PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: A6181077

PROTOCOL TITLE: A Randomized Phase 2 Study of SU011248 Versus Standard-of-Care for Patients Previously Treated, Advanced, Triple Receptor Negative (ER, PR, and HER2) Breast Cancer

Study Centers: Fifty nine centers took part in the study and randomized subjects; 27 in the United States (US), 5 each in Bulgaria and Spain, 4 in Turkey, 3 each in France, Italy, Ukraine and the United Kingdom (UK), and 2 each in Canada, Czech Republic, and Hungary.

Study Initiation Date and Final Completion Dates: 25 January 2006 to 15 June 2011

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To compare the progression-free survival (PFS) for sunitinib versus standard-of-care therapy in subjects with previously treated, triple receptor negative (estrogen and progestin receptors and HER-2/neu), locally recurrent or metastatic breast cancer (BC).

Secondary Objectives:

- To assess the safety of sunitinib versus standard-of-care in this subject population;
- To assess measures of duration of tumor control and overall survival (OS);
- To assess patient-reported outcomes (PROs);
- To determine sunitinib and SU012662 (active metabolite of sunitinib) trough plasma concentrations (C_{trough}) and to potentially explore the relationship between C_{trough}, efficacy, and safety;
- To explore the relationship between specific biomarkers and cancer- and treatment-related outcomes.

METHODS:

Study Design: This was a multicenter, randomized, open-label, Phase 2 clinical trial comparing the efficacy and safety of sunitinib to standard-of-care chemotherapy in subjects with previously treated, triple receptor negative, locally recurrent or metastatic BC. To be eligible for this study, subjects were required to have previously received treatment with an anthracycline and a taxane in the adjuvant or advanced disease setting. One or 2 prior treatments for advanced disease were allowed; a relapse during or within 6 months of adjuvant therapy was considered the subject's first-line treatment.

Subjects were randomized into 2 treatment arms and stratified by whether subjects received 1 or ≥2 prior chemotherapy regimens. Safety was assessed throughout the trial. Interim safety and efficacy analysis was conducted when 1/3 (approximately 55 events) of PFS events had occurred.

Subjects were randomly assigned (1:1) to either sunitinib (Arm A) or the baseline standard-of-care (as defined by the Investigator's discretion) (Arm B) regimen. Oral sunitinib was administered daily in a continuous regimen (continuous daily dosing [CDD]), expressed as 3-week cycles, with a starting dosage of 37.5 mg/day. Subjects who experienced dose-limiting toxicity could have 1-week off-treatment periods inserted into the regimen as needed and could dose reduce. Subjects experiencing minimal toxicities after the second or third cycle were able to increase sunitinib dosage to 50 mg daily. Subsequent cycles could have further dose titration depending upon individual tolerability, as long as the sunitinib was 25 to 50 mg daily with or without weekly off-treatment periods. A maximum of 4 weeks off study drug was permitted.

On the comparator arm, the choice of chemotherapy regimen for individual subjects was at the discretion of the Investigator within the following limits:

- Capecitabine: 1000 to 1250 mg/m^2 orally, twice daily on Days 1 to 14 of repeated 3-week cycles;
- Vinorelbine: 25 to 30 mg/m^2 rapid intravenous (IV) infusion or 60 to 80 mg/m^2 oral weekly, expressed in 3-week cycles;
- Docetaxel: 75 to 100 mg/m^2 as a 1-hour IV infusion every 3 weeks;
- Paclitaxel: 175 to 200 mg/m^2 as a 3-hour IV infusion every 3 weeks;
- Paclitaxel: 80 to 90 mg/m^2 as a 1-hour IV infusion weekly, in a continuous regimen expressed in 3-week cycles or administered for 3 weeks followed by 1 week off treatment (the 3/1 regimen required extra care in scheduling disease assessments);
- Gemcitabine: 800 to 1250 mg/m^2 as a short IV infusion on Days 1 and 8 of repeated 3-week cycles.

Disease assessments were to be performed at 6-week intervals, regardless of treatment regimen or treatment delays resulting from toxicity. Assessments included computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis, and physical examination (every 6 weeks) and bone scans at 12-week intervals in all subjects having bone lesions at Baseline according to the Investigator or the core imaging laboratory. An extra bone scan was required at Week 6 in all subjects enrolling with bone-only disease.

Radiographs and accompanying clinical disease evaluation information from all subjects underwent retrospective central review for study eligibility (ie, documentation of failure of first-line treatment in the advanced disease setting) and central review for objective disease response and progression while on study.

Treatment on study continued until disease progression was documented according to the Response Evaluation Criteria in Solid Tumors (RECIST) or it was in the best interest of the subject to discontinue as judged by the Investigator (decisions could be based on achievement of maximum benefit or tolerability issues). At the time of RECIST-defined progression as documented by the Investigator, subjects randomized to chemotherapy could crossover to single-agent sunitinib. Subjects randomized to or crossed over to sunitinib could continue beyond the time of RECIST-defined progression at the discretion of the Investigator if the subject was perceived to be experiencing clinical benefit. OS was to be assessed for 3 years from first study treatment.

Blinding was not performed in this study because of the different doses of the standard-of-care therapy in Arms A and B. The primary endpoint, PFS, was evaluated by an external, independent central radiological laboratory. An external independent data monitoring committee (DMC) periodically reviewed accumulating safety data and planned interim analyses.

