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

PROTOCOL NO.: A6181099

PROTOCOL TITLE: A Randomized, Phase 3 Study of Sunitinib in Combination With Capecitabine Compared With Capecitatine in Patients With Previously Treated Breast Cancer

Study Centers: A total of 105 centers took part in the study and enrolled subjects; 25 in the United States (US), 10 each in Germany and Italy, 8 in the United Kingdom (UK), 7 each in France and Spain, 5 each in Belgium, Greece and Poland, 4 each in Canada and Ireland, 3 each in the Russian Federation, Austria and Denmark, 2 each in the Netherlands, the Czech Republic and 1 each in Romania, and Norway.

Study Initiation and Final Completion Dates: 05 February 2007 to 20 June 2011

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To demonstrate that the combination of sunitinib plus capecitabine was superior to capecitabine monotherapy in prolonging the progression-free survival (PFS) for advanced breast cancer (ABC) subjects.

Secondary Objectives:

- To compare measures of duration of tumor control and overall survival (OS).
- To compare the safety of sunitinib plus capecitabine versus (vs) capecitabine monotherapy.
- To compare the patient reported outcomes (PRO) of health-related quality of life (QOL) and disease-related symptoms.
- To assess measurement and valuation of health status.

METHODS

Study Design: This was a multinational, multicenter, randomized (1:1), Phase 3 clinical trial comparing the efficacy and safety of the combination capecitabine plus sunitinib with capecitabine in ABC subjects. Subjects that had bone-only disease who were hormone receptor-positive were required to have progressed on hormone-therapy to be eligible. In addition, subjects having human epidermal growth factor 2 (HER2) positive disease were eligible for the study only if they had previously received treatment with trastuzumab and, where community standard of care, lapatinib in the adjuvant or advanced disease setting. Treatment with lapatinib was not mandatory. Randomization was stratified according to the number of metastatic organ systems (≤2 vs >2 sites), receptor status (triple negative [HER2-/estrogen receptor-/progesterone receptor-] vs all others), and number of prior chemotherapy regimens (1 vs >1).

A scheduled safety analysis by the Data Monitoring Committee (DMC) occurred after 12 subjects in the sunitinib/capecitabine arm had received study treatment for at least 6 weeks. The DMC reviewed the data periodically throughout the study.

Treatment was administered in 3-week cycles, to 2 treatment Arms:

Arm A (sunitinib + capecitabine) and

Arm B (capecitabine alone).

In Arm A sunitinib was administered orally at the starting dose of 37.5 mg once daily in a regimen of continuous daily dosing (CDD). Subjects experiencing dose-limiting toxicity attributed to sunitinib were to have a 1-week treatment break inserted into the regimen as needed. Capecitabine was administered at different starting doses in the 2 arms.

Subjects were continue on treatment on study until objective progressive disease (PD) was documented according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 or withdrawal from the study for other reasons. In Arm A, if either capecitabine or sunitinib was discontinued for reasons other than PD, subjects were to continue to receive the remaining agent until PD. Subjects discontinuing both agents before PD were followed for tumor assessment until PD, or until the initiation of a subsequent anti-cancer therapy in the absence of documented PD, or until death, whichever occurred first. In Arm B, if capecitabine was discontinued for reasons other than PD, subjects were to be followed for tumor assessment until PD or until the initiation of a subsequent anti-cancer therapy in the absence of documented PD, or until death, whichever occurred first.

Crossover: At the time PD was documented according to RECIST, subjects in Arm B could be eligible to crossover to single-agent sunitinib administered at the starting dose of 37.5 mg daily on CDD regimen. Following radiological documentation of PD and initiation of subsequent anticancer therapy, subjects were to remain under observation for survival with bimonthly data collection for up to 3 years from first study treatment. Table 1 presents a schedule of study events.

Table 1. Schedule of Events

Procedures	Screening	Treatment Period[a]				Post-Treatment		
		Cycle 1[b]			Subsequent Cycles	End of Treatment/ Withdrawal[d]	28 Days Post-Treatment[e]	Follow-Up
	Day ≤28 Prior to Randomization	Day 1[c]	Day 7	Day 14	Day 1			
Baseline documentation								
Informed consent[f]	X							
Medical/oncologic history	X							
Physical examination[g]	X	X			X	X	(X)	
Baseline signs and symptoms		X						
Laboratory studies								
Hematology	X	X	X	X	X	X	(X)	
Blood chemistry	X	X			X	X	(X)	
Coagulation[h]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Thyroid testing	X	(X)			(X)	(X)	(X)	
Pregnancy test[i]	X	(X)			(X)			
Urinalysis[j]	X				(X)	X	(X)	
12-lead ECG[k]	X			X	(X)	X		
MUGA/echocardiogram[l]	X				(X)	X		
Study randomization[m]	X							
Sunitinib dosing		X→	→	→	X→			
Capecitabine dosing		X→	→	→X	X→			
Tumor assessments								
Tumor imaging[n]	X				X[o]	(X)	(X)	(X)
Bone scan	X[p]				X[q]	(X)	(X)	(X)
Other clinical assessments								
Adverse events[r]	X	X	X	X	X	X	X	
PRO assessments[s]		X			X	X		
Study drug compliance[t]					X	X		
Concomitant medications and treatments[u]	X	X	X	X	X	X	X	
Survival follow-up[v]								X

Table 1. Schedule of Events

() = optional procedure or assessment; X→ = start dosing; → = continue dosing
ECG = electrocardiogram; MUGA = multigated acquisition; PRO = patient-reported outcomes.

a. All assessments were to be performed prior to dosing unless otherwise indicated. Each cycle was 21 days long, except when off-treatment periods were added to allow the resolution of toxicities. Cycle 1, Day 1 was the first day of sunitinib and/or capecitabine treatment. The allowable window for all other visits was ±2 days.

b. Following crossover to sunitinib after documented progression per Response Evaluation Criteria in Solid Tumors (RECIST) on capecitabine, Cycle 1 procedures were repeated for the first cycle of sunitinib.

c. Laboratories and physical examination were not required if acceptable Screening assessments had been performed within 7 days prior to the start of treatment.

d. Assessments not required if completed during the previous week on study (3 weeks for MUGA scan/echocardiogram and ECGs, 6 weeks for tumor assessments).

e. Assessments required as necessary for adverse event follow-up.

f. Obtained prior to undergoing any study specific procedure and could occur prior to the 28-day Screening period.

g. Examination of major body systems, height (at Screening visit only), Eastern Cooperative Oncology Group (ECOG) performance status, body weight, and vital signs (temperature, blood pressure [BP], heart rate, respiratory rate).

h. Required only for subjects receiving coumarin-derived oral anticoagulants.

i. Post-Screening testing as required by local authorities or regulations.

j. Urinalysis by dipstick performed at Baseline, Cycle 3 Day 1, as clinically indicated, and at the end of treatment. If results indicated ≥2 + proteinuria, follow-up quantitative urine protein analysis was to be performed.

k. Three consecutive 12-lead ECGs at least 2 minutes apart to determine the mean corrected QT (QTc) interval. ECGs were performed at the same time of the day (eg, morning) and time matched (± 1 hour). If the mean QTc interval was prolonged (>500 msec), then the ECGs were re-read by a cardiologist at the clinical site for confirmation. Additional ECGs were performed as indicated and 2 weeks following intrasubject sunitinib dose adjustments and at the time of discontinuation of each study treatment. Crossover subjects: For the first cycle of crossover, repeat ECG was required on Day 14.

l. At baseline, Cycle 2 Day 1, every 3-months (4 cycles) while receiving study treatment, and at the end of each study treatment. Additional assessments were performed as clinically indicated. If a cardiac event was observed, then a MUGA/echocardiogram should be repeated within 3-4 weeks.

m. Arm A: sunitinib 37.5 mg once daily in the morning and capecitabine 2000 mg/m^2/day on Days 1-14; Arm B: capecitabine 2500 mg/m^2/day on Days 1-14; doses on both arms could be adjusted. If either study treatment was not started on Day 1, then it was started on Day 2.

n. Computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis and clinical assessment of superficial disease (these lesions were photographed). A brain CT or MRI was performed at Screening to confirm eligibility; follow-up brain scans were required only if brain metastases were suspected.

o. Every 6 weeks from randomization; these assessments followed an every-6-week schedule regardless of changes to the dosing schedule (ie, assessments were not delayed following treatment interruptions). Additional scans were performed whenever progressive disease (PD) was suspected (eg, symptomatic deterioration) and to confirm a partial response (PR) or complete response (CR; at least 4 weeks after initial documentation of response). The allowable window for tumor assessments was ±7 days, except for Screening.

p. Bone scan was required at Screening within 6 weeks prior to randomization. Subsequent assessments (starting at Week 12 then every 12 weeks from the randomization date) were required only if bone disease at Screening was confirmed by the Principal Investigator or core imaging laboratory or when new

Table 1. Schedule of Events

metastatic bone disease suspected by the Principal Investigator. A bone scan was required at the time of confirmation of objective response for patients who had bone metastases. The allowable window for on-study bone scan assessments was ±7 days. Assessment delay to conform to treatment delays was not permitted.

q. For subjects with bone-only disease: Bone scan was required at Screening within 6 weeks prior to randomization. For subjects that only had bone metasteses at Screening that was confirmed by the Principal Investigator, all on-study bone scans were required. On-study bone scans were completed at Week 6 (Day 42), Week 12 (Day 84), and then every 12 weeks from the randomization date. The allowable window for on-study bone scan assessments was ±7 days. Assessment delay to conform to treatment delays was not permitted. Post treatment bone scans were required until documented progression.

r. Subjects were followed for adverse events 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 resolved or were determined to be "chronic" or "stable," whichever was later. Serious adverse events were monitored and reported from the time the subject provided informed consent as described in the protocol.

s. The European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ) C30 and EORTC QLQ breast cancer module and EuroQol 5-dimensional questionnaire were completed by the subject in the clinic prior to study drug dosing or any assessments. Assessments were performed in Cycle 1, Cycle 3, and every 6 weeks thereafter. Crossover subjects were to complete the questionnaire on Day 1 of Cycle 1 of crossover only, and not at any other time point.

t. The sunitinib bottle(s) including any unused capsules were returned to the clinic for drug accountability starting on the first day of Cycle 2. Capecitabine compliance followed local practice.

u. Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment until 28 days after last treatment.

v. Subjects who discontinued both sunitinib and capecitabine for reasons other than PD could reduce subsequent clinic visits to 6 weeks, which were required to include tumor assessment until PD or a subsequent anti-cancer therapy. If PD had not been documented prior to institution of new anti-tumor therapy, a full disease assessment was required. After PD, survival status was collected via telephone every 2 months until death or 3 years from first study treatment.

Number of Subjects (Planned and Analyzed): It was planned to enroll 430 subjects (215 in each treatment arm) in the study. A total of 442 subjects (85 in France, 63 in US, 42 in Germany, 38 in Spain, 36 in the UK, 32 in Poland, 30 in Italy, 23 in Belgium, 19 in Greece, 17 in Canada, 14 in the Russian Federation, 13 in Austria, 12 in Ireland, 6 in the Czech Republic, 5 in Romania, 3 each in Denmark and the Netherlands, and 1 in Norway) were randomized to treatment (221 subjects per treatment arm in intent-to-treat [ITT] population).

