ratio (sunitinib/capecitabine) was 0.75. The final analysis was to be performed when a minimum of 525 events were observed and 6 months after the last subject had been randomized. An accrual of 632 subjects was to result in a total study duration of about 22 months (16 months accrual plus 6 months follow-up for the last subject enrolled).

Descriptive statistics were used to summarize all subject/baseline characteristics, treatment administration/compliance, efficacy endpoints, and safety parameters.

All efficacy analyses, except for analyses of DR, were performed on the ITT population. Analyses of DR were performed for Responders only.

The primary efficacy analysis was the comparison of median PFS between the 2 treatment arms using the log-rank test stratified by the following factors:

- Visceral vs nonvisceral disease.
- Progression <12 months after adjuvant/neoadjuvant chemotherapy with taxane or no response after metastatic chemotherapy with taxane or 2 prior chemotherapy regimens in the metastatic setting ("taxane refractory subjects") vs progression ≥12 months after adjuvant/neoadjuvant chemotherapy with taxane or subjects who responded to metastatic chemotherapy to taxane ("taxane sensitive subjects"); and
- Estrogen receptor (ER)- progesterone receptor (PgR)- tumors vs ER+PgR+ or ER-PgR+ or ER+PgR- tumors.

PFS was summarized by treatment arm using Kaplan-Meier methods and displayed graphically. The Kaplan-Meier method was used to obtain the estimates of median progression-free time associated with each treatment. The 95% confidence intervals (CIs) of the median event-free time were provided. Covariates were not included in the calculation of median survival time.

The hazard ratio along with 95% CI were estimated for PFS by stratified Cox proportional hazard model and was stratified by the factors used in the stratified log-rank test, and by treatment in the model.

The primary analysis of PFS as well as the analyses of OR, TTP, and DR were performed using the investigator assessment of disease response and progression due to the lack of central review data upon the early termination of the study. No results from sensitivity analyses, supportive analysis using an unstratified log-rank test on the primary PFS endpoint, or those from TTR analysis are included since the study was stopped early for futility.

For the purposes of endpoint definitions, the term "on-study" included the period from randomization until PD or initiation of subsequent anticancer therapy in the absence of PD, or death, whichever occurred first. Tumor-related endpoints were censored on the day following the date of the last on-study tumor assessment documenting absence of the endpoint for subjects who were given antitumor treatment other than the study treatment, or were removed from treatment prior to documentation of the endpoint. Subjects having no tumor assessments after Screening had tumor-related endpoints censored on the date of randomization.

Safety data were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject disposition by treatment group for the ITT population is provided in Table 2.

Table 2. Summary of Subject Disposition – Intent-to-Treat Population

Number (%) of Subjects	Sunitinib (N=238)	Capecitabine (N=244)
Assigned to study treatment[a]: 482		
Randomized	238	244
Treated[b]	238	240
Randomized but not treated	0	4
Discontinued	238 (100)	240 (98.4)
Subject died	1 (0.4)	7 (2.9)
Related to study drug	35 (14.7)	14 (5.7)
Adverse event	26 (10.9)	13 (5.3)
Study terminated by Sponsor	9 (3.8)	1 (0.4)
Not related to study drug	202 (84.9)	223 (91.4)
Adverse event	12 (5.0)	11 (4.5)
Global deterioration of health status	10 (4.2)	7 (2.9)
Lost to follow-up	1 (0.4)	3 (1.2)
Objective progression or relapse	150 (63.0)	169 (69.3)
Other	14 (5.9)	17 (7.0)
Protocol violation	5 (2.1)	1 (0.4)
Subject refused continued treatment for reason other than adverse event	10 (4.2)	15 (6.1)

N = number of subjects by treatment groups.
a. Assigned to study treatment = randomized subjects.
b. Treated = subjects who took at least 1 dose of study drug.

A summary of data sets analyzed by treatment group is provided in Table 3.

Table 3. Data Sets Analyzed

Number of Subjects	Sunitinib	Capecitabine
Intent-to-treat	238	244[a]
As treated	238	240

a. Four subjects randomized to capecitabine were not treated on study.

A summary of demographic characteristics by treatment group for the ITT population is provided in Table 4.