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

Table 1. Schedule of Activities

Procedures	Screening	Treatment Period[a]				Post-Treatment	
		Cycles 1, 2, and 3[b]			Subsequent Cycles[c]	End of Treatment/ Withdrawal[d]	Post-Treatment[e]
	Day ≤21 Prior to Randomization	Day 1[f]	Day 8	Day 15	Day 1		
Baseline documentation							
Informed consent[g]	X						
Medical/oncologic history	X						
Physical examination[h]	X	X		X	X	X	(X)
Baseline signs and symptoms		X[i]					
Laboratory studies							
Hematology[j]	X	X	X	X	X	X	(X)
Blood chemistry[j]	X	X			X	X	(X)
Thyroid testing[k]	X	X[l]			X[m]	X	
Pregnancy test (as appropriate)	X						
Urinalysis[n]	X	X[m]			(X)	X	(X)
12-lead ECG[o]	X				(X)	X	
MUGA/echocardiogram[p]	X	X[o]			(X)	X	(X)
Study randomization	X						
Study treatment							
Sunitinib dosing		X→	→	→	X→		
Chemotherapy (as appropriate)		X	(X)	(X)	(X)		
Tumor assessments							
Tumor imaging[q]	X	X			X[r]	X	
Bone scan	X[s]				X[t]	(X)	
Other clinical assessments							
Adverse events[u]	X	X	X	X	X	X	X
PRO assessments[v]		X[m]			X[m]	X	
Sunitinib compliance[w]		X			X	X	
Concomitant medications and treatments[x]	X	X	X	X	X	X	X
Survival follow-up							X
Special laboratory assessments							
Sunitinib trough sample collection[y]		X		X	X[x]		
Soluble protein samples[z]		X			X	X	
CEC and CTC samples[aa]		X		X[bb]		X	

Table 1. Schedule of Activities

() = optional procedure or assessment; X→ = start dosing; → = continue dosing.
CEC = circulating endothelial cell; CR = complete response; CRF = case report form; CT = computed tomography; CTC = circulating tumor cell; ECG = electrocardiogram; EORTC = European Organization for the Research and Treatment of Cancer; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PR = partial response; PRO = patient reported outcome; QTc = corrected QT interval; TSH = thyroid stimulation hormone.

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 standard-of-care treatment. The allowable window for all other visits in Cycles 1-3 was ±2 days; allowable window for Day 1 of subsequent cycles was -2/+1.

b. Following crossover to sunitinib after treatment failure on chemotherapy or following dose escalation to 50 mg sunitinib daily, Cycle 1 procedures were repeated for the first cycle.

c. Subjects receiving treatment with chemotherapy were evaluated in clinic at the interval appropriate for the therapy. Subjects on sunitinib who were on a stable dose for at least 6 months without significant safety issues could reduce clinic visits to 6-week intervals.

d. Assessments not required if completed during the previous 3 weeks on study (6 weeks for tumor assessments).

e. Subjects had to be evaluated up to 28 days after last dose of study treatment, then; post-study survival status was collected by telephone contact every 2 months until death or until 3 years from first study treatment.

f. Laboratories, multigated acquisition (MUGA) scans, and physical examination were not required if acceptable screening assessments had been performed within 7 days prior to the start of treatment.

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

h. Examination of major body systems, h8 (at screening visit only), Eastern Cooperative Oncology Group (ECOG) performance status, body weight, and vital signs (temperature, blood pressure [BP], heart rate, respiratory rate).

i. Cycle 1 only.

j. Additional hematology and blood chemistry tests as necessary for chemotherapy regimens. Cycle 1 Day 8 hematology could be performed at a local laboratory for subject convenience.

k. Additional tests were required at screening if thyroid stimulation hormone (TSH) was elevated (>10 μU/L) without history of thyroid disease and during the study if TSH decreased to <0.5 μU/L. Thyroid testing was not required for subjects taking thyroid supplements.

l. Cycle 3 only.

m. Odd numbered cycles only.

n. Urinalysis by dipstick performed at Baseline, Cycle 3 Day 1, as clinically indicated, and at the end of treatment, with only dipstick urine protein results captured on the CRF. If results indicated ≥2 + proteinuria, follow-up quantitative urine protein analysis was to be performed (and result captured on the adverse event CRF if adverse event criteria were met).

o. A single 12-lead electrocardiogram (ECG) was performed to determine the mean corrected QT (QTc) interval. ECGs were to be 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 ECG was repeated and if still prolonged, 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 15.

p. 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.

q. CT or MRI scan of the chest, abdomen, and pelvis and clinical examination of superficial lesions. Post-baseline pelvis assessments could be performed by ultrasound if Baseline results were normal as assessed by the core imaging laboratory. A brain CT or MRI was performed at screening; follow-up brain scans were required only if positive at Baseline or if brain metastases were suspected. Clinically evaluated lesions were photographed at each assessment.

r. Every 6 weeks (±7 days) 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 to be performed whenever progressive disease was suspected (eg, symptomatic

Table 1. Schedule of Activities

deterioration) and to confirm a 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.

s. Screening bone scan could be up to 35 days before randomization. Subsequent scans not required for subjects without bone lesions unless new bone lesions were suspected. A bone scan was required at the time of confirmation of objective response for subjects who have bone metastases. The allowable window for on-study bone scan assessments was ±7 days.

t. For subjects followed for bone lesions only, on treatment scans were required at Weeks 6 and 12 and every 12 weeks thereafter. Bone scans were performed every 12 weeks. Bone scans followed this schedule regardless of changes to the dosing schedule (ie, assessments were not delayed following treatment interruptions). Bone scans were also performed at any time new bone disease was suspected.

u. 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.

v. The European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and EORTC QLQ breast cancer module (BR23) 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. These assessments were discontinued for subjects who crossed over.

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

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

y. A single 4 mL blood sample was collected predose on the indicated days through on Cycles 1-5 and 7. The Cycle 1 Day 15 blood samples were obtained on the same day as the ECGs, after the ECG. Additionally, a single blood sample was obtained if clinically feasible at a time coincident with any serious cardiac event or other serious and/or unusual adverse event that is considered causally related to the study drug. Pharmacokinetic (PK) samples were not required for subjects randomized to chemotherapy, including after crossover. Trough sampling was discontinued with Amendment 2.

z. A 10 mL blood sample was collected on Day 1 of Cycles 1-5 and 7.

aa. 2 blood samples were collected at each time point. CTCs: 1 10-mL sample was collected in a CellSave tube and shipped immediately for analysis. CECs: 1 6-mL sample was collected in an EDTA (purple top) tube. For European sites, the sample was shipped immediately for analysis. For North American sites, the tube was processed, centrifuged and then buffy coat frozen at -80°C. If the blood sample for CEC or CTC assessment was not successfully obtained at Baseline, the subject was exempt from further sampling.

bb. Cycle 1 only.