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years with locally advanced or metastatic disease that could be measured. Subjects with bone-only disease were also allowed to enter the study. Previous treatment with an anthracycline and a taxane, in any setting and progression on first or second line regimen or adjuvant regimen if disease free interval <12 months.

Exclusion Criteria: Subjects with a history of inflammatory carcinoma if there is no other measurable disease, >2 chemotherapy agents in the advanced disease setting or with brain metastases were excluded.

Study Treatment:

Self-administration of sunitinib capsules took place on an outpatient basis. Capsules were taken once daily in the morning without regard to meals.

In Arm A, sunitinib was administered orally from Day 1 at the starting dose of 37.5 mg once daily on a CDD schedule in 3-week cycles. Subjects who experienced dose-limiting toxicity had at least a 1-week treatment rest inserted into the regimen as needed and could dose reduce to 25 mg depending on individual tolerability. Intrasubject re-escalation of sunitinib back to the previous dose level was permitted at the discretion of the Investigator and considering the subject's clinical status.

Capecitabine was administered orally twice daily within 30 minutes after the end of a meal, on Days 1 to 14 of 3-week cycles. The total daily dose was split into equal morning and evening doses, taken approximately 12 hours apart. Subjects were instructed to swallow the tablets whole with a glass of water. The total capecitabine dose was calculated using body surface area at the start of each cycle. The capecitabine dose could be reduced based on tolerability.

In Arm A, capecitabine was administered orally at a starting dose of 2,000 mg/m^2/day (1000 mg/m^2 twice daily) from Days 1-14 every 3 weeks.

In Arm B, capecitabine was administered orally at a starting dose of 2,500 mg/m^2/day (1250 mg/m^2 twice daily) from Days 1-14 every 3 weeks.

Doses missed during a treatment cycle for any reason were not replaced.

Efficacy and Safety Endpoints:

Primary Endpoint:

- PFS.

Secondary Endpoints:

- Overall response rate (ORR).
- Duration of response (DR).
- OS.
- Two- and 3-year survival.
- PRO changes in scores for health-related QOL 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).
- Overall safety profile characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events (AEs); laboratory abnormalities.

Safety Evaluations: The overall safety profile was characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of AEs and laboratory abnormalities.

Statistical Methods: Descriptive statistics and analyses were provided for subjects overall. Baseline was defined as the last evaluation before the first dose of study medication.

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 as well as subject characteristics.

As-Treated (AT) population: consisted of all ITT subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety; it was also a secondary population for analyzing efficacy.

PFS: defined as the time (in months) from randomization to objectively determined (ie, by tumor imaging and as judged by RECIST) PD based on an independent core radiology laboratory assessment or death from any cause.

PFS was summarized in the ITT population based on the independent radiology assessment using Kaplan-Meier methods and the median event time (with 2-sided 95% confidence interval [CI]) was provided. The hazard ratio and its 95% CI were estimated. A stratified log-rank test (1-sided, α=0.025) based on randomization stratification factors was used to compare PFS between the 2 treatment arms. An unstratified log-rank test (1-sided, α=0.025) and Cox regression model was also used for PFS. In addition, the potential influences of covariates and baseline stratification factors were evaluated.

The stratified log-rank test (1-sided, α=0.025) was used to evaluate the primary efficacy endpoint, PFS, in the AT population.

ORR: defined as the total proportion of subjects with measurable disease at baseline with either confirmed complete response (CR) or partial response (PR) as characterized by RECIST relative to all randomized subjects.

The number and percent of subjects who achieved objective response (CR or PR) were summarized along with the corresponding exact 2-sided 95% CI calculated using a method based on the F distribution. An unstratified Pearson χ^2 test and a stratified Pearson χ^2 test using the baseline stratification factors was used to compare ORR between the 2 treatment arms.

DR: defined as the time from the first documentation of objective tumor response (subsequently confirmed) to the first documentation of objective tumor progression or death due to any cause (only calculated for subjects with objective response).

DR was calculated as ([the date response ended (ie. date of PD or death] – [first CR or PR date that was subsequently confirmed + 1 day])/30.4. DR (in months) was only calculated for the subgroup of subjects with a confirmed objective tumor response.

DR was summarized using Kaplan-Meier methods. DR was calculated for the subgroup of subjects with objective disease response. The median event time and 2-sided 95% CI for the median were provided.

OS: defined as the time from randomization to the first documentation of death due to any cause (in months) was calculated as ([date of death – first randomization date + 1])/30.4. OS was summarized using Kaplan-Meier methods. The median event time and 2-sided 95% CI for the median were provided. A stratified log-rank test was used to compare OS between the 2 treatment arms and the hazard ratio and its 95% CI was estimated. A supportive analysis was performed using an unstratified test.

Survival Probability: The 2- or 3-year survival probabilities were defined as the probabilities of survival 2 years or 3 years after the date of randomization, respectively, estimated using the Kaplan-Meier method. The 2-sided 95% CI was calculated for the log (-log [2-year or 3-year survival probability]) using the normal approximation, which was then back-transformed to give the CI for the 2-year or 3-year survival probability itself.

RESULTS

Subject Disposition and Demography: A total of 442 subjects (221 subjects in treatment arm) were randomized to treatment and comprised the ITT population. A total of 432 subjects (217 subjects in Arm A and 215 subjects in Arm B) comprised the AT population. An overall summary of subject disposition is presented in Table 2 and a summary of subject disposition at the end of the study is presented in Table 3.

Table 2. Subject Populations and Disposition – Before Crossover

Variable	Arm A (Sunitinib + Capecitabine)	Arm B (Capecitabine)	Total
Randomized/ITT population (N)[a]	221	221	442
Randomized/ITT but did not take any drug (n [%])	4 (1.8)	6 (2.7)	10 (2.3)
Received sunitinib and capecitabine	217 (98.2)	0	217 (49.1)
Received sunitinib only	0	0	0
Received capecitabine only	0	215 (97.3)	215 (48.6)
AT population[b]	217	215	432
Subject Status (n [%])			
Subjects who were still on study	0	78 (35.3)	78 (17.6)
Subjects who discontinued from the study	221 (100.0)	143 (64.7)	364 (82.4)
Primary reason for discontinuation of sunitinib (n [%])			
Completed	0	-	-
Adverse event	70 (31.7)	-	-
Protocol violation	1 (0.5)	-	-
Subject died	1 (0.5)	-	-
Objective progression or relapse	115 (52.0)	-	-
Global deterioration of health status	2 (0.9)	-	-
Subject refused continued treatment for reason other than AE	14 (6.3)	-	-
Other	14 (6.3)	-	-
Primary reason for discontinuation of capecitabine (n [%])			
Completed	0	0	0
Adverse event	73 (33.0)	26 (11.8)	99 (22.4)
Protocol violation	1 (0.5)	3 (1.4)	4 (0.9)
Lost to follow-up	0	2 (0.9)	2 (0.5)
Subject died	2 (0.9)	2 (0.9)	4 (0.9)
Decision of Sponsor	0	3 (1.4)	3 (0.7)
Objective progression or relapse	111 (50.2)	142 (64.3)	253 (57.2)
Global deterioration of health status	2 (0.9)	6 (2.7)	8 (1.8)
Subject refused continued treatment for reason other than AE	12 (5.4)	13 (5.9)	25 (5.7)
Other	16 (7.2)	6 (2.7)	22 (5.0)
Primary reason for discontinuation from study (n [%])			
Adverse event	0	0	0
Protocol violation	1 (0.5)	2 (0.9)	3 (0.7)
Lost to follow-up	1 (0.5)	2 (0.9)	3 (0.7)
Subject died	8 (3.6)	6 (2.7)	14 (3.2)

Table 2. Subject Populations and Disposition – Before Crossover

Variable	Arm A (Sunitinib + Capecitabine)	Arm B (Capecitabine)	Total
Decision of Sponsor	0	3 (1.4)	3 (0.7)
Objective progression or relapse	158 (71.5)	93 (42.1)	251 (56.8)
Subject refused continued treatment for reason other than AE	8 (3.6)	7 (3.2)	15 (3.4)
Other	45 (20.4)	30 (13.6)	75 (17.0)
Duration of follow-up (Months)[c]			
Median	31.4	23.4	29.5
(95% confidence interval)	(30.5, 36.1)	(12.7, 26.9)	(27.9, 30.8)

% = (n/N)*100. AE = adverse events; AT = as-treated; ITT = intent-to-treat; N = number of subject; n = number of subject with specified criteria.

a. The 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.

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

c. Duration of follow—up for a subject is the time period from randomization to the last date of follow-up or death and is estimated using the reversed Kaplan-Meier approach, where death is censored and remaining alive is an event.

Table 3. Subject Populations and Disposition – After Crossover

Variable	Crossover From Capecitabine
Randomized/ ITT population (n)[a]	78
Received sunitinib and capecitabine	0
Received sunitinib only	78 (100.0)
Received capecitabine only	0
AT population[b]	78 (100.0)
Subjects who discontinued from the study	78 (100.0)
Primary reason for discontinuation of sunitinib (n [%])	
Completed	0
Adverse event	8 (10.3)
Subject died	6 (7.7)
Objective progression or relapse	58 (74.4)
Global deterioration of health status	4 (5.1)
Subject refused continued treatment for reason other than AE	1 (1.3)
Other	1 (1.3)
Primary reason for discontinuation from the study (n [%])	
Subject died	10 (12.8)
Objective progression or relapse	63 (80.8)
Global deterioration of health status	1 (1.3)
Other	4 (5.1)

AE = adverse event; AT = as-treated; ITT = intent-to-treat; n = number of subject with specified criteria.
a. The ITT population includes all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects receive study drug or receive a different drug from that to which they were randomized.
b. The AT population consists of all subjects who received at least 1 dose of study drug 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.

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

Variable	Arm A (Sunitinib + Capecitabine) (N=221)	Arm B (Capecitabine Alone) (N=221)
Sex, n (%)		
Male	3 (1.4)	1 (0.5)
Female	218 (98.6)	220 (99.5)
Race, n (%)		
White	207 (93.7)	208 (94.1)
Black	7 (3.2)	4 (1.8)
Asian	2 (0.9)	2 (0.9)
Other	5 (2.3)	7 (3.2)
Age (years)		
Mean (standard deviation)	52.9 (11.11)	54.3 (10.06)
Median	52.0	54.0
Minimum, maximum	27.0, 79.0	31.0, 77.0
<65	182 (82.4)	185 (83.7)
≥65	39 (17.6)	36 (16.3)
ECOG performance status, n (%)[a]		
0	130 (58.8)	126 (57.0)
1	89 (40.3)	93 (42.1)
≥2	2 (0.9)	2 (0.9)
Childbearing potential, n (%)		
Yes	39 (17.6)	38 (17.2)
No	182 (82.4)	183 (82.8)

ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; N = number of subjects in treatment group; n = number of subject.
a. ECOG performance status scores were summarized with data collected on a date close to and prior or equal to the first drug date for treated subjects and on the latest date for not treated subjects.

Efficacy Results:

In the primary analysis of PFS (independent radiology assessment, ITT population), the median PFS was similar on the 2 treatment arms, being 5.5 months vs 5.9 months in Arm A vs Arm B, respectively. One hundred and thirty-two subjects (59.7%) in Arm A vs 116 subjects (52.5%) in Arm B experienced objective tumor progression or died. The median PFS was 5.5 (95% CI: 4.5 to 6.0 months) vs 5.9 months (95% CI: 5.4 to 7.6 months) with a stratified hazard ratio of 1.2239 (95% CI: 0.9487 to 1.5789; 1-sided log rank test p = 0.9409). 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, and in sensitivity analyses using different definitions of progression (Table 5).