Table 4. Demographic Characteristics – Intent-to-Treat Population

Number (%) of Subjects	Sunitinib (N=238)	Capecitabine (N=244)
Gender		
Female	238 (100.0)	244 (100.0)
Age (years):		
<18	0	0
18-44	50 (21.0)	70 (28.7)
45-64	159 (66.8)	129 (52.9)
≥65	29 (12.2)	45 (18.4)
Mean	52.7	52.3
SD	10.6	11.5
Range	25-80	23-80
Race:		
White	119 (50.0)	131 (53.7)
Black	4 (1.7)	4 (1.6)
Asian	92 (38.7)	88 (36.1)
Other[a]	23 (9.7)	21 (8.6)
Weight (kg):		
Mean	64.8	63.8
SD	14.7	12.8
Range	33.6-132.0	35.2-105.0
N	236 (99.2)	242 (99.2)
Height (cm):		
Mean	158.3	159
SD	7.2	7
Range	139.5-178.0	142.0-180.0
N	237 (99.6)	243 (99.6)

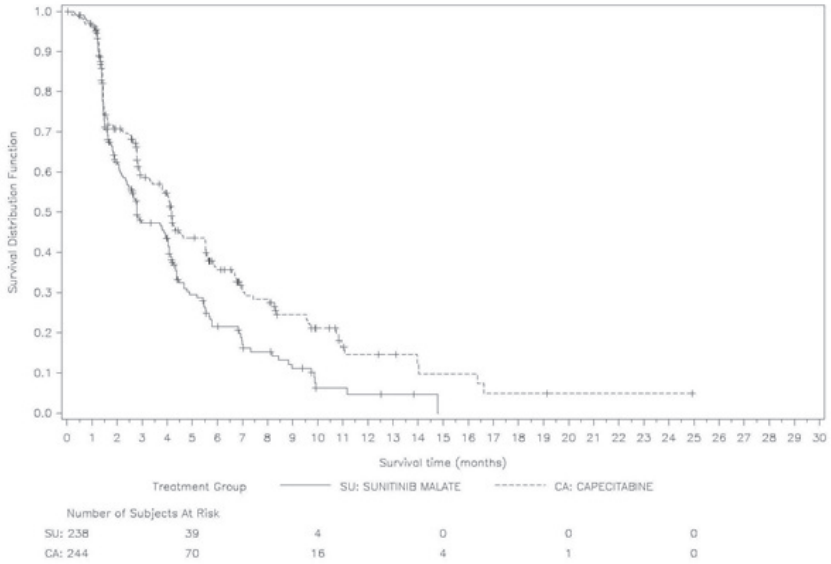
N = number of subjects by treatment groups; SD = standard deviation.
a. Other races = Hispanic (32 subjects); mulatto (3 subjects); mestizo (3 subjects); mestice (2 subjects); Caucasian (1 subject), mixed (1 subject); American Indian (1 subject); and Latin, Hispanic (1 subject).

Efficacy Results:

This study was terminated early due to futility.

Primary Efficacy Evaluation: PFS results are summarized in Table 5. A Kaplan-Meier plot of PFS is provided in Figure 1.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival – Intent-to-Treat



Secondary Efficacy Evaluation: TTP, DR, and OS results are summarized in Table 5.

Table 5. Summary of Time-to-Event Endpoints - Intent to-Treat Population

Variable	Number of Events		Hazard Ratio[a]	95% CI of Hazard Ratio	P-Value
	Sunitinib	Capecitabine			
Progression-free survival investigator assessment					
ITT population [N]	238	244			
Events (n [%])	151 (63.4)	147 (60.2)	1.470	(1.156, 1.869)	0.002[b]
Median (months)	2.8	4.2			
95% CI	(2.4, 4.0)	(3.8, 5.5)			
Time to tumor progression Investigator assessment					
ITT population [N]	238	244			
Events (n [%])	149 (62.6)	142 (58.2)	1.516	(1.188, 1.933)	<0.001[b]
Median (months)	2.8	4.2			
95% CI	(2.5, 4.0)	(3.8, 5,5)			
Duration of response Investigator Assessment					
ITT population [N]	238	244			
Events (n [%])	27 (11.3)	40 (16.4)	2.788	(1.042, 7.459)	N/A
Median (months)	6.9	9.3			
95% CI	(3.1, 8.5)	(5.5, 9.7)			
Overall survival Investigator assessment					
ITT population [N]	238	244			
Events (n [%])	97 (40.8)	91 (37.3)	1.202	(0.896-1.611)	0.219[b]
Median (months)	15.3	16.9			
95% CI	(12.0, 24.7)	(14.5, 26.0)			

Country was not included in randomization risk strata.
CI = confidence interval; ITT = intent-to-treat; N/A = not applicable; N = number of subjects by treatment groups; n = number of subjects.
a. Based on the Cox proportional hazards model stratified by randomization risk strata.
b. 2-sided p-value from the log-rank test stratified by randomization risk strata.

Overall Response:

A summary of OR is provided in Table 6. A summary of best overall OR data, according to RECIST is provided in Table 7.