Number of Subjects (Planned and Analyzed): A total sample size of approximately 200 subjects (100 in each treatment arm) was planned for this study. One hundred thirteen versus 104 subjects on sunitinib versus standard-of-care, respectively, were randomized to treatment. Three (2.7%) subjects versus 1 (1.0%) subject in sunitinib versus standard-of-care, respectively, discontinued before receiving treatment. One hundred ten versus 103 subjects in sunitinib versus standard-of-care, respectively, comprised the as-treated population.

Of 217 subjects, 63 were randomized in the US, 49 in Italy, 21 in France, 20 in Spain, 18 in Canada, 11 in the UK, 8 each in Czech Republic and Ukraine, 7 in Bulgaria, and 6 each in Hungary and Turkey.

Diagnosis and Main Criteria for Inclusion: Both male and female subjects aged 18 years and older, who were diagnosed with recurrent or metastatic breast cancer with estrogen receptor (ER), progestin receptor (PR) and HER2/neu receptor (HER2) negative status, who received prior treatment with an anthracycline and a taxane in the adjuvant or advanced disease setting, and who had relapse following adjuvant chemotherapy within 6 months of last treatment and/or received one or two chemotherapy regimens for advanced disease were included in the study. Subjects with more than two chemotherapy regimens for advanced disease and with uncontrolled/symptomatic spread of cancer to the brain were excluded from the study.

Study Treatment: Sunitinib-malate salt was supplied to the clinic pharmacy by the Sponsor as hard gelatin capsules containing 12.5 mg, 25 mg, and 50 mg equivalents of sunitinib free-base, in light-resistant bottles containing 30 or 35 capsules. All chemotherapy agents prescribed in the control arm of the study were prepared and dispensed according to product labeling and according to local standards of care in the regions in which the study was conducted.

Subjects were randomly assigned to receive one of the standard treatment regimens described above or treatment with 37.5 mg sunitinib once on a continuous daily dosing (CDD) regimen expressed in 3-week cycles. Subjects experiencing dose-limiting toxicity attributed to sunitinib could have 1-week treatment rests inserted into the regimen as needed and could dose reduce. Subjects who experienced minimal treatment-related effects (ie, Grade ≤1) could dose escalate sunitinib to 50 mg daily after completing 2 cycles (6 weeks), or at the discretion of the Investigator could continue unchanged through 1 more cycle (total 9 weeks) and, if toxicity continued to be minimal, were to dose escalate sunitinib to 50 mg daily in the fourth cycle. Subsequent cycles could have further dose titration depending upon individual tolerability.

Self-administration of sunitinib capsules took place on an outpatient basis. Capsules were taken once daily in the morning without regard to meals. All chemotherapy agents prescribed in the control arm of the study were administered according to the local standards of care.

Efficacy, Pharmacokinetic, Pharmacodynamic, Outcome Research, and Safety Endpoints:

Primary Efficacy Endpoint: PFS.

Secondary Efficacy Endpoints:

- Objective Response Rate (ORR);
- Duration of Response (DR);
- OS;
- 1-year survival.

Outcome Research Endpoints: PROs of health-related quality of life and disease-related symptoms as measured by European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the breast cancer module (QLQ-BR23).

Pharmacokinetic Endpoints: C_{trough} of sunitinib, SU012662, and Total drug (sunitinib + SU012662).

Pharmacodynamic Endpoints:

- Concentrations of plasma proteins (eg, soluble vascular endothelial growth factor receptor 2 (VEGFR2) and VEGFR3, vascular endothelial growth factor-A (VEGF-A), placental growth factor [PlGF], and soluble kinase insert domain for tyrosine [KIT]) that may be associated with angiogenesis and tumor proliferation;
- Circulating endothelial cell (CEC) and circulating tumor cell (CTC) assessment.

Safety Endpoints:

- Characterization and analysis of adverse events (AEs) (type, incidence, severity; graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events, or CTCAE, version 3.0, timing, seriousness, and relatedness to study drug);
- Any laboratory abnormalities.

Safety Evaluations: Safety evaluations included AEs from the first day of treatment to 28 days after the last dose of study drug; clinical laboratory tests (hematology performed on Days 1, 8, 15 and 22 of each cycle and serum chemistry performed on Days 1 and 15 of each cycle; Day 22 hematology and Day 15 serum chemistry assessments could be omitted after Cycle 3); multigated acquisition (MUGA) scan or echocardiogram to determine left ventricular ejection fraction (LVEF; performed at screening, Cycle 2 Day 1 for subjects with prior anthracycline exposure, every 3 months for subjects while on study without prior

anthracycline exposure, as clinically indicated and at termination); electrocardiogram (ECG; performed at screening, Day 15 of Cycle 1, time of discontinuation of each study treatment, 2 weeks following intrasubject sunitinib dose adjustments, and as clinically indicated); and vital signs and Eastern Cooperative Oncology Group (ECOG) performance status (performed on Days 1, 8 and 15 of each cycle).

Statistical Methods: The statistical analyses sets and methods used in the study are as follows:

Intent-to-Treat Population: 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.

As-Treated Population: The as-treated (AT) population included all subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The AT population was the primary population for evaluating treatment administration/compliance and safety. Secondary analyses of other endpoints (including measures of efficacy and clinical efficacy) could use the AT population.

If subjects were randomized but not treated, then they were reported under their randomized treatment group for efficacy analyses. However, they were by definition excluded from the safety analyses. If subjects were randomized but took incorrect treatment, then they were reported under their randomized treatment group for all efficacy analyses, but were reported under the treatment they actually received for all safety analyses.

Statistical Methods: Time-to-event endpoints between 2 treatment arms were compared with a 1-sided stratified log-rank test and an unstratified log-rank test at the α=0.025 overall significance level. The estimated hazard ratio and 2-sided 95% confidence interval (CI) is provided. Additionally for each treatment arm, the median event time and a 2-sided 95% CI are provided for each level of stratification factors or Baseline characteristics.

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

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

Supportive analyses for the time-to-event endpoints such as PFS and DR were performed on the ITT population based on Investigators' assessment. In addition, analyses were performed

for ORR in the ITT population based on the Investigators' assessment. Subjects with SD for at least 24 weeks were summarized.