In the secondary analyses, the results for OS were similar to those for PFS. Median OS was 16.5 months vs 17.2 months in Arm A vs Arm B. The probability of survival at 1 year was 0.635 (95% CI: 0.567 to 0.696) vs 0.654 (95% CI: 0.585 to 0.715).

Twenty (20) subjects in each arm (48.8% and 55.6%, respectively) progressed and had observations for DR. The median DR was 9.0 vs 8.8 months.

PFS, OS and DR in ITT and AT populations are summarized in Table 5.

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

Variable	Number of Events Arm A (Sunitinib + Capecitabine)	Number of Events Arm B (Capecitabine Alone)	Hazard Ratio[a]	95% CI of Hazard Ratio[a]	p-value[a]
Progression-Free Survival					
Independent radiology assessment					
ITT population, N	221	221	-	-	-
Events, n (%)	132 (59.7)	116 (52.5)	a: 1.2239	0.9487 to 1.5789	0.9409
Median (weeks)	5.5	5.9	b: 1.2522	0.9753 to 1.6076	0.9681
95% CI	4.5 to 6.0	5.4 to 7.6	-	-	-
AT population, N	217	215	-	-	-
Events, n (%)	132 (60.8)	116 (54.0)	a: 1.2239	0.9487 to 1.5789	0.9409
Median (months)	5.5	5.9	b: 1.2522	0.9753 to 1.6076	0.9618
95% CI	4.5 to 6.0	5.4 to 7.6			
Investigators' assessment					
ITT population, N	221	221	-	-	-
Events, n (%)	160 (72.4)	152 (68.8)	a: 1.1084	0.8817 to 1.3935	0.8120
Median (months)	5.4	5.5	b: 1.1300	0.9045 to 1.4117	0.8599
95% CI	4.4 to 5.8	4.3 to 6.8			
Overall Survival					
ITT population, N	221	221	-	-	-
Events, n (%)	169 (76.5)	158 (71.5)	a: 1.0372	0.8322 to 1.2927	0.6275
Median (months)	16.5	17.2	b: 1.0439	0.8399 to 1.2974	0.6510
95% CI	14.5 to 19.6	15.5 to 19.3			
Duration of Response					
Independent radiology assessment					
ITT population, N	221	221	-	-	-
Events, n (%)	20 (48.8)	20 (55.8)	-	-	-
Median (months)	9.0	8.8	-	-	-
95% CI	5.7 to 20.7	5.7 to 13.8	-	-	-
Investigators' assessment					
ITT population, N	221	221	-	-	-
Events, n (%)	46 (82.1)	26 (57.8)	-	-	-
Median (months)	5.7	7.6	-	-	-
95% CI	4.3 to 6.9	6.5 to 9.9	-	-	-

AT = as-treated; CI = confidence interval; ITT = intent-to-treat; N = number of subject; n = number of subject with specified criteria.

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

ORR is summarized for both analysis populations by the independent radiology assessment and by Investigator assessment for the ITT population in Table 6. In the independent radiology assessment in the ITT population, ORR was 18.6% (95% CI: 13.7 to 24.3) vs 16.3% (95% CI: 11.7 to 21.8); stratified odds ratio: 1.17 (95% CI: 0.69 to 1.97, exact 1-sided log-rank p-value = 0.3143) Arm A vs Arm B, respectively (treatment difference and 95% CI: 2.3 [-4.8 to 9.3%]). One hundred twenty (54.3%) vs 132 subjects (59.7%) had stable disease (SD).

Table 6. Summary of Analyses of Objective Response Rate (ITT)

Variable	Arm A (Sunitinib + Capecitabine) (N=221)	Arm B (Capecitabine Alone) (N=221)
Independent radiology assessment		
Best overall response, n (%)[a]		
CR	0 (0.0)	0 (0.0)
PR	41 (18.6)	36 (16.3)
SD	120 (54.3)	132 (59.7)
PD	37 (16.7)	33 (14.9)
Missing/not evaluable	23 (10.4)	20 (9.0)
Subjects with SD ≥26 weeks[b]	30 (13.6)	36 (16.3)
ORR, n (%)	41 (18.6)	36 (16.3)
95% exact CI of ORR (%)	(13.7, 24.3)	(11.7, 21.8)
Treatment difference and 95% exact CI (%)[c]	2.3 (-4.8, 9.3)	
Stratified analysis[d]		
Odds ratio[e]	1.17	
(95% exact CI)	(0.69 to 1.97)	
Exact 1-sided p-value	0.3143	
Investigators' assessment		
Best overall response, n (%)		
CR	0 (0.0)	2 (0.9)
PR	56 (25.3)	43 (19.5)
SD	103 (46.6)	114 (51.6)
PD	37 (16.7)	42 (19.0)
Missing/not evaluable	25 (11.3)	20 (9.0)
Subjects with SD ≥26 weeks	29 (13.1)	35 (15.8)
ORR, n (%)	56 (25.3)	45 (20.4)
95% exact CI of ORR	(19.7, 31.6)	(15.3, 26.3)
Treatment difference and 95% exact CI (%)	5 (-2.8, 12.8)	
Stratified analysis		
Odds ratio	1.32	
(95% exact CI)	(0.83 to 2.13)	
Exact 1-sided p-value	0.1269	

Any assessments after anticancer therapy (follow-up systemic therapy or concomitant radiation therapy/surgery) was received and any assessments which had a 14-week gap with previous assessment was not used to derive confirmed overall response.
CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = number of subjects in treatment group; n = number of subject; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
a. Percentage of subjects in the ITT population.
b. Exclude subjects with best overall response of PR or CR.
c. Difference was calculated as sunitinib + capecitabine – capecitabine; 95% CI was calculated based on normal distribution.
d. Difference was calculated as sunitinib + capecitabine – capecitabine; 95% CI was calculated based on normal distribution.
e. An odds ratio >1 was in favor of sunitinib + capecitabine; an odds ratio <1 was in favor of capecitabine.

PROs assessments were not analyzed, because the study did not meet its primary endpoint.

Safety Results: Treatment-emergent (non-serious) AEs (all causalities) experienced by ≥5% of subjects are presented in Table 7.

Table 7. Treatment-Emergent (Non-Serious) Adverse Events Experienced by ≥5% of Subjects (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine) N=215 n (%)
With adverse events	214 (98.6)	208 (96.7)
Blood and lymphatic system disorders	147 (67.7)	66 (30.7)
Anaemia	53 (24.4)	35 (16.3)
Leukopenia	51 (23.5)	19 (8.8)
Neutropenia	104 (47.9)	39 (18.1)
Thrombocytopenia	102 (47.0)	14 (6.5)
Ear and labyrinth disorders	13 (6.0)	15 (7.0)
Vertigo	8 (3.7)	13 (6.0)
Endocrine disorders	22 (10.1)	2 (0.9)
Hypothyroidism	22 (10.1)	2 (0.9)
Eye disorders	48 (22.1)	42 (19.5)
Conjunctivitis	4 (1.8)	16 (7.4)
Lacrimation increased	23 (10.6)	24 (11.2)
Gastrointestinal disorders	189 (87.1)	156 (72.6)
Abdominal pain	38 (17.5)	29 (13.5)
Abdominal pain upper	48 (22.1)	30 (14.0)
Constipation	41 (18.9)	42 (19.5)
Diarrhoea	121 (55.8)	95 (44.2)
Dry mouth	19 (8.8)	16 (7.4)
Dyspepsia	38 (17.5)	13 (6.0)
Dysphagia	13 (6.0)	1 (0.5)
Flatulence	13 (6.0)	11 (5.1)
Gastrooesophageal reflux disease	12 (5.5)	5 (2.3)
Gingivitis	11 (5.1)	2 (0.9)
Nausea	122 (56.2)	91 (42.3)
Oesophagitis	14 (6.5)	2 (0.9)
Stomatitis	61 (28.1)	26 (12.1)
Vomiting	90 (41.5)	55 (25.6)
General disorders and administration site conditions	168 (77.4)	137 (63.7)
Asthenia	75 (34.6)	49 (22.8)
Chest pain	12 (5.5)	12 (5.6)
Fatigue	65 (30.0)	53 (24.7)
Mucosal inflammation	49 (22.6)	24 (11.2)
Oedema peripheral	16 (7.4)	19 (8.8)
Pain	11 (5.1)	8 (3.7)
Pyrexia	21 (9.7)	15 (7.0)
Hepatobiliary disorders	28 (12.9)	17 (7.9)
Hyperbilirubinaemia	13 (6.0)	13 (6.0)
Jaundice	11 (5.1)	0
Infections and infestations	71 (32.7)	77 (35.8)
Nasopharyngitis	16 (7.4)	10 (4.7)
Rhinitis	1 (0.5)	13 (6.0)
Urinary tract infection	16 (7.4)	11 (5.1)
Investigations	83 (38.2)	61 (28.4)
Alanine aminotransferase increased	11 (5.1)	15 (7.0)
Aspartate aminotransferase increased	19 (8.8)	13 (6.0)
Blood alkaline phosphatase increased	12 (5.5)	8 (3.7)
Platelet count decreased	15 (6.9)	4 (1.9)

Table 7. Treatment-Emergent (Non-Serious) Adverse Events Experienced by ≥5% of Subjects (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine) N=215 n (%)
Weight decreased	20 (9.2)	17 (7.9)
Metabolism and nutrition disorders	88 (40.6)	70 (32.6)
Decreased appetite	67 (30.9)	44 (20.5)
Hypokalaemia	11 (5.1)	8 (3.7)
Musculoskeletal and connective tissue disorders	93 (42.9)	91 (42.3)
Arthralgia	24 (11.1)	25 (11.6)
Back pain	25 (11.5)	23 (10.7)
Bone pain	13 (6.0)	12 (5.6)
Musculoskeletal pain	13 (6.0)	13 (6.0)
Myalgia	19 (8.8)	7 (3.3)
Pain in extremity	25 (11.5)	33 (15.3)
Nervous system disorders	122 (56.2)	87 (40.5)
Dizziness	14 (6.5)	9 (4.2)
Dysgeusia	58 (26.7)	18 (8.4)
Headache	57 (26.3)	32 (14.9)
Neuropathy peripheral	9 (4.1)	13 (6.0)
Paraesthesia	15 (6.9)	16 (7.4)
Peripheral sensory neuropathy	16 (7.4)	6 (2.8)
Psychiatric disorders	43 (19.8)	38 (17.7)
Anxiety	14 (6.5)	10 (4.7)
Insomnia	18 (8.3)	20 (9.3)
Respiratory, thoracic and mediastinal disorders	88 (40.6)	71 (33.0)
Cough	30 (13.8)	28 (13.0)
Dyspnoea	31 (14.3)	26 (12.1)
Epistaxis	31 (14.3)	10 (4.7)
Skin and subcutaneous tissue disorders	148 (68.2)	151 (70.2)
Alopecia	16 (7.4)	12 (5.6)
Dry skin	14 (6.5)	16 (7.4)
Erythema	15 (6.9)	12 (5.6)
Nail disorder	14 (6.5)	19 (8.8)
Palmar-plantar erythrodysaesthesia syndrome	118 (54.4)	131 (60.9)
Rash	18 (8.3)	24 (11.2)
Skin fissures	3 (1.4)	12 (5.6)
Vascular disorders	66 (30.4)	40 (18.6)
Hot flush	11 (5.1)	6 (2.8)
Hypertension	46 (21.2)	8 (3.7)

Subjects were only counted once per treatment for each row.
Excluded events that occurred prior to dosing or after subjects crossed over from capecitabine to sunitinib.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject; v = version.