Table 6. Summary of Best Overall Response - Intent to-Treat Population

Variable	Treatment		Treatment Difference (%)	P-Value[a]
	Sunitinib, n (%)	Capecitabine, n (%)		
Investigator Assessment				
ITT population [N]	238	244		
ORR	27 (11.3)	40 (16.4)	-5.049	0.109
Complete response	1 (<1.0)	1 (<1.0)		
Partial response	26 (10.9)	39 (16.0)		
95% CI[b]	(7.6, 16.1)	(12.0, 21.6)	(-11.2, 1.1)	

CI = confidence interval; ITT = intent-to-treat; N = ITT population per treatment group; n = number of subjects; ORR = objective response rate.
a. From a Pearson chi-square test.
b. Based on binomial distribution for ORR and based on a normal distribution for treatment difference.

Table 7. Summary of Best Confirmed RECIST-Defined Objective Response – Intent-to-Treat Population

Variable	Sunitinib (N=238)	Capecitabine (N=244)
Best Objective Response, n (%)		
Complete Response (CR)	1 (<1.0)	1 (<1.0)
Partial Response (PR)	26 (10.9)	39 (16.0)
Stable/No Response	87 (36.6)	105 (43.0)
Objective Progression[a]	84 (35.3)	64 (26.2)
Indeterminate	37 (15.5)	33 (13.5)
Missing	2 (<1.0)	2 (<1.0)
Overall Objective Response (CR + PR), n (%)	27 (11.3)	40 (16.4)
95% exact CI[b]	7.6, 16.1	12.0, 21.6

Symptomatic deterioration was the best objective response for 1 (<1.0%) subject in the sunitinib arm and no subjects in the capecitabine arm.
CI = confidence interval; CR = complete response; N = number of subjects by treatment groups; PR = partial response; RECIST = response evaluation criteria in solid tumors.
a. Objective Progression = PD (progressive disease).
b. Using exact method based on binomial distribution.

TTR and PRO analyses were not performed since this study was stopped early due to futility.

Safety Results:

An overview of treatment-emergent (all-causality and treatment-related) AEs by treatment group for the as-treated population is provided in Table 8.

Table 8. Overview of Treatment-Emergent (All-Causality and Treatment Related) Adverse Events – As-Treated Population

Number of Subjects	All-Causality Sunitinib (N=238) n (%)	Treatment-Related Sunitinib (N=238) n (%)	All-Causality Capecitabine (N=240) n (%)	Treatment-Related Capecitabine (N=240) n (%)
Subjects evaluable for adverse events	238	238	240	240
Number of adverse events[a]	2515	1837	1727	1109
Subjects with adverse events	230 (96.6)	219 (92.0)	235 (97.9)	220 (91.7)
Subjects with serious adverse events	72 (30.3)	37 (15.5)	44 (18.3)	12 (5.0)
Subjects with grade 3 or 4 adverse events	166 (69.7)	133 (55.9)	110 (45.8)	82 (34.2)
Subjects with grade 5 adverse events	25 (10.5)	6 (2.5)	16 (6.7)	2 (0.8)
Subjects discontinued due to adverse events	38 (16.0)	27 (11.3)	25 (10.4)	12 (5.0)
Subjects with dose reduced due to adverse events	38 (16.0)	36 (15.1)	63 (26.3)	59 (24.6)
Subjects with temporary discontinuation due to adverse events	158 (66.4)	133 (55.9)	125 (52.1)	104 (43.3)

Except for the number of AEs, subjects were counted only once per treatment in each row.
Serious adverse events – according to the investigator's assessment.
AE = adverse event; SAE = serious adverse event; N = number of subjects by treatment groups; n = number of subjects.
a. AEs and SAEs are not separated out.

The most commonly reported treatment-emergent all causality AEs for the sunitinib treatment group were diarrhea, nausea, vomiting, fatigue, and palmar-plantar erythrodysesthesia syndrome (Table 9).

The most commonly reported treatment-emergent all causality AEs for the capecitabine treatment group were palmar plantar erythrodysesthesia syndrome, diarrhea, nausea, fatigue, and decreased appetite (Table 9).

Table 9. Summary of Treatment-Emergent (All-Causality) Adverse Events by MedDRA Preferred Term Reported in at Least 5% of Subjects – As-Treated Population