Cox proportional hazard models were used to explore the potential influences of covariates and the Baseline stratification factor on time-to-event endpoints. In addition, evaluation of potential influences of Baseline subject characteristics such as age, ethnic origin, and ECOG performance status on the endpoints was possible. A backward selection process (with treatment in the model) was applied to these variables to identify the final set of relevant factors. Treatment-by-factor interactions were explored only for the set of factors included in the final model. The estimated hazard ratio and 2-sided 95% confidence interval are provided. Additionally for each treatment arm, the median event time and a 2-sided 95% confidence interval were provided for each level of stratification factors or Baseline characteristics.

Descriptive statistics for the EORTC QLQ-C30 and BR23 were presented for each treatment arm for each assessment and for change from Baseline.

Summary descriptive statistics, figures, and listings of observed and dose-corrected plasma C_{trough} values by cycle and day were presented for sunitinib, SU012662, and Total drug.

The significance of changes in circulating biomarkers (plasma proteins, CEC, Circulating Endothelial Progenitor Cells [CEP] and CTC) from Baseline levels were determined from analysis of the ratio to Baseline values using the Wilcoxon signed-rank test and a hypothetical median ratio to Baseline of 1.0. Baseline biomarker levels, and ratios to Baseline at each time point, were compared between treatment groups using the Wilcoxon rank sum test. Tumor response was determined from tumor assessment data. Baseline biomarker levels, and ratios to Baseline at each time point, were compared within each treatment arm between subjects having a clinical benefit response ([CBR]; CR or PR or SD ≥6 months) and subjects that did not experience a CBR (SD <6 months or PD). Kaplan-Meier curves were compared within each treatment arm after stratification by < or ≥ median baseline biomarker levels and by < or ≥ median ratios to Baseline at each time point using the proportional hazards model.

Descriptive statistics were used to summarize the safety data.

RESULTS:

Subject Disposition and Demography: Table 2 and Table 3 present a summary of subject disposition and of the different subject populations before crossover and after crossover, respectively. One hundred thirteen versus 104 subjects were randomized to receive sunitinib versus standard-of-care regimen, respectively, and comprised the ITT population. Three (2.7%) subjects versus 1 (1.0%) subject discontinued before receiving treatment. One hundred ten versus 103 subjects on sunitinib versus the standard care regimen, respectively, comprised the AT population.

Table 2. Subject Disposition and Subject Analyzed – Before Crossover

Variable	Sunitinib	Standard-of-Care	Total
Randomized/intent-to-treat population [N][a]	113	104	217
Randomized/ITT but took wrong drug [n (%)]	0 (0.0)	0 (0.0)	0 (0.0)
Randomized/ITT but did not take any drug [n (%)]	3 (2.7)	1 (1.0)	4 (1.8)
As-treated population[b]	110 (97.3)	103 (99.0)	213 (98.2)
Subject status [n (%)]			
Subjects completed study	0 (0.0)	0 (0.0)	0 (0.0)
Ongoing subjects	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued subjects during active treatment period	110 (97.3)	29 (27.9)	139 (64.1)
Crossover subjects	0 (0.0)	74 (71.2)	74 (34.1)
Non-treated subjects	3 (2.7)	1 (1.0)	4 (1.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Primary reason for withdrawal from study during active treatment period [n (%)]			
Adverse event	7 (6.2)	0 (0.0)	7 (3.2)
Protocol violation	0 (0.0)	1 (1.0)	1 (0.5)
Consent withdrawn	2 (1.8)	3 (2.9)	5 (2.3)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	84 (74.3)	21 (20.2)	105 (48.4)
Subject died	17 (15.0)	3 (2.9)	20 (9.2)
Decision of Sponsor	0 (0.0)	1 (1.0)	1 (0.5)
Did not meet entrance criteria	2 (1.8)	1 (1.0)	3 (1.4)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Laboratory abnormality(ies)	1 (0.9)	0 (0.0)	1 (0.5)
Withdrawn due to pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Subject refused continued treatment for reason other than AE	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Duration of follow-up (months)[c]			
Median	38.68	3.39	15.56
(95% confidence interval)	(23.82, 44.18)	(2.89, 4.64)	(8.16, 23.75)

% = (n/N)×100

Standard-of-care: capecitabine, vinorelbine (oral or intravenous infusion), docetaxel, gemcitabine, or paclitaxel 175-200 or 80-90.

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

a. The randomized/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 receive a different drug from that to which they were randomized.

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

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

Table 3. Subject Disposition and Subject Analyzed – After Crossover

Variable	Standard-of-Care Postcrossover
Crossover subjects	74
Subject status [n (%)]	
Subjects completed study	0 (0.0)
Ongoing subjects	0 (0.0)
Discontinued subjects during active treatment period	74 (100.0)
Missing	0 (0.0)
Primary reason for withdrawal from study during active treatment period [n (%)]	
Adverse event	8 (10.8)
Protocol violation	0 (0.0)
Consent withdrawn	2 (2.7)
Lost to follow-up	1 (1.4)
Lack of efficacy	49 (66.2)
Subject died	13 (17.6)
Decision of Sponsor	0 (0.0)
Did not meet entrance criteria	0 (0.0)
Other	1 (1.4)
Laboratory abnormality(ies)	0 (0.0)
Withdrawn due to pregnancy	0 (0.0)
Subject refused continued treatment for reason other than AE	0 (0.0)
Missing	0 (0.0)

% = (n/N)×100
Standard-of-care: capecitabine, vinorelbine (oral or intravenous infusion), docetaxel, gemcitabine, or paclitaxel 175-200 or 80-90.
AE = adverse event; ITT = intent-to-treat; N = total number of subjects; n = number of subjects with specified criteria.

Demographic and Baseline characteristics are summarized by treatment arm for the ITT population in Table 3. All subjects on both arms were female, and the median age on both arms was 52 years (range: 32.0 to 81.0 years on sunitinib versus 31.0 to 81.0 years of receiving a standard care treatment regimen).