Treatment-related AEs experienced by ≥5% of subjects are presented in Table 8.

Table 8. Treatment-Related Adverse Events Experienced by ≥5% of Subjects (AT Population)

Number (%) of Subjects with Adverse Events by: and MedDRA (v14.0) Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine) N=215 n (%)	Total N=432 n (%)
Any treatment-related adverse events	215 (99.1)	201 (93.5)	416 (96.3)
Palmar-plantar erythrodysaesthesia syndrome	118 (54.4)	133 (61.9)	251 (58.1)
Diarrhoea	118 (54.4)	92 (42.8)	210 (48.6)
Nausea	116 (53.5)	80 (37.2)	196 (45.4)
Neutropenia	104 (47.9)	38 (17.7)	142 (32.9)
Vomiting	80 (36.9)	47 (21.9)	127 (29.4)
Thrombocytopenia	102 (47.0)	13 (6.0)	115 (26.6)
Asthenia	72 (33.2)	42 (19.5)	114 (26.4)
Fatigue	59 (27.2)	49 (22.8)	108 (25.0)
Decreased appetite	59 (27.2)	36 (16.7)	95 (22.0)
Stomatitis	60 (27.6)	26 (12.1)	86 (19.9)
Anaemia	51 (23.5)	29 (13.5)	80 (18.5)
Mucosal inflammation	50 (23.0)	24 (11.2)	74 (17.1)
Dysgeusia	56 (25.8)	17 (7.9)	73 (16.9)
Abdominal pain upper	43 (19.8)	28 (13.0)	71 (16.4)
Leukopenia	51 (23.5)	18 (8.4)	69 (16.0)
Abdominal pain	26 (12.0)	21 (9.8)	47 (10.9)
Constipation	24 (11.1)	23 (10.7)	47 (10.9)
Dyspepsia	33 (15.2)	13 (6.0)	46 (10.6)
Lacrimation increased	22 (10.1)	22 (10.2)	44 (10.2)
Hypertension	41 (18.9)	2 (0.9)	43 (10.0)
Epistaxis	28 (12.9)	8 (3.7)	36 (8.3)
Rash	15 (6.9)	20 (9.3)	35 (8.1)
Dry mouth	19 (8.8)	15 (7.0)	34 (7.9)
Headache	22 (10.1)	11 (5.1)	33 (7.6)
Nail disorder	14 (6.5)	18 (8.4)	32 (7.4)
Pain in extremity	16 (7.4)	15 (7.0)	31 (7.2)
Dry skin	13 (6.0)	16 (7.4)	29 (6.7)
Paraesthesia	15 (6.9)	13 (6.0)	28 (6.5)
Aspartate aminotransferase increased	16 (7.4)	10 (4.7)	26 (6.0)
Alopecia	14 (6.5)	11 (5.1)	25 (5.8)
Hyperbilirubinaemia	13 (6.0)	12 (5.6)	25 (5.8)
Weight decreased	14 (6.5)	10 (4.7)	24 (5.6)

AE and SAE results are not separated out.
% = (n/N)*100
AE = adverse event; AT = as-treated; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject; SAE = serious adverse event; v = version.

Serious AEs (SAEs) (all causality) are presented in Table 9.

Table 9. Serious Adverse Events - All Causality (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine) N=215 n (%)	Total N=432 n (%)
Any serious adverse events	85 (39.2)	59 (27.4)	144 (33.3)
Blood and lymphatic system disorders	17 (7.8)	1 (0.5)	18 (4.2)
Anaemia	7 (3.2)	1 (0.5)	8 (1.9)
Bone marrow failure	1 (0.5)	0 (0.0)	1 (0.2)
Leukopenia	2 (0.9)	0 (0.0)	2 (0.5)
Neutropenia	3 (1.4)	0 (0.0)	3 (0.7)
Pancytopenia	1 (0.5)	0 (0.0)	1 (0.2)
Thrombocytopenia	7 (3.2)	0 (0.0)	7 (1.6)
Cardiac disorders	3 (1.4)	2 (0.9)	5 (1.2)
Cardiac failure acute	1 (0.5)	0 (0.0)	1 (0.2)
Congestive cardiomyopathy	0 (0.0)	1 (0.5)	1 (0.2)
Pericardial effusion	1 (0.5)	0 (0.0)	1 (0.2)
Supraventricular tachycardia	0 (0.0)	1 (0.5)	1 (0.2)
Ventricular extrasystoles	1 (0.5)	0 (0.0)	1 (0.2)
Ear and labyrinth disorders	1 (0.5)	0 (0.0)	1 (0.2)
Vertigo	1 (0.5)	0 (0.0)	1 (0.2)
Endocrine disorders	2 (0.9)	0 (0.0)	2 (0.5)
Hypothyroidism	2 (0.9)	0 (0.0)	2 (0.5)
Gastrointestinal disorders	28 (12.9)	20 (9.3)	48 (11.1)
Abdominal pain	2 (0.9)	2 (0.9)	4 (0.9)
Abdominal pain upper	1 (0.5)	0 (0.0)	1 (0.2)
Anal fissure	1 (0.5)	0 (0.0)	1 (0.2)
Ascites	1 (0.5)	2 (0.9)	3 (0.7)
Colitis	0 (0.0)	1 (0.5)	1 (0.2)
Colonic obstruction	0 (0.0)	1 (0.5)	1 (0.2)
Constipation	0 (0.0)	2 (0.9)	2 (0.5)
Diarrhoea	9 (4.1)	13 (6.0)	22 (5.1)
Diverticular perforation	1 (0.5)	0 (0.0)	1 (0.2)
Duodenal stenosis	0 (0.0)	1 (0.5)	1 (0.2)
Dyspepsia	1 (0.5)	0 (0.0)	1 (0.2)
Dysphagia	1 (0.5)	1 (0.5)	2 (0.5)
Enteritis	1 (0.5)	0 (0.0)	1 (0.2)
Gastritis	2 (0.9)	1 (0.5)	3 (0.7)
Gastrointestinal haemorrhage	1 (0.5)	0 (0.0)	1 (0.2)
Intestinal obstruction	0 (0.0)	1 (0.5)	1 (0.2)
Nausea	6 (2.8)	1 (0.5)	7 (1.6)
Pancreatitis haemorrhagic	1 (0.5)	0 (0.0)	1 (0.2)
Peritonitis	1 (0.5)	0 (0.0)	1 (0.2)
Small intestinal obstruction	1 (0.5)	1 (0.5)	2 (0.5)
Stomatitis	0 (0.0)	1 (0.5)	1 (0.2)
Subileus	2 (0.9)	1 (0.5)	3 (0.7)
Upper gastrointestinal haemorrhage	1 (0.5)	0 (0.0)	1 (0.2)
Vomiting	11 (5.1)	6 (2.8)	17 (3.9)
General disorders and administration site conditions	25 (11.5)	20 (9.3)	45 (10.4)
Asthenia	6 (2.8)	0 (0.0)	6 (1.4)
Chest pain	1 (0.5)	2 (0.9)	3 (0.7)
Chills	0 (0.0)	1 (0.5)	1 (0.2)
Death	1 (0.5)	0 (0.0)	1 (0.2)
Disease progression	10 (4.6)	7 (3.3)	17 (3.9)

Table 9. Serious Adverse Events - All Causality (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine) N=215 n (%)	Total N=432 n (%)
Fatigue	2 (0.9)	2 (0.9)	4 (0.9)
General physical health deterioration	3 (1.4)	1 (0.5)	4 (0.9)
Malaise	1 (0.5)	0 (0.0)	1 (0.2)
Mucosal inflammation	2 (0.9)	1 (0.5)	3 (0.7)
Pain	0 (0.0)	1 (0.5)	1 (0.2)
Pyrexia	2 (0.9)	6 (2.8)	8 (1.9)
Ulcer	0 (0.0)	1 (0.5)	1 (0.2)
Hepatobiliary disorders	4 (1.8)	1 (0.5)	5 (1.2)
Cytolytic hepatitis	1 (0.5)	0 (0.0)	1 (0.2)
Hepatic failure	1 (0.5)	0 (0.0)	1 (0.2)
Hepatic haemorrhage	1 (0.5)	0 (0.0)	1 (0.2)
Hyperbilirubinaemia	1 (0.5)	1 (0.5)	2 (0.5)
Jaundice	1 (0.5)	0 (0.0)	1 (0.2)
Infections and infestations	8 (3.7)	8 (3.7)	16 (3.7)
Breast infection	1 (0.5)	0 (0.0)	1 (0.2)
Cellulitis	1 (0.5)	0 (0.0)	1 (0.2)
Erysipelas	1 (0.5)	0 (0.0)	1 (0.2)
Gastroenteritis	0 (0.0)	1 (0.5)	1 (0.2)
Infection	1 (0.5)	0 (0.0)	1 (0.2)
Neutropenic sepsis	1 (0.5)	1 (0.5)	2 (0.5)
Pneumonia	2 (0.9)	1 (0.5)	3 (0.7)
Pyelonephritis	0 (0.0)	1 (0.5)	1 (0.2)
Sepsis	0 (0.0)	3 (1.4)	3 (0.7)
Tooth infection	1 (0.5)	0 (0.0)	1 (0.2)
Urinary tract infection	0 (0.0)	1 (0.5)	1 (0.2)
Injury, poisoning and procedural complications	2 (0.9)	4 (1.9)	6 (1.4)
Fall	0 (0.0)	1 (0.5)	1 (0.2)
Hip fracture	0 (0.0)	1 (0.5)	1 (0.2)
Radiation skin injury	1 (0.5)	0 (0.0)	1 (0.2)
Radius fracture	0 (0.0)	1 (0.5)	1 (0.2)
Subdural haematoma	1 (0.5)	0 (0.0)	1 (0.2)
Wrist fracture	0 (0.0)	1 (0.5)	1 (0.2)
Investigations	2 (0.9)	2 (0.9)	4 (0.9)
Ejection fraction decreased	1 (0.5)	0 (0.0)	1 (0.2)
Electrocardiogram ST segment depression	1 (0.5)	0 (0.0)	1 (0.2)
Haemoglobin decreased	0 (0.0)	2 (0.9)	2 (0.5)
Metabolism and nutrition disorders	6 (2.8)	1 (0.5)	7 (1.6)
Decreased appetite	1 (0.5)	0 (0.0)	1 (0.2)
Dehydration	1 (0.5)	1 (0.5)	2 (0.5)
Diabetes mellitus	1 (0.5)	0 (0.0)	1 (0.2)
Hypercalcaemia	1 (0.5)	0 (0.0)	1 (0.2)
Hypokalaemia	1 (0.5)	1 (0.5)	2 (0.5)
Hyponatraemia	1 (0.5)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (1.8)	4 (1.9)	8 (1.9)
Back pain	1 (0.5)	0 (0.0)	1 (0.2)
Bone pain	1 (0.5)	0 (0.0)	1 (0.2)
Muscular weakness	1 (0.5)	0 (0.0)	1 (0.2)
Musculoskeletal chest pain	1 (0.5)	0 (0.0)	1 (0.2)
Myalgia	1 (0.5)	0 (0.0)	1 (0.2)