MedDRA (Version 14.0) Preferred Term	Sunitinib (N=238) n (%)	Capecitabine (N=240) n (%)
Any AE	228 (95.8)	229 (95.4)
Anaemia	23 (9.7)	22 (9.2)
Leukopenia	19 (8)	13 (5.4)
Neutropenia	43 (18.1)	28 (11.7)
Thrombocytopenia	38 (16)	5 (2.1)
Hypothyroidism	31 (13)	2 (0.8)
Abdominal distension	13 (5.5)	6 (2.5)
Abdominal pain	21 (8.8)	26 (10.8)
Abdominal pain upper	29 (12.2)	21 (8.8)
Constipation	38 (16)	23 (9.6)
Diarrhoea	97 (40.8)	95 (39.6)
Dry mouth	18 (7.6)	10 (4.2)
Dyspepsia	34 (14.3)	13 (5.4)
Gastritis	12 (5)	4 (1.7)
Gingival bleeding	15 (6.3)	1 (0.4)
Nausea	94 (39.5)	75 (31.3)
Stomatitis	39 (16.4)	22 (9.2)
Vomiting	88 (37)	34 (14.2)
Asthenia	49 (20.6)	39 (16.3)
Face oedema	17 (7.1)	0
Chest pain	9 (3.8)	16 (6.7)
Fatigue	82 (34.5)	61 (25.4)
Mucosal inflammation	59 (24.8)	36 (15)
Oedema peripheral	19 (8)	21 (8.8)
Pyrexia	24 (10.1)	23 (9.6)
Nasopharyngitis	15 (6.3)	15 (6.3)
Urinary tract infection	12 (5)	4 (1.7)
Alanine aminotransferase increased	14 (5.9)	5 (2.1)
Aspartate aminotransferase increased	15 (6.3)	6 (2.5)
Blood thyroid stimulating hormone increased	12 (5)	0
Neutrophil count decreased	16 (6.7)	6 (2.5)
Platelet count decreased	27 (11.3)	3 (1.3)
White blood cell count decreased	15 (6.3)	12 (5)
Decreased appetite	67 (28.2)	48 (20)
Arthralgia	19 (8)	16 (6.7)
Back pain	23 (9.7)	18 (7.5)
Bone pain	12 (5)	8 (3.3)
Myalgia	16 (6.7)	9 (3.8)
Pain in extremity	23 (9.7)	21 (8.8)
Dizziness	10 (4.2)	15 (6.3)
Dysgeusia	61 (25.6)	11 (4.6)
Headache	38 (16)	23 (9.6)
Insomnia	21 (8.8)	14 (5.8)

Table 9. Summary of Treatment-Emergent (All-Causality) Adverse Events by MedDRA Preferred Term Reported in at Least 5% of Subjects – As-Treated Population

MedDRA (Version 14.0) Preferred Term	Sunitinib (N=238) n (%)	Capecitabine (N=240) n (%)
Cough	28 (11.8)	18 (7.5)
Dyspnoea	25 (10.5)	25 (10.4)
Epistaxis	20 (8.4)	6 (2.5)
Dry skin	13 (5.5)	13 (5.4)
Palmar-plantar erythrodysaesthesia syndrome	80 (33.6)	149 (62.1)
Rash	28 (11.8)	19 (7.9)
Skin discolouration	18 (7.6)	1 (0.4)
Yellow skin	19 (8)	0
Skin hyperpigmentation	6 (2.5)	23 (9.6)
Hypertension	53 (22.3)	6 (2.5)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects by treatment group; n = number of subjects.

The most commonly reported treatment-emergent treatment-related AEs for the sunitinib treatment group were diarrhea (39.1%), palmar-plantar erythrodysesthesia syndrome (33.2%), nausea (32.8%), fatigue (30.7%), and vomiting (29.0%; Table 10).

The most commonly reported treatment-emergent treatment-related AEs for the capecitabine treatment group were palmar-plantar erythrodysesthesia syndrome (62.1%), diarrhea (34.6%), nausea (28.8%), and fatigue (21.7%; Table 10).

A total of 166 (69.7%) subjects in the sunitinib treatment group and 110 (45.8%) in the capecitabine treatment group subjects had a Grade 3 or 4 AE.

For subjects in the sunitinib treatment group, there were 120 (50.4%) subjects with Grade 3 AEs. The most frequently reported Grade 3 AE was neutropenia (25 [10.5%] subjects). For subjects in the sunitinib treatment group, there were 23 (9.7%) subjects with Grade 4 AEs. The most frequently reported Grade 4 AEs were thrombocytopenia and platelet count decreased (3 [1.3%] subjects each).

For subjects in the capecitabine treatment group, there were 89 (37.1%) subjects with Grade 3 AEs. The most frequently reported Grade 3 AE was diarrhea (9 [3.8%] subjects). For subjects in the capecitabine treatment group, there were 11 (4.6%) subjects with Grade 4 AEs. The most frequently reported Grade 4 AE was pulmonary embolism (5 [2.1%] subjects).