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

Variable	Sunitinib (N=113)	Standard-of-Care (N=104)
Age (years)		
N	113	104
Mean (SD)	51.5 (10.01)	51.6 (10.91)
Median	52.0	52.0
Min, max	(32.0, 81.0)	(31.0, 81.0)
Age (years), n (%)		
<65 years	103 (91.2)	90 (86.5)
≥65 years	10 (8.8)	14 (13.5)
Sex, n (%)		
Female	113 (100.0)	104 (100.0)
Male	0 (0.0)	0 (0.0)
Race, n (%)		
White	100 (88.5)	86 (82.7)
Black	7 (6.2)	7 (6.7)
Asian	3 (2.7)	4 (3.8)
Other	3 (2.7)	6 (5.8)
Missing	0 (0.0)	1 (1.0)
Weight (kg)		
N	113	103
Mean (SD)	72.0 (14.77)	71.4 (13.27)
Median	69.7	70
Min, max	(50.0, 127.3)	(45.0, 105.0)
ECOG performance status, n (%)		
0	75 (66.4)	66 (63.5)
1	36 (31.9)	37 (35.6)
≥2	2 (1.8)	1 (1.0)
Missing	0 (0.0)	0 (0.0)
Childbearing potential, n (%)		
Yes	31 (27.4)	28 (26.9)
No	82 (72.6)	76 (73.1)
Missing	0 (0.0)	0 (0.0)

ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; Max = maximum; Min = minimum; N = number of subjects in each treatment group; n = number of subjects with specified criteria; SD = standard deviation.

Efficacy Results:

Progression-Free Survival: The primary analysis of PFS was conducted in the ITT population and based on disease progression as determined by a centralized, blinded, third-party radiology laboratory and/or deaths as determined by Investigators. Secondary analyses of PFS were performed in the AT population.

PFS based on the central radiology assessment is summarized for the ITT population in Table 5. Ninety-three (82.3%) versus 79 subjects (76.0%) on sunitinib versus standard-of-care, respectively, had experienced objective tumor progression or died on sunitinib versus standard-of-care, respectively. The median PFS was 2.0 (95% CI: 1.5 to 2.8 months) versus 2.7 months (95% CI: 1.7 to 2.8 weeks) with a stratified hazard ratio of 1.203 (95% CI: 0.8889 to 1.6280; 1-sided log-rank test p-value =0.8885).

Table 5. Summary of Analyses of Progression-Free Survival (Core Radiology Assessment; ITT Population)

Variable	Sunitinib (N=113)	Standard-of-Care (N=104)
Progression status, n (%)		
Subjects who had disease progression or died	93 (82.3)	79 (76.0)
Subjects with censored endpoints	20 (17.7)	25 (24.0)
Progression-free survival (months)		
Quartile (95% CI)		
25%	1.4 (1.3, 1.4)	1.4 (1.3, 1.4)
50% (median)	2.0 (1.5, 2.8)	2.7 (1.7, 2.8)
75%	4.0 (2.8, 4.5)	5.2 (2.9, 6.8)
Stratified analysis:		
Hazard ratio (sunitinib versus standard-of-care)[a]	1.203	
(95% CI)	(0.8889, 1.6280)	
Log-rank test statistic (p-value)[b]	-1.2188 (0.8885)	
Unstratified analysis:		
Hazard ratio (sunitinib versus standard-of-care)[a]	1.179	
(95% CI)	(0.8720, 1.5942)	
Log-rank test statistic (p-value)[c]	-1.0877 (0.8616)	

Progression free survival (PFS) was defined as the time from the data of randomization to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurred first.
CI = confidence interval; ITT = intent-to-treat; IVRS = interactive voice response system; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

a. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of sunitinib; a hazard ratio greater than 1 is in favor of standard-of-care.
b. 1-sided log-rank test stratified for the number of prior chemotherapy regimens (1 versus >1), which is from IVRSs.
c. The unstratified 1-sided log-rank test did not adjust for the stratification factor.

PFS based on the Investigators' assessment is summarized for the ITT population in Table 6. One hundred (88.5%) subjects versus 93 (89.4%) subjects on sunitinib versus standard-of-care, respectively, had experienced objective progression months or died on sunitinib versus standard–of-care, respectively. The median PFS was 1.7 months (95% CI: 1.5 to 2.6 months) versus 2.5 months (95% CI: 1.4 to 2.9 weeks) months on sunitinib versus standard-of-care, respectively, with a stratified hazard ratio of 1.203 (95% CI: 0.8889 to 1.6280; 1-sided log-rank test p-value =0.8885).

Table 6. Summary of Analyses of Progression-Free Survival (Investigators' Assessment; ITT Population)

Variable	Sunitinib (N=113)	Standard-of-Care (N=104)
Progression status, n (%)		
Subjects who had disease progression or died	100 (88.5)	93 (89.4)
Subjects with censored endpoints	13 (11.5)	11 (10.6)
Progression-free survival (months)		
Quartile (95% CI)		
25%	1.4 (1.3, 1.4)	1.3 (1.3, 1.4)
50% (median)	1.7 (1.5, 2.6)	2.5 (1.4, 2.9)
75%	4.0 (2.8, 4.4)	4.2 (3.5, 5.5)
Range of event time	(0.4, 21.4)	(0.5, 18.0)
Stratified analysis:		
Hazard ratio (sunitinib versus standard-of-care)[a]	1.1598	
(95% CI)	(0.8703, 1.5457)	
Log-rank test statistic (p-value)[b]	-1.0247 (0.8472)	
Unstratified analysis:		
Hazard ratio (sunitinib versus standard-of-care)[a]	1.1448	
(95% CI)	(0.8613, 1.5215)	
Log-rank test statistic (p-value)[c]	-0.9435 (0.8273)	

Progression free survival (PFS) was defined as the time from the data of randomization to the date of the first documentation of objective tumor progression or death due to any cause, whichever occurred first.
CI = confidence interval; ITT = intent-to-treat; IVRS = interactive voice response system; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

a. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of sunitinib; a hazard ratio greater than 1 is in favor of standard-of-care.
b. 1-sided log-rank test stratified for the number of prior chemotherapy regimens (1 versus >1), which is from IVRSs.
c. The unstratified 1-sided log-rank test does not adjust for the stratification factor.

PFS was analyzed stratifying the Baseline factors. The treatment effect was not significant with or without controlling for Baseline factors. In supportive analyses based on core radiology assessments in the AT population, the PFS results were similar to those in the primary analysis.