Table 9. Serious Adverse Events - All Causality (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine) N=215 n (%)	Total N=432 n (%)
Osteolysis	0 (0.0)	1 (0.5)	1 (0.2)
Pain in extremity	0 (0.0)	1 (0.5)	1 (0.2)
Pathological fracture	0 (0.0)	2 (0.9)	2 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9)	3 (1.4)	5 (1.2)
Breast cancer	2 (0.9)	1 (0.5)	3 (0.7)
Lung neoplasm	0 (0.0)	1 (0.5)	1 (0.2)
Malignant pleural effusion	0 (0.0)	1 (0.5)	1 (0.2)
Nervous system disorders	5 (2.3)	4 (1.9)	9 (2.1)
Cerebral haemorrhage	1 (0.5)	0 (0.0)	1 (0.2)
Cerebrovascular accident	1 (0.5)	1 (0.5)	2 (0.5)
Convulsion	1 (0.5)	0 (0.0)	1 (0.2)
Diabetic coma	0 (0.0)	1 (0.5)	1 (0.2)
Facial paresis	1 (0.5)	0 (0.0)	1 (0.2)
Hypoaesthesia	0 (0.0)	1 (0.5)	1 (0.2)
Neuralgia	0 (0.0)	1 (0.5)	1 (0.2)
Paraplegia	1 (0.5)	0 (0.0)	1 (0.2)
Psychiatric disorders	0 (0.0)	1 (0.5)	1 (0.2)
Psychotic disorder	0 (0.0)	1 (0.5)	1 (0.2)
Renal and urinary disorders	3 (1.4)	2 (0.9)	5 (1.2)
Nephrolithiasis	0 (0.0)	1 (0.5)	1 (0.2)
Renal failure	1 (0.5)	1 (0.5)	2 (0.5)
Renal infarct	1 (0.5)	0 (0.0)	1 (0.2)
Renal pain	1 (0.5)	0 (0.0)	1 (0.2)
Reproductive system and breast disorders	1 (0.5)	1 (0.5)	2 (0.5)
Metrorrhagia	1 (0.5)	1 (0.5)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	16 (7.4)	10 (4.7)	26 (6.0)
Cough	0 (0.0)	1 (0.5)	1 (0.2)
Dyspnoea	4 (1.8)	3 (1.4)	7 (1.6)
Haemoptysis	1 (0.5)	2 (0.9)	3 (0.7)
Hydrothorax	2 (0.9)	0 (0.0)	2 (0.5)
Pleural effusion	1 (0.5)	3 (1.4)	4 (0.9)
Pneumonitis	0 (0.0)	1 (0.5)	1 (0.2)
Pneumothorax	1 (0.5)	1 (0.5)	2 (0.5)
Pulmonary embolism	8 (3.7)	2 (0.9)	10 (2.3)
Skin and subcutaneous tissue disorders	0 (0.0)	3 (1.4)	3 (0.7)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	3 (1.4)	3 (0.7)
Surgical and medical procedures	1 (0.5)	0 (0.0)	1 (0.2)
Ureteral catheterisation	1 (0.5)	0 (0.0)	1 (0.2)
Uncoded	1 (0.5)	0 (0.0)	1 (0.2)
Haematemesis secondary to thrombcytopenia	1 (0.5)	0 (0.0)	1 (0.2)
Vascular disorders	4 (1.8)	2 (0.9)	6 (1.4)
Hypertension	2 (0.9)	0 (0.0)	2 (0.5)
Iliac artery thrombosis	1 (0.5)	0 (0.0)	1 (0.2)
Thrombosis	1 (0.5)	1 (0.5)	2 (0.5)
Venous thrombosis	0 (0.0)	1 (0.5)	1 (0.2)

% = (n/N)*100; AT = as-treated; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject.

Treatment-related SAEs are summarized in Table 10.

Table 10. Treatment-Related Serious Adverse Events (AT Population)

Number (%) of Subjects with Adverse Events by: MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) (N=217) n (%)	Arm B (Capecitabine Alone) (N=215) n (%)
Any treatment-related serious adverse events	57 (26.3)	32 (14.9)
Vomiting	11 (5.1)	5 (2.3)
Diarrhoea	9 (4.1)	13 (6.0)
Anaemia	7 (3.2)	1 (0.5)
Thrombocytopenia	7 (3.2)	0 (0.0)
Pulmonary embolism	7 (3.2)	0 (0.0)
Nausea	6 (2.8)	1 (0.5)
Asthenia	6 (2.8)	0 (0.0)
Neutropenia	3 (1.4)	0 (0.0)
Fatigue	2 (0.9)	2 (0.9)
Gastritis	2 (0.9)	1 (0.5)
Mucosal inflammation	2 (0.9)	1 (0.5)
Leukopenia	2 (0.9)	0 (0.0)
Hypothyroidism	2 (0.9)	0 (0.0)
General physical health deterioration	2 (0.9)	0 (0.0)
Hypertension	2 (0.9)	0 (0.0)
Abdominal pain	1 (0.5)	2 (0.9)
Chest pain	1 (0.5)	2 (0.9)
Hyperbilirubinemia	1 (0.5)	1 (0.5)
Dehydration	1 (0.5)	0 (0.0)
Renal failure	1 (0.5)	1 (0.5)
Dyspnea	1 (0.5)	1 (0.5)
Pancytopenia	1 (0.5)	0 (0.0)
Cardiac failure acute	1 (0.5)	0 (0.0)
Ventricular extrasystoles	1 (0.5)	0 (0.0)
Vertigo	1 (0.5)	0 (0.0)
Abdominal pain upper	1 (0.5)	0 (0.0)
Dyspepsia	1 (0.5)	0 (0.0)
Enteritis	1 (0.5)	0 (0.0)
Gastrointestinal hemorrhage	1 (0.5)	0 (0.0)
Haematemesis secondary to thrombocytopenia	1 (0.5)	0 (0.0)
Pancreatitis haemorrhagic	1 (0.5)	0 (0.0)
Upper gastrointestinal hemorrhage	1 (0.5)	0 (0.0)
Death	1 (0.5)	0 (0.0)
Malaise	1 (0.5)	0 (0.0)
Cytolytic hepatitis	1 (0.5)	0 (0.0)
Jaundice	1 (0.5)	0 (0.0)
Breast infection	1 (0.5)	0 (0.0)
Cellulitis	1 (0.5)	0 (0.0)
Tooth infection	1 (0.5)	0 (0.0)
Ejection fraction decreased	1 (0.5)	0 (0.0)
Electrocardiogram ST segment depression	1 (0.5)	0 (0.0)
Decreased appetite	1 (0.5)	0 (0.0)
Hypokalaemia	1 (0.5)	0 (0.0)
Muscular weakness	1 (0.5)	0 (0.0)
Myalgia	1 (0.5)	0 (0.0)
Cerebral hemorrhage	1 (0.5)	0 (0.0)

Table 10. Treatment-Related Serious Adverse Events (AT Population)

Number (%) of Subjects with Adverse Events by: MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) (N=217) n (%)	Arm B (Capecitabine Alone) (N=215) n (%)
Convulsion	1 (0.5)	0 (0.0)
Facial paresis	1 (0.5)	0 (0.0)
Renal infarct	1 (0.5)	0 (0.0)
Metrorrhagia	1 (0.5)	0 (0.0)
Iliac artery thrombosis	1 (0.5)	0 (0.0)
Thrombosis	1 (0.5)	0 (0.0)
Pyrexia	0 (0.0)	5 (2.3)
Sepsis	0 (0.0)	3 (1.4)
Palmar-plantar erythrodysasthesia syndrome	0 (0.0)	3 (1.4)
Haemoglobin decreased	0 (0.0)	2 (0.9)
Congestive cardiomyopathy	0 (0.0)	1 (0.5)
Ascites	0 (0.0)	1 (0.5)
Colitis	0 (0.0)	1 (0.5)
Colonic obstruction	0 (0.0)	1 (0.5)
Dysphagia	0 (0.0)	1 (0.5)
Intestinal obstruction	0 (0.0)	1 (0.5)
Small intestinal obstruction	0 (0.0)	1 (0.5)
Stomatitis	0 (0.0)	1 (0.5)
Subileus	0 (0.0)	1 (0.5)
Ulcer	0 (0.0)	1 (0.5)
Gastroenteritis	0 (0.0)	1 (0.5)
Neutropenic sepsis	0 (0.0)	1 (0.5)
Pyelonephritis	0 (0.0)	1 (0.5)
Diabetic coma	0 (0.0)	1 (0.5)
Cough	0 (0.0)	1 (0.5)
Hemoptysis	0 (0.0)	1 (0.5)

% = (n/N)*100; AT = as-treated; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject.

AEs that led to permanent discontinuation of study drug are summarized in Table 11.

Table 11. Adverse Events Leading to Discontinuation of Study Drug (Sunitinib or Capecitabine; AT Population)

MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217		Arm B (Capecitabine Alone) N=215
	Sunitinib n (%)	Capecitabine n (%)	Capecitabine n (%)
Any adverse events led to discontinuation	85 (39.2)	89 (41.0)	36 (16.7)
Neutropenia	9 (4.1)	17 (7.8)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	8 (3.7)	8 (3.7)	6 (2.8)
Thrombocytopenia	7 (3.2)	8 (3.7)	0 (0.0)
Asthenia	6 (2.8)	5 (2.3)	0 (0.0)
Fatigue	5 (2.3)	5 (2.3)	1 (0.5)
Pulmonary embolism	4 (1.8)	1 (0.5)	0 (0.0)
Vomiting	4 (1.8)	5 (2.3)	0 (0.0)
Disease progression	4 (1.8)	3 (1.4)	3 (1.4)
Nausea	3 (1.4)	2 (0.9)	2 (0.9)
Anaemia	2 (0.9)	4 (1.8)	0 (0.0)
Dyspnoea	2 (0.9)	3 (1.4)	1 (0.5)
Diarrhoea	2 (0.9)	2 (0.9)	3 (1.4)
Pleural effusion	0.0	0 (0.0)	2 (0.9)
Back pain	2 (0.9)	1 (0.5)	0 (0.0)
Hydrothorax	2 (0.9)	1 (0.5)	0 (0.0)
Stomatitis	2 (0.9)	1 (0.5)	1 (0.5)
Abdominal pain	1 (0.5)	1 (0.5)	0 (0.0)
Abdominal pain upper	1 (0.5)	2 (0.9)	0 (0.0)
Anal inflammation	1 (0.5)	1 (0.5)	0 (0.0)
Blood alkaline phosphate increased	1 (0.5)	1 (0.5)	0 (0.0)
Cardiac failure acute	1 (0.5)	1 (0.5)	0 (0.0)
Chest pain	1 (0.5)	1 (0.5)	2 (0.9)
Cytolytic hepatitis	1 (0.5)	1 (0.5)	0 (0.0)
Dehydration	1 (0.5)	1 (0.5)	0 (0.0)
Diplopia	1 (0.5)	1 (0.5)	0 (0.0)
Dysgeusia	1 (0.5)	1 (0.5)	0 (0.0)
Dyspepsia	1 (0.5)	1 (0.5)	0 (0.0)
Epistaxis	1 (0.5)	1 (0.5)	0 (0.0)
General physical health deterioration	1 (0.5)	1 (0.5)	1 (0.5)
Haematoma	1 (0.5)	1 (0.5)	0 (0.0)
Headache	1 (0.5)	1 (0.5)	0 (0.0)
Hyperbilirubinaemia	1 (0.5)	1 (0.5)	0 (0.0)
Hypertension	1 (0.5)	0 (0.0)	0 (0.0)
Iliac artery thrombosis	1 (0.5)	1 (0.5)	0 (0.0)
Infection	1 (0.5)	1 (0.5)	0 (0.0)
Lung infection	1 (0.5)	1 (0.5)	0 (0.0)
Lymphadenopathy	1 (0.5)	1 (0.5)	0 (0.0)
Pancreatitis haemorrhagic	1 (0.5)	1 (0.5)	0 (0.0)
Paraplegia	1 (0.5)	1 (0.5)	0 (0.0)
Pericardial effusion	1 (0.5)	1 (0.5)	1 (0.5)
Peritonitis	1 (0.5)	1 (0.5)	0 (0.0)
Skin infection	1 (0.5)	1 (0.5)	0 (0.0)
Superior vena cava syndrome	1 (0.5)	1 (0.5)	0 (0.0)
Conjunctival haemorrhage	1 (0.5)	0 (0.0)	0 (0.0)
Constipation	1 (0.5)	0 (0.0)	0 (0.0)
Decreased appetite	1 (0.5)	0 (0.0)	0 (0.0)