Table 10. Summary of Treatment-Emergent (Treatment-Related) Adverse Events by MedDRA Preferred Term Reported in at Least 5% of Subjects – As-Treated Population

MedDRA (Version 14.0) Preferred Term	Sunitinib (N=238) n (%)	Capecitabine (N=240) n (%)
Any treatment-related AE[a]	219 (92.0)	220 (91.7)
Diarrhoea	93 (39.1)	83 (34.6)
Palmar-plantar erythrodysesthesia syndrome	79 (33.2)	149 (62.1)
Nausea	78 (32.8)	69 (28.8)
Fatigue	73 (30.7)	52 (21.7)
Vomiting	69 (29.0)	28 (11.7)
Decreased appetite	60 (25.2)	40 (16.7)
Dysgeusia	60 (25.2)	11 (4.6)
Mucosal inflammation	60 (25.2)	36 (15.0)
Hypertension	47 (19.7)	2 (0.8)
Neutropenia	42 (17.6)	27 (11.3)
Asthenia	41 (17.2)	30 (12.5)
Stomatitis	39 (16.4)	21 (8.8)
Thrombocytopenia	39 (16.4)	6 (2.5)
Dyspepsia	30 (12.6)	11 (4.6)
Hypothyroidism	30 (12.6)	1 (0.4)
Platelet count decreased	29 (12.2)	3 (1.3)
Headache	27 (11.3)	9 (3.8)
Rash	26 (10.9)	15 (6.3)
Abdominal pain upper	22 (9.2)	18 (7.5)
Constipation	19 (8.0)	13 (5.4)
Epistaxis	19 (8.0)	4 (1.7)
Yellow skin	19 (8.0)	0
Anemia	18 (7.6)	15 (6.3)
Dry mouth	18 (7.6)	10 (4.2)
Skin discoloration	18 (7.6)	1 (0.4)
Leukopenia	17 (7.1)	13 (5.4)
Neutrophil count decreased	16 (6.7)	6 (2.5)
Edema peripheral	15 (6.3)	6 (2.5)
White blood cell count decreased	15 (6.3)	12 (5.0)
Face edema	14 (5.9)	0
Abdominal pain	13 (5.5)	19 (7.9)
Alanine aminotransferase increased	13 (5.5)	5 (2.1)
Aspartate aminotransferase increased	13 (5.5)	6 (2.5)
Myalgia	13 (5.5)	6 (2.5)
Gingival bleeding	12 (5.0)	1 (0.4)
Dry skin	11 (4.6)	12 (5.0)
Skin hyperpigmentation	6 (2.5)	23 (9.6)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects by treatment group; n = number of subject.
a. AEs and SAEs are not separated out.

A summary of treatment-emergent serious adverse events (SAEs) by preferred term reported in at least 1 subjects in either treatment group is provided in Table 11. A total of 72 (30.3%) sunitinib subjects and 44 (18.3%) capecitabine subjects had at least 1 SAE.

The most frequently reported SAEs were disease progression (5.9%), followed by thrombocytopenia and pneumonia (2.1% each) in the sunitinib treatment group. The most frequently reported SAEs were disease progression (3.3%) and diarrhea (2.9%), followed by dyspnea and pleural effusion (each 2.1%) in the capecitabine treatment group.

Table 11. Summary of Treatment-Emergent (All-Causality) Serious Adverse Events by Preferred Term – As-Treated Population

MedDRA (Version14.0) Preferred Term	Sunitinib (N=238) n (%)	Capecitabine (N=240) n (%)
Any SAE	72 (30.3)	44 (18.3)
Anaemia	2 (0.8)	1 (0.4)
Febrile neutropenia	2 (0.8)	2 (0.8)
Haematotoxicity	0	1 (0.4)
Leukopenia	0	1 (0.4)
Thrombocytopenia	5 (2.1)	1 (0.4)
Angina pectoris	0	1 (0.4)
Cardiac failure	3 (1.3)	0
Cardiac failure congestive	2 (0.8)	0
Diplopia	1 (0.4)	0
Abdominal pain	2 (0.8)	1 (0.4)
Abdominal pain upper	0	1 (0.4)
Ascites	3 (1.3)	0
Constipation	1 (0.4)	0
Diarrhoea	3 (1.3)	7 (2.9)
Diarrhoea haemorrhagic	0	1 (0.4)
Dysphagia	1 (0.4)	0
Gastric haemorrhage	2 (0.8)	0
Gastric ulcer	1 (0.4)	0
Gastrointestinal haemorrhage	3 (1.3)	0
Gastrointestinal perforation	0	1 (0.4)
Ileus	1 (0.4)	0
Mallory-Weiss syndrome	1 (0.4)	0
Melaena	1 (0.4)	0
Nausea	1 (0.4)	1 (0.4)
Pancreatitis acute	1 (0.4)	0
Peritonitis	1 (0.4)	0
Rectal haemorrhage	0	1 (0.4)
Upper gastrointestinal haemorrhage	1 (0.4)	1 (0.4)
Vomiting	3 (1.3)	2 (0.8)
Death	0	1 (0.4)
Disease progression	14 (5.9)	8 (3.3)
Fatigue	3 (1.3)	0
General physical health deterioration	1 (0.4)	0
Local swelling	0	1 (0.4)
Medical device complication	1 (0.4)	0
Mucosal inflammation	1 (0.4)	1 (0.4)
Pain	1 (0.4)	0
Pyrexia	0	3 (1.3)
Cholecystitis	1 (0.4)	0
Cholecystitis acute	2 (0.8)	0
Hepatic failure	1 (0.4)	0
Hepatic function abnormal	2 (0.8)	0
Anal abscess	1 (0.4)	0
Appendicitis	1 (0.4)	0
Bacteraemia	1 (0.4)	0
Cellulitis	1 (0.4)	1 (0.4)
Dengue fever	1 (0.4)	0
Enterocolitis infectious	1 (0.4)	0