Objective Response Rate: ORR is summarized by the central radiology and Investigators' assessments in Table 7. In the core radiology assessment in the ITT population, ORR was 2.7% (95% CI: 0.6 to 7.6) versus 6.7% (95% CI: 2.7 to 13.4; stratified odds ratio: 0.38 (95% CI: 0.06 to 1.71, 1-sided log rank test, p-value =0.9624) on sunitinib versus the standard care treatment regimen, respectively. Eight (7.1%) versus 10 subjects (9.6%) had stable disease lasting 24 weeks or more, not including CR or PR.

The results were essentially the same when stratified by Baseline and prognostic factors, when limited to subjects with measurable disease at Baseline, and when based on the Investigators' assessment of disease. Concordance between the core radiology assessment of disease and the Investigators' assessments was not high. On sunitinib, of the 3 subjects to be responders by the central radiology assessment, 1 (33.3% responders) was considered responders by the Investigators' assessments, and 2 (66.7%) were considered to have SD. On standard-of-care, of the 7 subjects on sunitinib considered to be responders by the Investigators, 6 (85.7% responders) were considered responders by the central radiology assessment, 1 (14.3%) was considered to have SD.

Table 7. Summary of Analyses of Objective Response Rate (ITT Population)

Variable	Sunitinib (N=113)	Standard-of-Care (N=104)
Subjects with baseline disease assessments, n	110	103
Core radiology assessment:		
Confirmed overall response, n (%)[a]		
Complete response (CR)	0 (0.0)	0 (0.0)
Partial response (PR)	3 (2.7)	7 (6.7)
Stable disease (SD)	47 (41.6)	48 (46.2)
Progressive disease (PD)	53 (46.9)	39 (37.5)
Not evaluable (NE)	10 (8.8)	10 (9.6)
Missing	0 (0.0)	0 (0.0)
Subjects with stable disease ≥24 weeks, n (%)[b]	8 (7.1)	10 (9.6)
Overall confirmed objective response rate (CR + PR), n (%)	3 (2.7)	7 (6.7)
95% exact CI	(0.6, 7.6)	(2.7, 13.4)
Difference between percentages (sunitinib less standard-of-care)	-4.1	
(95% CI)[c]	(-9.7, 1.6)	
Stratified analysis[d]:		
Odds ratio[e]	0.38	
(95% exact CI)	(0.06, 1.71)	
Exact 1-sided p-value	0.9624	
Unstratified analysis:		
Odds ratio[e]	0.38	
(95% exact CI)	(0.06, 1.72)	
Exact 1-sided p-value	0.962	
Investigators' assessment:		
Confirmed overall response n (%)[a]		
Complete response (CR)	0 (0.0)	2 (1.9)
Partial response (PR)	10 (8.8)	10 (9.6)
Stable disease (SD)	37 (32.7)	35 (33.7)
Progressive disease (PD)	54 (47.8)	46 (44.2)
Not evaluable (NE)	12 (10.6)	11 (10.6)
Missing	0 (0.0)	0 (0.0)
Subjects with stable disease ≥24 weeks [n (%)][b]	5 (4.4)	9 (8.7)
Overall confirmed objective response rate (CR + PR) [n (%)]	10 (8.8)	12 (11.5)
95% exact CI	(4.3, 15.7)	(6.1, 19.3)
Difference between percentages (sunitinib less standard-of-care)	-2.7	
(95% CI)[c]	(-10.8, 5.4)	
Stratified analysis[d]:		
Odds ratio[e]	0.74	
(95% exact CI)	(0.27, 1.98)	
Exact 1-sided p-value	0.814	
Unstratified analysis:		
Odds ratio[e]	0.74	
(95% exact CI)	(0.27, 1.98)	
Exact 1-sided p-value	0.8107	

Any assessments after concomitant radiation therapy was received and any PD assessments which had 14 weeks gap with previous assessment were not used to derive confirmed overall response. Response was determined based upon RECIST.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ITT = intent-to-treat; IVRS = interactive voice response system; N = number of subjects in each treatment group; n = number of subjects with specified criteria; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

a. Percentages of subjects in ITT population.
b. Excludes subjects with a best response of PR or CR.
c. Difference was calculated as sunitinib – standard-of-care; 95% CI was calculated based on a normal distribution.
d. The stratified analysis was from CMH test stratified the number of prior chemotherapy regimens (1 versus >1), based IVRS data.
e. An odds ratio >1 was in favor of sunitinib; an odds ratio <1 was in favor of standard-of-care.

Duration of Response: Duration of response is summarized for the ITT population for the core radiology results and for the Investigators' assessment in Table 8. Three versus 7 subjects on sunitinib versus standard-of-care, respectively, had objective responses by the central radiology assessment, and 3 responders on sunitinib versus 3 on standard-of-care regimen subsequently progressed. There were not sufficient data to reliably estimate DR based on the core radiology results.

Ten versus 12 subjects on sunitinib versus standard-of-care, respectively, had objective responses by the Investigators' assessment, and 9 versus 9 responders subsequently progressed. The median DR was 3.6 (95% CI: 2.8 to 6.2 months) versus 4.6 months (95% CI: 3.1 to 11.2 months) based on the Investigators' assessment.

Table 8. Summary of Duration of Response (ITT Population)

Variable	Sunitinib (N=113)	Standard-of-Care (N=104)
Core radiology assessment		
Total number of responders, N*[a]	3	7
Status after response, n (%)		
Subjects who had disease progression or died	3 (100.0)	3 (42.9)
Subjects with censored data	0 (0.0)	4 (57.1)
Duration of response (months)		
Quartile (95% CI)		
25%	2.8 (2.8, 7.3)	5.2 (4.1, -)[b]
50% (median)	3.0 (2.8, 7.3)	(5.2, -)[b]
75%	7.3 (2.8, 7.3)	(5.4, -)[b]
Investigators' assessment		
Total number of responders, N*[a]	10	12
Status after response, n (%)		
Subjects who had disease progression or died	9 (90.0)	9 (75.0)
Subjects with censored data	1 (10.0)	3 (25.0)
Duration of response (months)		
Quartile (95% CI)		
25%	2.8 (1.7, 5.1)	3.1 (2.3, 4.6)[b]
50% (median)	3.6 (2.8, 6.2)	4.6 (3.1, 11.2)[b]
75%	7.3 (2.8, 7.3)	11.2 (4.2,)[b]

CI = confidence interval; DR = duration of response; ITT = intent-to-treat; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

a. N* = number of subjects with objective responses; only these subjects were included in the analysis of DR.

b. The upper bound of the confidence interval could not be estimated because there were not enough data relative to the possible number of data points to estimate the percentiles.