Table 11. Adverse Events Leading to Discontinuation of Study Drug (Sunitinib or Capecitabine; AT Population)

MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217		Arm B (Capecitabine Alone) N=215
	Sunitinib n (%)	Capecitabine n (%)	Capecitabine n (%)
Electrocardiogram QT prolonged	1 (0.5)	0 (0.0)	0 (0.0)
Gait disturbance	1 (0.5)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage	1 (0.5)	0 (0.0)	0 (0.0)
Hypokinesia	1 (0.5)	0 (0.0)	0 (0.0)
Jaundice	1 (0.5)	0 (0.0)	0 (0.0)
Left ventricular dysfunction	1 (0.5)	0 (0.0)	0 (0.0)
Malaise	1 (0.5)	0 (0.0)	0 (0.0)
Metrorrhagia	1 (0.5)	0 (0.0)	0 (0.0)
Mucosal inflammation	1 (0.5)	0 (0.0)	0 (0.0)
Renal infarct	1 (0.5)	0 (0.0)	0 (0.0)
Subcutaneous nodule	1 (0.5)	0 (0.0)	0 (0.0)
Thrombosis	1 (0.5)	0 (0.0)	0 (0.0)
Yellow skin	1 (0.5)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	2 (0.9)	0 (0.0)
Ascites	0 (0.0)	1 (0.5)	0 (0.0)
Breast cancer	0 (0.0)	1 (0.5)	1 (0.5)
Burning sensation	0 (0.0)	1 (0.5)	0 (0.0)
Electrocardiogram ST segment depression	1 (0.5)	1 (0.5)	0 (0.0)
Platelet count decreased	0 (0.0)	1 (0.5)	2 (0.9)
Skin exfoliation	0 (0.0)	1 (0.5)	0 (0.0)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (0.5)	0 (0.0)
White blood cell count decreased	0 (0.0)	1 (0.5)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.5)
Diabetic coma	0 (0.0)	0 (0.0)	1 (0.5)
Duodenal stenosis	0 (0.0)	0 (0.0)	1 (0.5)
Herpes zoster	0 (0.0)	0 (0.0)	1 (0.5)
Intestinal obstruction	0 (0.0)	0 (0.0)	1 (0.5)
Neuropathy peripheral	0 (0.0)	0 (0.0)	1 (0.5)
Neutropenic sepsis	0 (0.0)	0 (0.0)	1 (0.5)
Nodule	0 (0.0)	0 (0.0)	1 (0.5)
Oedema	0 (0.0)	0 (0.0)	1 (0.5)
Venous thrombosis	0 (0.0)	0 (0.0)	1 (0.5)
Sixth nerve paralysis	0 (0.0)	0 (0.0)	1 (0.5)

% = (n/N)*100; AT = as-treated; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject.

AEs that led to interruption or reduction of sunitinib are summarized in Table 12.

Table 12. Adverse Events That Led to a Delay or Change[a] in Sunitinib Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) (N=217) n (%)	Arm B (Capecitabine Alone|) (N=215) n (%)	Total (N=432) n (%)
Any adverse events that led to a delay or change in sunitinib	164 (75.6)	0	164 (38.0)
Blood and lymphatic system disorders	88 (40.6)	0	88 (20.4)
Anaemia	14 (6.5)	0	14 (3.2)
Haemorrhagic diathesis	1 (0.5)	0	1 (0.2)
Leukopenia	9 (4.1)	0	9 (2.1)
Lymphopenia	3 (1.4)	0	3 (0.7)
Neutropenia	52 (24.0)	0	52 (12.0)
Pancytopenia	1 (0.5)	0	1 (0.2)
Thrombocytopenia	43 (19.8)	0	43 (10.0)
Cardiac disorders	3 (1.4)	0	3 (0.7)
Left ventricular dysfunction	1 (0.5)	0	1 (0.2)
Palpitations	1 (0.5)	0	1 (0.2)
Ventricular extrasystoles	1 (0.5)	0	1 (0.2)
Ear and labyrinth disorders	1 (0.5)	0	1 (0.2)
Vertigo	1 (0.5)	0	1 (0.2)
Endocrine disorders	1 (0.5)	0	1 (0.2)
Hypothyroidism	1 (0.5)	0	1 (0.2)
Gastrointestinal disorders	66 (30.4)	0	66 (15.3)
Abdominal pain	5 (2.3)	0	5 (1.2)
Abdominal pain upper	5 (2.3)	0	5 (1.2)
Constipation	1 (0.5)	0	1 (0.2)
Diarrhoea	29 (13.4)	0	29 (6.7)
Dyspepsia	1 (0.5)	0	1 (0.2)
Dysphagia	3 (1.4)	0	3 (0.7)
Enteritis	1 (0.5)	0	1 (0.2)
Gastritis	1 (0.5)	0	1 (0.2)
Gingival bleeding	2 (0.9)	0	2 (0.5)
Gingivitis	2 (0.9)	0	2 (0.5)
Haematemesis	1 (0.5)	0	1 (0.2)
Haematochezia	1 (0.5)	0	1 (0.2)
Mouth ulceration	1 (0.5)	0	1 (0.2)
Nausea	17 (7.8)	0	17 (3.9)
Oesophagitis	3 (1.4)	0	3 (0.7)
Oral pain	2 (0.9)	0	2 (0.5)
Rectal haemorrhage	1 (0.5)	0	1 (0.2)
Stomatitis	6 (2.8)	0	6 (1.4)
Upper gastrointestinal haemorrhage	1 (0.5)	0	1 (0.2)
Vomiting	27 (12.4)	0	27 (6.3)
General disorders and administration site conditions	50 (23.0)	0	50 (11.6)
Asthenia	25 (11.5)	0	25 (5.8)
Axillary pain	1 (0.5)	0	1 (0.2)
Fatigue	16 (7.4)	0	16 (3.7)
General physical health deterioration	3 (1.4)	0	3 (0.7)
Malaise	1 (0.5)	0	1 (0.2)
Mucosal inflammation	9 (4.1)	0	9 (2.1)
Pyrexia	5 (2.3)	0	5 (1.2)

Table 12. Adverse Events That Led to a Delay or Change[a] in Sunitinib Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) (N=217) n (%)	Arm B (Capecitabine Alone|) (N=215) n (%)	Total (N=432) n (%)
Hepatobiliary disorders	5 (2.3)	0	5 (1.2)
Hepatic function abnormal	1 (0.5)	0	1 (0.2)
Hyperbilirubinaemia	3 (1.4)	0	3 (0.7)
Jaundice	2 (0.9)	0	2 (0.5)
Infections and infestations	15 (6.9)	0	15 (3.5)
Breast infection	1 (0.5)	0	1 (0.2)
Bronchitis	1 (0.5)	0	1 (0.2)
Cellulitis	2 (0.9)	0	2 (0.5)
Escherichia urinary tract infection	1 (0.5)	0	1 (0.2)
Influenza	2 (0.9)	0	2 (0.5)
Laryngitis	1 (0.5)	0	1 (0.2)
Nasopharyngitis	1 (0.5)	0	1 (0.2)
Oesophageal candidiasis	1 (0.5)	0	1 (0.2)
Osteomyelitis	1 (0.5)	0	1 (0.2)
Rectal abscess	1 (0.5)	0	1 (0.2)
Subcutaneous abscess	1 (0.5)	0	1 (0.2)
Tooth abscess	2 (0.9)	0	2 (0.5)
Urinary tract infection	1 (0.5)	0	1 (0.2)
Injury, poisoning and procedural complications	2 (0.9)	0	2 (0.5)
Overdose	2 (0.9)	0	2 (0.5)
Investigations	19 (8.8)	0	19 (4.4)
Aspartate aminotransferase increased	1 (0.5)	0	1 (0.2)
Blood bilirubin increased	2 (0.9)	0	2 (0.5)
Blood thyroid stimulating hormone increased	1 (0.5)	0	1 (0.2)
Ejection fraction decreased	1 (0.5)	0	1 (0.2)
Electrocardiogram QT prolonged	1 (0.5)	0	1 (0.2)
Haemoglobin	1 (0.5)	0	1 (0.2)
Neutrophil count decreased	4 (1.8)	0	4 (0.9)
Platelet count decreased	9 (4.1)	0	9 (2.1)
Transaminases increased	1 (0.5)	0	1 (0.2)
Weight decreased	1 (0.5)	0	1 (0.2)
White blood cell count decreased	2 (0.9)	0	2 (0.5)
Metabolism and nutrition disorders	5 (2.3)	0	5 (1.2)
Decreased appetite	1 (0.5)	0	1 (0.2)
Dehydration	1 (0.5)	0	1 (0.2)
Hypercalcaemia	1 (0.5)	0	1 (0.2)
Hypertriglyceridaemia	1 (0.5)	0	1 (0.2)
Hyperuricaemia	1 (0.5)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	10 (4.6)	0	10 (2.3)
Arthralgia	1 (0.5)	0	1 (0.2)
Back pain	1 (0.5)	0	1 (0.2)
Bone pain	2 (0.9)	0	2 (0.5)
Muscular weakness	1 (0.5)	0	1 (0.2)
Musculoskeletal chest pain	2 (0.9)	0	2 (0.5)
Musculoskeletal pain	2 (0.9)	0	2 (0.5)
Myalgia	3 (1.4)	0	3 (0.7)
Pain in extremity	1 (0.5)	0	1 (0.2)