Table 11. Summary of Treatment-Emergent (All-Causality) Serious Adverse Events by Preferred Term – As-Treated Population

MedDRA (Version14.0) Preferred Term	Sunitinib (N=238) n (%)	Capecitabine (N=240) n (%)
Erysipelas	1 (0.4)	0
Fungal peritonitis	0	1 (0.4)
Oesophageal candidiasis	1 (0.4)	0
Peritonitis bacterial	0	1 (0.4)
Pneumonia	5 (2.1)	0
Sepsis	2 (0.8)	2 (0.8)
Septic shock	0	1 (0.4)
Sinusitis	1 (0.4)	0
Skin infection	1 (0.4)	1 (0.4)
Tooth infection	1 (0.4)	0
Urinary tract infection	1 (0.4)	0
Wound infection	1 (0.4)	0
Fall	0	1 (0.4)
Hip fracture	0	1 (0.4)
Patella fracture	0	1 (0.4)
Postoperative respiratory distress	1 (0.4)	0
Subdural haematoma	0	1 (0.4)
Blood bilirubin increased	1 (0.4)	0
C-reactive protein increased	1 (0.4)	0
Haemoglobin decreased	1 (0.4)	0
Liver function test abnormal	1 (0.4)	0
Platelet count decreased	2 (0.8)	0
Cachexia	0	1 (0.4)
Dehydration	1 (0.4)	2 (0.8)
Hypoglycaemia	1 (0.4)	0
Hypokalaemia	2 (0.8)	0
Hyponatraemia	1 (0.4)	0
Back pain	1 (0.4)	0
Bone pain	1 (0.4)	0
Muscular weakness	1 (0.4)	0
Neoplasm progression	2 (0.8)	1 (0.4)
Aphasia	1 (0.4)	0
Cerebral haemorrhage	1 (0.4)	0
Depressed level of consciousness	1 (0.4)	0
Dizziness	0	1 (0.4)
Headache	3 (1.3)	0
Spinal cord compression	0	1 (0.4)
Confusional state	1 (0.4)	0
Delirium	1 (0.4)	0
Hydronephrosis	1 (0.4)	0
Proteinuria	1 (0.4)	0
Urethral stenosis	1 (0.4)	0
Urinary retention	1 (0.4)	0
Ovarian disorder	0	1 (0.4)
Asphyxia	0	1 (0.4)
Dyspnoea	3 (1.3)	5 (2.1)
Epistaxis	3 (1.3)	0
Pleural effusion	3 (1.3)	5 (2.1)
Pneumothorax	1 (0.4)	0

Table 11. Summary of Treatment-Emergent (All-Causality) Serious Adverse Events by Preferred Term – As-Treated Population

MedDRA (Version14.0) Preferred Term	Sunitinib (N=238) n (%)	Capecitabine (N=240) n (%)
Pulmonary embolism	1 (0.4)	3 (1.3)
Respiratory arrest	0	1 (0.4)
Respiratory failure	1 (0.4)	0
Skin ulcer	1 (0.4)	0
Deep vein thrombosis	1 (0.4)	1 (0.4)
Haematoma	1 (0.4)	0
Hypertension	2 (0.8)	0
Hypotension	0	1 (0.4)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects by treatment group; n = number of subject; SAE = serious adverse event.

The most frequently reported sunitinib-related SAEs were thrombocytopenia (2.1%) followed by diarrhea and gastrointestinal hemorrhage (1.3% each); Table 12.