Overall Survival and 1 Year Survival Probability: OS is summarized for the ITT population in Table 9. Median OS was 9.4 (95% CI: 5.8 to 11.2 months) versus 10.5 (95% CI: 8.5 to 13.8 months) months on sunitinib versus standard-of-care, respectively (stratified hazard ratio 1.1599, 95% CI: 0.8648 to 1.5558, 1-sided log-rank test p-value =0.8394). The probability of survival at 1 year was 0.376 (95% CI: 0.285 to 0.466) versus 0.446 (95% CI: 0.346 to 0.541).

The treatment effect was not statistically significant in any stratification subgroup for OS.

Table 9. Summary of Overall Survival (ITT Population)

Variable	Sunitinib (N=113)	Standard-of-Care (N=104)
Survival status, n (%)		
Died	96 (85.0)	87 (83.7)
Still alive	17 (15.0)	17 (16.3)
Overall survival (months)		
Quartile (95% CI)		
25%	3.1 (2.4, 5.0)	5.3 (3.8, 6.5)
50% (median)	9.4 (5.8, 11.2)	10.5 (8.5, 13.8)
75%	15.9 (12.9, 20.6)	21.2 (16.1, 25.0)
Min, Max	0.4, 46.1	1.0, 39.0
1-year survival probability (95% CI)	0.376 (0.285, 0.466)	0.446 (0.346, 0.541)
Stratified analysis:		
Hazard ratio (sunitinib versus standard-of-care)[a]	1.1599	
(95% CI)	(0.8648, 1.5558)	
Log-rank test statistic (p-value)[b]	-0.9920 (0.8394)	
Unstratified analysis:		
Hazard ratio (sunitinib versus standard-of-care)[a]	1.676	
(95% CI)	(0.8716, 1.5640)	
Log-rank test statistic (p-value)	-1.0404 (0.8509)	

CI = confidence interval; ITT = intent-to-treat; IVRS = interactive voice response system; Max = maximum; Min = minimum; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

a. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of sunitinib; a hazard ratio greater than 1 is in favor of standard-of-care.

b. 1-sided log-rank test stratified for the number of prior chemotherapy regimens (1 versus >1), which is from IVRSs.

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

Pharmacokinetic Results:

C_{trough} of Sunitinib, SU012662, and Total Drug (Sunitinib+SU012662): Summary of observed and dose-corrected trough plasma concentrations for sunitinib, SU012662, and Total drug on Day 1 of Cycles 1-5 and 7, and Day 15 of Cycles 1-3 are presented in Table 10.

For the sunitinib arm, the observed C_{trough} mean values on Day 1 of Cycles 2-5 and 7, and Day 15 of Cycles 1-3 ranged from 42.2 ng/mL to 65.5 ng/mL for sunitinib, 21.3 ng/mL to 40.4 ng/mL for SU012662, and 63.6 ng/mL to 105 ng/mL for Total drug. Similarly, the steady state dose-corrected C_{trough} mean values on Day 1 of Cycles 2-5 and 7, and Day 15 of Cycles 1 to 3 ranged from 58.4 ng/mL to 73.4 ng/mL for sunitinib, 28.6 ng/mL to 41.9 ng/mL for SU012662, and 92.5 ng/mL to 111 ng/mL for Total drug.

Table 10. Summary of Observed- and Dose-Corrected Trough Plasma Concentrations (C_{trough}) of Sunitinib, SU012662, and Total Drug on Day 1 of Cycles 1-5 and 7, and Day 15 of Cycles 1-3 Following Administration of Sunitinib 37.5 mg on Continuous Daily Dosing Schedule

		Arithmetic Mean (%CV) [Median]							
		Observed C_{trough}				Dose-corrected[a] C_{trough}			
Cycle[b]	Day	n	Sunitinib (ng/mL)	SU012662 (ng/mL)	Total Drug (ng/mL)	n	Sunitinib (ng/mL)	SU012662 (ng/mL)	Total Drug (ng/mL)
1	1	54	0.12 (735) [0.0]	0.02 (735) [0.0]	0.14 (735) [0.0]	ND	ND	ND	ND
	15	44	65.5 (47) [66.5]	29.4 (37) [30.6]	94.9 (40) [95.2]	42	67.5 (43) [67.6]	29.9 (34) [30.6]	97.4 (36) [95.2]
2	1	42	62.1 (60) [66.3]	32.3 (53) [34.3]	94.4 (54) [104]	35	73.4 (41) [70.0]	37.2 (36) [36.6]	111 (35) [110]
	15	33	58.2 (51) [54.1]	33.4 (62) [26.9]	91.6 (51) [81.2]	27	69.8 (47) [60.2]	37.3 (56) [30.1]	107 (45) [91.7]
3	1	26	50.0 (71) [52.5]	28.5 (77) [24.3]	78.6 (68) [85.8]	16	69.3 (43) [66.0]	39.8 (54) [36.4]	109 (41) [95.1]
	15	21	64.6 (44) [63.9]	40.4 (38) [41.3]	105 (38) [107]	18	65.3 (46) [63.6]	40.1 (36) [39.3]	105 (38) [100]
4	1	18	51.3 (64) [51.3]	30.9 (62) [28.3]	82.2 (59) [88.9]	12	68.7 (50) [62.1]	38.7 (45) [32.6]	107 (43) [93.5]
5	1	12	48.1 (51) [47.1]	36.1 (61) [27.9]	84.2 (51) [81.7]	10	58.4 (46) [59.0]	41.9 (48) [38.0]	100 (39) [106]
7	1	6	42.2 (54) [36.2]	21.3 (24) [20.1]	63.6 (39) [59.1]	4	64.0 (73) [49.1]	28.6 (28) [31.2]	92.5 (57) [80.3]

Total drug = sunitinib + SU012662.
C_{trough} = trough plasma concentration; CV = coefficient of variation; ITT = intent-to-treat; n = number of subjects with observations.
a. For dose-correction, the reference dose was 37.5 mg.
b. Each cycle was 3 weeks in duration.