Table 12. Adverse Events That Led to a Delay or Change[a] in Sunitinib Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) (N=217) n (%)	Arm B (Capecitabine Alone|) (N=215) n (%)	Total (N=432) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9)	0	2 (0.5)
Breast cancer	1 (0.5)	0	1 (0.2)
Malignant pleural effusion	1 (0.5)	0	1 (0.2)
Nervous system disorders	9 (4.1)	0	9 (2.1)
Convulsion	1 (0.5)	0	1 (0.2)
Dizziness	1 (0.5)	0	1 (0.2)
Dysaesthesia	1 (0.5)	0	1 (0.2)
Dysgeusia	1 (0.5)	0	1 (0.2)
Facial paresis	1 (0.5)	0	1 (0.2)
Headache	3 (1.4)	0	3 (0.7)
Paraesthesia	2 (0.9)	0	2 (0.5)
Psychiatric disorders	2 (0.9)	0	2 (0.5)
Confusional state	1 (0.5)	0	1 (0.2)
Insomnia	1 (0.5)	0	1 (0.2)
Renal and urinary disorders	2 (0.9)	0	2 (0.5)
Proteinuria	1 (0.5)	0	1 (0.2)
Renal failure	1 (0.5)	0	1 (0.2)
Reproductive system and breast disorders	2 (0.9)	0	2 (0.5)
Metrorrhagia	1 (0.5)	0	1 (0.2)
Vaginal haemorrhage	1 (0.5)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	10 (4.6)	0	10 (2.3)
Dyspnoea	1 (0.5)	0	1 (0.2)
Dyspnoea exertional	1 (0.5)	0	1 (0.2)
Epistaxis	2 (0.9)	0	2 (0.5)
Haemoptysis	1 (0.5)	0	1 (0.2)
Hydrothorax	1 (0.5)	0	1 (0.2)
Lung infiltration	1 (0.5)	0	1 (0.2)
Pleural effusion	1 (0.5)	0	1 (0.2)
Pulmonary embolism	2 (0.9)	0	2 (0.5)
Rhinorrhoea	1 (0.5)	0	1 (0.2)
Skin and subcutaneous tissue disorders	31 (14.3)	0	31 (7.2)
Erythema	1 (0.5)	0	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	27 (12.4)	0	27 (6.3)
Purpura	1 (0.5)	0	1 (0.2)
Rash	2 (0.9)	0	2 (0.5)
Rash generalised	1 (0.5)	0	1 (0.2)
Skin exfoliation	1 (0.5)	0	1 (0.2)
Surgical and medical procedures	1 (0.5)	0	1 (0.2)
Tooth extraction	1 (0.5)	0	1 (0.2)
Uncoded	1 (0.5)	0	1 (0.2)
Haematemesis secondary to thrombcytopenia	1 (0.5)	0	1 (0.2)
Vascular disorders	8 (3.7)	0	8 (1.9)
Hypertension	7 (3.2)	0	7 (1.6)
Orthostatic hypotension	1 (0.5)	0	1 (0.2)
Trousseau's syndrome	1 (0.5)	0	1 (0.2)

Table 12. Adverse Events That Led to a Delay or Change[a] in Sunitinib Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) (N=217) n (%)	Arm B (Capecitabine Alone|) (N=215) n (%)	Total (N=432) n (%)

% = (n/N)*100; AT = as-treated; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject.
a. Delay or change include actions of study treatment dose stopped temporarily or reduced. Actions of dose stopped temorarily or reduced come from the adverse event case report form (CRF) page.

AEs that led to interruption or reduction of capecitabine are summarized in Table 13.

Table 13. Adverse Events That Led to a Delay or Change[a] in Capecitabine Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine Alone) N=215 n (%)	Total N=432 n (%)
Any adverse events that led to a delay or change in capecitabine	181 (83.4)	144 (67.0)	325 (75.2)
Blood and lymphatic system disorders	112 (51.6)	29 (13.5)	141 (32.6)
Anaemia	16 (7.4)	6 (2.8)	22 (5.1)
Haematotoxicity	2 (0.9)	0 (0.0)	2 (0.5)
Haemorrhagic diathesis	1 (0.5)	0 (0.0)	1 (0.2)
Leukocytosis	1 (0.5)	0 (0.0)	1 (0.2)
Leukopenia	16 (7.4)	2 (0.9)	18 (4.2)
Lymphopenia	2 (0.9)	0 (0.0)	2 (0.5)
Neutropenia	78 (35.9)	24 (11.2)	102 (23.6)
Pancytopenia	1 (0.5)	0 (0.0)	1 (0.2)
Thrombocytopenia	51 (23.5)	2 (0.9)	53 (12.3)
Cardiac disorders	1 (0.5)	3 (1.4)	4 (0.9)
Atrial fibrillation	0 (0.0)	1 (0.5)	1 (0.2)
Congestive cardiomyopathy	0 (0.0)	1 (0.5)	1 (0.2)
Supraventricular tachycardia	0 (0.0)	1 (0.5)	1 (0.2)
Ventricular extrasystoles	1 (0.5)	0 (0.0)	1 (0.2)
Ear and labyrinth disorders	1 (0.5)	2 (0.9)	3 (0.7)
Tinnitus	0 (0.0)	1 (0.5)	1 (0.2)
Vertigo	1 (0.5)	1 (0.5)	2 (0.5)
Endocrine disorders	1 (0.5)	0 (0.0)	1 (0.2)
Hypothyroidism	1 (0.5)	0 (0.0)	1 (0.2)
Eye disorders	2 (0.9)	1 (0.5)	3 (0.7)
Conjunctivitis	1 (0.5)	1 (0.5)	2 (0.5)
Eye irritation	1 (0.5)	0 (0.0)	1 (0.2)
Eye pain	1 (0.5)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	89 (41.0)	49 (22.8)	138 (31.9)
Abdominal pain	4 (1.8)	3 (1.4)	7 (1.6)
Abdominal pain upper	4 (1.8)	2 (0.9)	6 (1.4)
Anal inflammation	2 (0.9)	0 (0.0)	2 (0.5)
Colonic obstruction	0 (0.0)	1 (0.5)	1 (0.2)
Constipation	1 (0.5)	1 (0.5)	2 (0.5)
Diarrhoea	38 (17.5)	32 (14.9)	70 (16.2)
Dyspepsia	2 (0.9)	0 (0.0)	2 (0.5)
Dysphagia	2 (0.9)	0 (0.0)	2 (0.5)
Enteritis	1 (0.5)	0 (0.0)	1 (0.2)
Gastritis	0 (0.0)	1 (0.5)	1 (0.2)
Gastrointestinal haemorrhage	1 (0.5)	0 (0.0)	1 (0.2)
Gingival bleeding	1 (0.5)	0 (0.0)	1 (0.2)
Gingival oedema	1 (0.5)	0 (0.0)	1 (0.2)
Gingivitis	2 (0.9)	0 (0.0)	2 (0.5)
Haematemesis	1 (0.5)	0 (0.0)	1 (0.2)
Haemorrhoids	0 (0.0)	1 (0.5)	1 (0.2)
Ileitis	0 (0.0)	1 (0.5)	1 (0.2)
Nausea	23 (10.6)	12 (5.6)	35 (8.1)
Oedema mouth	1 (0.5)	0 (0.0)	1 (0.2)
Oesophagitis	3 (1.4)	1 (0.5)	4 (0.9)

Table 13. Adverse Events That Led to a Delay or Change[a] in Capecitabine Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine Alone) N=215 n (%)	Total N=432 n (%)
Oral pain	2 (0.9)	0 (0.0)	2 (0.5)
Rectal haemorrhage	1 (0.5)	2 (0.9)	3 (0.7)
Stomatitis	9 (4.1)	4 (1.9)	13 (3.0)
Subileus	0 (0.0)	1 (0.5)	1 (0.2)
Tongue ulceration	1 (0.5)	0 (0.0)	1 (0.2)
Vomiting	35 (16.1)	14 (6.5)	49 (11.3)
General disorders and administration site conditions	49 (22.6)	25 (11.6)	74 (17.1)
Asthenia	19 (8.8)	4 (1.9)	23 (5.3)
Axillary pain	1 (0.5)	0 (0.0)	1 (0.2)
Chest pain	0 (0.0)	2 (0.9)	2 (0.5)
Fatigue	15 (6.9)	4 (1.9)	19 (4.4)
Gait disturbance	1 (0.5)	0 (0.0)	1 (0.2)
General physical health deterioration	3 (1.4)	2 (0.9)	5 (1.2)
Influenza like illness	0 (0.0)	3 (1.4)	3 (0.7)
Malaise	1 (0.5)	0 (0.0)	1 (0.2)
Mucosal inflammation	11 (5.1)	3 (1.4)	14 (3.2)
Oedema	1 (0.5)	1 (0.5)	2 (0.5)
Pain	0 (0.0)	1 (0.5)	1 (0.2)
Pyrexia	5 (2.3)	8 (3.7)	13 (3.0)
Hepatobiliary disorders	7 (3.2)	5 (2.3)	12 (2.8)
Hepatic function abnormal	1 (0.5)	0 (0.0)	1 (0.2)
Hyperbilirubinaemia	6 (2.8)	5 (2.3)	11 (2.5)
Jaundice	1 (0.5)	0 (0.0)	1 (0.2)
Infections and infestations	14 (6.5)	13 (6.0)	27 (6.3)
Breast infection	1 (0.5)	0 (0.0)	1 (0.2)
Bronchitis	0 (0.0)	2 (0.9)	2 (0.5)
Cellulitis	2 (0.9)	0 (0.0)	2 (0.5)
Cystitis	0 (0.0)	2 (0.9)	2 (0.5)
Device related infection	1 (0.5)	0 (0.0)	1 (0.2)
Gastroenteritis	0 (0.0)	1 (0.5)	1 (0.2)
Gastroenteritis viral	0 (0.0)	3 (1.4)	3 (0.7)
Influenza	2 (0.9)	0 (0.0)	2 (0.5)
Laryngitis	1 (0.5)	0 (0.0)	1 (0.2)
Nasopharyngitis	2 (0.9)	1 (0.5)	3 (0.7)
Onychomycosis	0 (0.0)	1 (0.5)	1 (0.2)
Oral infection	0 (0.0)	1 (0.5)	1 (0.2)
Osteomyelitis	1 (0.5)	0 (0.0)	1 (0.2)
Paronychia	0 (0.0)	1 (0.5)	1 (0.2)
Rectal abscess	1 (0.5)	0 (0.0)	1 (0.2)
Sepsis	0 (0.0)	2 (0.9)	2 (0.5)
Subcutaneous abscess	1 (0.5)	0 (0.0)	1 (0.2)
Tooth abscess	1 (0.5)	0 (0.0)	1 (0.2)
Urinary tract infection	1 (0.5)	0 (0.0)	1 (0.2)
Viral infection	0 (0.0)	2 (0.9)	2 (0.5)
Viral upper respiratory tract infection	0 (0.0)	1 (0.5)	1 (0.2)
Injury, poisoning and procedural complications	2 (0.9)	2 (0.9)	4 (0.9)
Fall	0 (0.0)	1 (0.5)	1 (0.2)