Table 12. Summary of Treatment-Emergent (Sunitinib-Related) Serious Adverse Events by Preferred Term Reported in at Least 1 Subject

MedDRA (Version14.0) Preferred Term	Sunitinib (N=238) n (%)
Any SAE	37 (15.5)
Thrombocytopenia	5 (2.1)
Diarrhoea	3 (1.3)
Gastrointestinal haemorrhage	3 (1.3)
Cardiac failure	2 (0.8)
Cardiac failure congestive	2 (0.8)
Epistaxis	2 (0.8)
Fatigue	2 (0.8)
Hepatic function abnormal	2 (0.8)
Hypertension	2 (0.8)
Platelet count decreased	2 (0.8)
Pneumonia	2 (0.8)
Anaemia	1 (0.4)
Aphasia	1 (0.4)
Bacteraemia	1 (0.4)
Blood bilirubin increased	1 (0.4)
Cerebral haemorrhage	1 (0.4)
Confusional state	1 (0.4)
Deep vein thrombosis	1 (0.4)
Dehydration	1 (0.4)
Depressed level of consciousness	1 (0.4)
Dyspnoea	1 (0.4)
Enterocolitis infectious	1 (0.4)
Erysipelas	1 (0.4)
Gastric haemorrhage	1 (0.4)
Haematoma	1 (0.4)
Haemoglobin decreased	1 (0.4)
Headache	1 (0.4)
Hypoglycaemia	1 (0.4)
Ileus	1 (0.4)
Liver function test abnormal	1 (0.4)
Mallory-Weiss syndrome	1 (0.4)
Melaena	1 (0.4)
Mucosal inflammation	1 (0.4)
Muscular weakness	1 (0.4)
Nausea	1 (0.4)
Oesophageal candidiasis	1 (0.4)
Pleural effusion	1 (0.4)
Pneumothorax	1 (0.4)
Proteinuria	1 (0.4)
Pulmonary embolism	1 (0.4)
Wound infection	1 (0.4)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects by treatment group; n = number of subject; SAE = serious adverse event.

A summary of treatment-emergent capecitabine-related SAEs by preferred term reported in at least 2 capecitabine subjects is provided in Table 13.

Table 13. Summary of Treatment-Emergent (Capecitabine-Related) Serious Adverse Events by Preferred Term Reported in at Least 2 Subjects in Capecitabine Treatment Group

MedDRA (Version14.0) Preferred Term	Capecitabine (N=240) n (%)
Any capecitabine-related SAE	12 (5.0)
Diarrhoea	6 (2.5)
Vomiting	2 (0.8)
Dehydration	2 (0.8)
Febrile neutropenia	2 (0.8)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects by treatment group; n = number of subject; SAE = serious adverse event.

A total of 27 (11.3%) subjects discontinued the study due to a sunitinib-related AE during the study. A total of 12 (5.0%) subjects discontinued the study due to a capecitabine-related AE during the study.

A total of 158 (66.4%) subjects in the sunitinib treatment group required temporary discontinuation of sunitinib due to an AE and 38 (16.0%) subjects required a dose reduction of sunitinib due to an AE. A total of 125 (52.1%) subjects required a temporary interruption of capecitabine dosing due to an AE and 63 (26.3%) subjects required a dose reduction of capecitabine due to an AE.

A total of 36 subjects (21 subjects in the sunitinib treatment group and 15 subjects in the capecitabine treatment group) died (had an AE resulting in death) on study through and including 28 calendar days after last administration of investigational product.

A total of 8 subjects died due to a treatment-related AE (6 sunitinib subjects and 2 capecitabine subjects); Table 14.

Table 14. Summary of Treatment-Related AEs Resulting in Death by Preferred Term - As-Treated Population

Adverse Event Preferred Term (MedDRA Version14.0)	Sunitinib (N=238) n (%)	Capecitabine (N=240) n (%)
Any AE	6 (2.5)	2 (0.8)[a]
Cardiac failure congestive	1 (0.4)	0
Cerebral hemorrhage	1 (0.4)	0
Gastrointestinal hemorrhage	1 (0.4)	0
Hepatic function abnormal	1 (0.4)	0
Hypotension	0	1 (0.4)
Pleural effusion	1 (0.4)	0
Pulmonary embolism	1 (0.4)	0
Septic shock	0	1 (0.4)
Subdural hematoma	0	1 (0.4)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects by treatment group; n = number of subjects.
a. One subject died of subdural hematoma and 1 subject died of hypotension and septic shock.

Clinical Laboratory Test Results:

Hematology: For subjects in the sunitinib treatment group, the most frequently reported hematological abnormalities were leukopenia (182; 78.1%), thrombocytopenia (154; 66.4%), and neutropenia (143; 61.9%). Hematological abnormalities that led to permanent discontinuation from the study for subjects in the sunitinib treatment group were neutropenia (3 subjects), thrombocytopenia (1 subject), neutrophil count decreased (1 subject), and anemia (1 subject).