Table 13. Adverse Events That Led to a Delay or Change[a] in Capecitabine Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine Alone) N=215 n (%)	Total N=432 n (%)
Lip injury	1 (0.5)	0 (0.0)	1 (0.2)
Overdose	1 (0.5)	0 (0.0)	1 (0.2)
Radius fracture	0 (0.0)	1 (0.5)	1 (0.2)
Investigations	21 (9.7)	9 (4.2)	30 (6.9)
Alanine aminotransferase increased	2 (0.9)	1 (0.5)	3 (0.7)
Aspartate aminotransferase increased	3 (1.4)	2 (0.9)	5 (1.2)
Blood alkaline phosphatase increased	2 (0.9)	1 (0.5)	3 (0.7)
Blood bilirubin increased	1 (0.5)	0 (0.0)	1 (0.2)
Blood lactate dehydrogenase increased	1 (0.5)	0 (0.0)	1 (0.2)
Blood thyroid stimulating hormone increased	0 (0.0)	1 (0.5)	1 (0.2)
Ejection fraction decreased	0 (0.0)	2 (0.9)	2 (0.5)
Haemoglobin	1 (0.5)	0 (0.0)	1 (0.2)
Haemoglobin decreased	1 (0.5)	2 (0.9)	3 (0.7)
Heart rate increased	0 (0.0)	1 (0.5)	1 (0.2)
Hepatic enzyme increased	1 (0.5)	0 (0.0)	1 (0.2)
Neutrophil count decreased	4 (1.8)	1 (0.5)	5 (1.2)
Platelet count decreased	9 (4.1)	1 (0.5)	10 (2.3)
Transaminases increased	1 (0.5)	1 (0.5)	2 (0.5)
Weight decreased	1 (0.5)	1 (0.5)	2 (0.5)
White blood cell count decreased	3 (1.4)	0 (0.0)	3 (0.7)
Metabolism and nutrition disorders	8 (3.7)	6 (2.8)	14 (3.2)
Decreased appetite	4 (1.8)	0 (0.0)	4 (0.9)
Dehydration	0 (0.0)	4 (1.9)	4 (0.9)
Hypercalcaemia	1 (0.5)	0 (0.0)	1 (0.2)
Hyperglycaemia	1 (0.5)	0 (0.0)	1 (0.2)
Hypertriglyceridaemia	1 (0.5)	0 (0.0)	1 (0.2)
Hyperuricaemia	1 (0.5)	0 (0.0)	1 (0.2)
Hypocalcaemia	0 (0.0)	1 (0.5)	1 (0.2)
Hypokalaemia	0 (0.0)	2 (0.9)	2 (0.5)
Hyponatraemia	0 (0.0)	1 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	13 (6.0)	9 (4.2)	22 (5.1)
Arthralgia	1 (0.5)	1 (0.5)	2 (0.5)
Back pain	1 (0.5)	1 (0.5)	2 (0.5)
Bone pain	3 (1.4)	0 (0.0)	3 (0.7)
Hypercreatinaemia	0 (0.0)	1 (0.5)	1 (0.2)
Musculoskeletal chest pain	1 (0.5)	0 (0.0)	1 (0.2)
Musculoskeletal pain	2 (0.9)	0 (0.0)	2 (0.5)
Myalgia	3 (1.4)	0 (0.0)	3 (0.7)
Osteolysis	0 (0.0)	1 (0.5)	1 (0.2)
Pain in extremity	2 (0.9)	5 (2.3)	7 (1.6)
Pathological fracture	0 (0.0)	1 (0.5)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1 (0.5)	2 (0.5)
Breast cancer	1 (0.5)	0 (0.0)	1 (0.2)
Lung neoplasm	0 (0.0)	1 (0.5)	1 (0.2)
Nervous system disorders	8 (3.7)	4 (1.9)	12 (2.8)
Cerebrovascular accident	0 (0.0)	1 (0.5)	1 (0.2)

Table 13. Adverse Events That Led to a Delay or Change[a] in Capecitabine Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine Alone) N=215 n (%)	Total N=432 n (%)
Convulsion	1 (0.5)	0 (0.0)	1 (0.2)
Dizziness	0 (0.0)	1 (0.5)	1 (0.2)
Dysaesthesia	2 (0.9)	0 (0.0)	2 (0.5)
Dysgeusia	1 (0.5)	0 (0.0)	1 (0.2)
Facial paresis	1 (0.5)	0 (0.0)	1 (0.2)
Headache	1 (0.5)	1 (0.5)	2 (0.5)
Neuropathy peripheral	0 (0.0)	2 (0.9)	2 (0.5)
Paraesthesia	2 (0.9)	0 (0.0)	2 (0.5)
Polyneuropathy	1 (0.5)	0 (0.0)	1 (0.2)
Psychiatric disorders	1 (0.5)	2 (0.9)	3 (0.7)
Insomnia	1 (0.5)	0 (0.0)	1 (0.2)
Mental status changes	0 (0.0)	1 (0.5)	1 (0.2)
Psychotic disorder	0 (0.0)	1 (0.5)	1 (0.2)
Renal and urinary disorders	2 (0.9)	2 (0.9)	4 (0.9)
Hydronephrosis	0 (0.0)	1 (0.5)	1 (0.2)
Proteinuria	1 (0.5)	0 (0.0)	1 (0.2)
Renal failure	1 (0.5)	1 (0.5)	2 (0.5)
Reproductive system and breast disorders	0 (0.0)	1 (0.5)	1 (0.2)
Metrorrhagia	0 (0.0)	1 (0.5)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	8 (3.7)	9 (4.2)	17 (3.9)
Cough	0 (0.0)	4 (1.9)	4 (0.9)
Dyspnoea	0 (0.0)	1 (0.5)	1 (0.2)
Dyspnoea exertional	1 (0.5)	0 (0.0)	1 (0.2)
Epistaxis	1 (0.5)	0 (0.0)	1 (0.2)
Haemoptysis	0 (0.0)	1 (0.5)	1 (0.2)
Hydrothorax	1 (0.5)	1 (0.5)	2 (0.5)
Lung infiltration	1 (0.5)	0 (0.0)	1 (0.2)
Pneumonitis	0 (0.0)	1 (0.5)	1 (0.2)
Pulmonary embolism	4 (1.8)	3 (1.4)	7 (1.6)
Skin and subcutaneous tissue disorders	57 (26.3)	84 (39.1)	141 (32.6)
Dry skin	0 (0.0)	1 (0.5)	1 (0.2)
Erythema	1 (0.5)	3 (1.4)	4 (0.9)
Nail disorder	0 (0.0)	1 (0.5)	1 (0.2)
Onycholysis	0 (0.0)	1 (0.5)	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	55 (25.3)	77 (35.8)	132 (30.6)
Purpura	1 (0.5)	0 (0.0)	1 (0.2)
Rash	0 (0.0)	5 (2.3)	5 (1.2)
Rash erythematous	0 (0.0)	1 (0.5)	1 (0.2)
Skin fissures	0 (0.0)	1 (0.5)	1 (0.2)
Skin reaction	0 (0.0)	1 (0.5)	1 (0.2)
Skin toxicity	0 (0.0)	1 (0.5)	1 (0.2)
Surgical and medical procedures	0 (0.0)	1 (0.5)	1 (0.2)
Breast reconstruction	0 (0.0)	1 (0.5)	1 (0.2)
Uncoded	1 (0.5)	0 (0.0)	1 (0.2)
Haematemesis secondary to thrombcytopenia	1 (0.5)	0 (0.0)	1 (0.2)
Vascular disorders	8 (3.7)	2 (0.9)	10 (2.3)
Deep vein thrombosis	0 (0.0)	1 (0.5)	1 (0.2)

Table 13. Adverse Events That Led to a Delay or Change[a] in Capecitabine Dose (AT Population)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA Preferred Term	Arm A (Sunitinib + Capecitabine) N=217 n (%)	Arm B (Capecitabine Alone) N=215 n (%)	Total N=432 n (%)
Hypertension	4 (1.8)	0 (0.0)	4 (0.9)
Orthostatic hypotension	1 (0.5)	0 (0.0)	1 (0.2)
Phlebitis	0 (0.0)	1 (0.5)	1 (0.2)
Thrombosis	2 (0.9)	0 (0.0)	2 (0.5)
Trousseau's syndrome	1 (0.5)	0 (0.0)	1 (0.2)

% = (n/N)*100; AT = as-treated; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject.
a. Delay or Change include actions of study treatment dose stopped temporarily or reduced. Actions of dose stopped temorarily or reduced come from the adverse event case report form (CRF) page.

Deaths: A summary of all deaths is presented in Table 14.

Table 14. Summary of All Deaths by Treatment (ITT Population)

Variable	Sunitinib + Capecitabine	Capecitabine Alone	
		No Crossover	Crossover
	N=221 n (%)	N=143 n (%)	N=78 n (%)
Subjects who died	169 (76.5)	93 (65.0)	65 (83.3)
Subjects who died on-study[a]	15 (6.8)	9 (6.3)	13 (16.7)
Disease under study	12 (5.4)	7 (4.9)	10 (12.8)
Disease under study, carcinomatosis	1 (0.5)	0 (0.0)	0 (0.0)
Disease under study, hemorrhage - GI	0 (0.0)	0 (0.0)	1 (1.3)
Disease under study, sepsis and disease progression	0 (0.0)	1 (0.7)	0 (0.0)
Disease under study, unknown	1 (0.5)	0 (0.0)	0 (0.0)
Enteritis	0 (0.0)	1 (0.7)	0 (0.0)
Study treatment, hemorrhagic shock	0 (0.0)	0 (0.0)	1 (1.3)
Study treatment, liver failure	0 (0.0)	0 (0.0)	1 (1.3)
Unknown, massive cerebral vascular accident (both hemispheres) after surgery	1 (0.5)	0 (0.0)	0 (0.0)
Subjects who died during follow-up[b]	152 (68.8)	84 (58.7)	52 (66.7)
Cardiac arrest	1 (0.5)	0 (0.0)	0 (0.0)
Cardiomiopathy	0 (0.0)	1 (0.7)	0 (0.0)
Disease under study	136 (61.5)	77 (53.8)	50 (64.1)
Hepatic insufficiency	1 (0.5)	0 (0.0)	0 (0.0)
Multiple metastases, polyorganic insufficiency	1 (0.5)	0 (0.0)	0 (0.0)
Organic failure by PD	1 (0.5)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.5)	0 (0.0)	0 (0.0)
Progressive deterioration of the subject status, disease under study	0 (0.0)	1 (0.7)	0 (0.0)
PD	1 (0.5)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.5)	0 (0.0)	0 (0.0)
Sepsis	1 (0.5)	0 (0.0)	0 (0.0)
Study treatment, heart failure	0 (0.0)	0 (0.0)	1 (0.3)
Study treatment, pulmonary embolism	1 (0.5)	0 (0.0)	0 (0.0)
Suicide	0 (0.0)	1 (0.7)	0 (0.0)
Unknown	7 (3.2)	4 (2.8)	1 (1.3)

GI = gastrointestinal; ITT = intent-to-treat; PD = progressive disease.
a. Deaths that occurred after the first study treatment dose date, but within 28 days after the last study treatment dose date.
b. Deaths that occurred more than 28 days after the last study treatment dose date.

CONCLUSIONS:

- Sunitinib + capecitabine was not more effective than capecitabine alone in subjects with ABC, with a median PFS of 5.5 vs 5.9 months.
- The other efficacy endpoints OS, DR, and ORR were not improved with sunitinib + capecitabine as compared with capecitabine alone.
- The overall frequency of AEs, including SAEs, was higher on sunitinib + capecitabine than on capecitabine alone. However, the AEs and safety profiles of sunitinib + capecitabine were consistent with those reported for both agents alone.