Hematological abnormalities reported as AEs in the sunitinib treatment group were anemia (25; 10.5%), leukopenia (19; 8.0%), neutropenia (43; 18.1%), febrile neutropenia (2; 0.8%), and thrombocytopenia (41; 17.2%).

For subjects in the capecitabine treatment group, the most frequently reported hematological abnormalities were anemia (62.9%), lymphopenia (56.7%), and leukopenia (44.6%). Hematological abnormalities that led to permanent discontinuation from the study for subjects in the capecitabine treatment group were neutropenia (4 subjects), decreased white blood cells (1 subject), leukopenia (1 subject), neutrophil count decreased (1 subject), and thrombocytopenia (1 subject).

Hematological abnormalities reported as AEs in the capecitabine treatment group were anemia (23; 9.6%), leukopenia (14; 5.8%), neutropenia (28; 11.7%), febrile neutropenia (3; 1.3%), and thrombocytopenia (6; 2.5%).

Chemistry: For subjects in the sunitinib treatment group, the most commonly reported chemistry laboratory abnormalities were increased aspartate aminotransferase (AST) (183; 78.9%), increased alkaline phosphatase (146; 63.8%), and increased alanine aminotransferase (ALT) (135; 57.9%). Of these abnormalities, only increased ALT was Grade 4 in 2 (0.9%) subjects.

The most commonly reported chemistry laboratory abnormalities that were Grade 4 included increased creatinine (4; 1.7%) and hypophosphatemia (4; 1.9%).

Chemistry laboratory abnormalities reported as AEs in at least 5 subjects in the sunitinib treatment group were ALT increased (14; 5.9%) and AST increased (15; 6.3%).

For subjects in the capecitabine treatment group, the most commonly reported chemistry laboratory abnormalities were increased AST (142; 61.5%), increased alkaline phosphatase (129; 56.6%), hyperglycemia 1(20; 52.6%), and increased ALT (115; 49.8%). Of these abnormalities, only increased ALT and hyperglycemia were Grade 4 in 1 (0.4%) subject each.

The most commonly reported chemistry laboratory abnormalities in the capecitabine arm that were Grade 4 included hypocalcemia in 2 (0.9%) capecitabine subjects.

Chemistry laboratory abnormalities reported as AEs in at least 5 subjects in the capecitabine treatment group were ALT increased (5; 2.1%), AST increased (6; 2.5%), and blood bilirubin increased (6; 2.5%).

Other Safety Results:

The most commonly reported urinalysis laboratory abnormalities were Grade 1 and Grade 2 urine protein for sunitinib (10; 15.2% and 12; 18.2% subjects, respectively) and capecitabine (12; 16.9% and 5; 7.0% subjects, respectively) subjects.

Eleven sunitinib subjects had ECG results considered clinically significant during active treatment including: hold study medication; counterclockwise heart rotation; nonspecific ST-T change; no evidence of cardiac problem right now; ventricular premature complex; Grade 3 corrected QT interval (QTc): 600 msec and Grade 2 prolonged QTc interval; sinus tachycardia; T waves negativity and left anterior hemiblock; atrioventricular heart block (first grade); prolonged QTc interval; and QT prolongation.

Seven capecitabine subjects had postbaseline ECG results considered clinically significant including: sinus tachycardia; sinus tachycardia with borderline right axis deviation; right axis deviation; left anterior fascicular block and right bundle branch block; left anterior fascicular block; early depolarization; and precardial negative T waves.

CONCLUSIONS:

- Based on the analysis of efficacy and safety results from this study, sunitinib 37.5 mg on a CDD schedule cannot be recommended as monotherapy in the ABC subject population and treatment setting under study.

- Sunitinib 37.5 mg on a CDD schedule was not more effective than capecitabine 1250 or 1000 mg/m^2 BID on a 2-week on/1-week off schedule in subjects with ABC that had failed a taxane +/- anthracycline chemotherapy, with a median investigator-assessed PFS of 2.8 months in the sunitinib arm vs 4.2 months in the capecitabine arm, and a hazard ratio of 1.47 (95% CI: 1.16, 1.87; p=0.002).

- Overall objective response rate (11.3% vs 16.4%), median DR (6.9 vs 9.3 months), median TTP (2.8 vs 4.2 months), and median OS (15.3 vs 24.6 months) were all greater in the capecitabine arm than in the sunitinib arm.

- The AEs reported in sunitinib subjects were of greater frequency and severity than in capecitabine subjects, but were consistent with the known safety profile of sunitinib, and generally tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy.

- The final OS data did not demonstrate statistically significant difference between the capecitabine arm and sunitinib arm (2-sided p-value=0.219, log-rank), although the median OS was numerically longer in the capecitabine arm than in the sunitinib arm (16.9 months vs 15.3 months, respectively).