Pharmacodynamic Results:

Concentrations of Plasma Proteins: In the sunitinib arm, PlGF levels increased significantly from Baseline levels at Cycle 2 Day 1 (median ratio to Baseline =3.52, p-value =0.001) but no significant changes from Baseline were seen at later time points. Plasma sKIT levels decreased significantly from Baseline levels at each time point, with median ratios to Baseline in the range 0.30 to 0.71, whereas plasma VEGF-A levels increased significantly at every time point except Cycle 7 Day 1, with median ratios to Baseline in the range 1.25 to 2.70. Plasma VEGF-C levels decreased significantly from Baseline levels at each time point except end of treatment (median ratios to Baseline in the range 0.63 to 0.82), while plasma sVEGFR-3 levels decreased significantly from Baseline levels from Cycle 2 Day 1 (median ratio to Baseline =0.51) to Cycle 5 Day 1 (median ratio to Baseline =0.48).

In the standard-of-care arm, none of the soluble proteins analyzed showed a significant change from Baseline at more than 1 time point. The only significant changes were small and observed at Cycle 2 Day 1; at this time point, the median sKIT ratio to Baseline was 1.03 (p-value =0.0314) and the median VEGF-A ratio to Baseline was 1.17 (p-value =0.0024).

None of the plasma proteins analyzed showed a significant difference in Baseline levels when the 2 treatment arms were compared. VEGF-A ratios to Baseline in the sunitinib arm were significantly higher than those in the standard-of-care arm from Cycle 2 Day 1 to Cycle 5 Day 1, whereas VEGF-C ratios in the sunitinib arm were significantly below those in the standard-of-care arm at Cycle 2 Day 1 and Cycle 5 Day 1. sVEGFR-3 ratios to Baseline were significantly lower in the sunitinib arm from Cycle 2 Day 1 to Cycle 7 Day 1, while sKIT ratios were significantly lower in the sunitinib arm at all timepoints evaluated. Median PlGF ratios to Baseline were marked higher in the sunitinib arm than the standard-of-care arm at Cycle 2 Day 1 (3.52 vs 0.95, respectively, p-value =0.0017) but sample size was too small for this analysis at later time points.

Analysis of correlations between soluble proteins and CBR showed that in the sunitinib arm, the median Baseline VEGF-C concentration in CBR subjects (1328.5 pg/ml) was significantly higher than that in subjects who did not experience a CBR (639.3 pg/ml; p-value =0.0298). In the standard-of-care arm, none of the differences in Baseline protein concentrations or ratios to Baseline achieved significance (p-value ≥0.05).

Circulating Endothelial Cells: In the sunitinib arm, no significant changes in cell counts were seen at any time point for total CEC, viable CEC, VEGFR1 + CEC, VEGFR3 + CEC or total CEP. Apoptotic CEC counts increased significantly on Cycle 3 Day 1 (median ratio to Baseline =1.30, p-value =0.0496) and VEGFR2 + CEC counts increased significantly on Cycle 1 Day 15 (median ratio to Baseline =1.45, p-value =0.0187). In the standard-of-care arm, no changes in cell counts were seen at any time point for total CEC, viable CEC, VEGFR1 + CEC, VEGFR2 + CEC or total CEP. Apoptotic CEC counts decreased significantly on Cycle 3 Day 1 (median ratio to Baseline =0.69, p-value =0.0025) and VEGFR3 + CEC counts decreased significantly on Cycle 2 Day 1 (median ratio to Baseline =0.41, p-value =0.021).

No significant differences were observed in counts at Baseline, or in ratios to Baseline at any time point, for total CEC, viable CEC, VEGFR1 + CEC, VEGFR2 + CEC or total CEP when the 2 treatment arms were compared. Apoptotic CEC ratios to Baseline at Cycle 3 Day 1 were significantly higher in the sunitinib arm than in the standard-of-care arm (median ratios to Baseline of 1.30 and 0.69, respectively, p-value =0.0473). VEGFR3 + CEC ratios to Baseline were significantly higher in the sunitinib arm than in the standard-of-care arm (median ratios of 1.49 and 0.41, respectively, p-value =0.0346).

Analysis of correlations between CEC or CEP counts and CBR showed that in the sunitinib arm, sample sizes in the CBR subset of the analysis were too small (<5) for statistical significance to be estimated at any time point for any cell type investigated. In the standard-of-care arm, the median apoptotic CEC ratio to Baseline at Cycle 3 Day 1 was significantly higher in subjects having a CBR than in subjects without a CBR (median ratios to Baseline of 1.08 and 0.58, respectively; p-value =0.0371). The median VEGFR2 + CEC count at Baseline was higher in CBR subjects than in those not having a CBR (median counts of 216.0 cells/ml and 52.89 cells/ml, respectively; p-value =0.0183), while in the same cell type ratios to Baseline at Cycle 2 Day 1 were significantly lower in CBR subjects compared with those not having a CBR (median VEGFR2 + CEC ratios to Baseline of 0.40 and 1.18, respectively; p-value =0.0092).

Circulating Tumor Cells: In the sunitinib arm, no significant changes in total CTC count from Baseline were seen during the study except at the end of treatment, when the median ratio to Baseline was 2.34 (p-value =0.0151). No significant changes were observed in insulin-like growth factor 1 receptor (IGF1R) + CTC at any time on study. In the standard-of-care arm, total CTC count was significantly reduced at Cycle 1 Day 15 (median ratio to Baseline =0.19, p-value =0.0066), with a trend to lower CTC at Cycle 2 Day 1 (p-value =0.0514). IGF1R + CTC counts were significantly reduced from Cycle 1 Day 15 to Cycle 3 Day 1.

Baseline counts for both total CTC and IGF1R + CTC were significantly lower in the standard-of-care arm than in the sunitinib arm (p-values of 0.0333 and 0.0775, respectively). Total CTC ratios to Baseline were significantly lower in the standard-of-care arm compared with the sunitinib arm at Cycle 1 Day 15 (p-value =0.0125) and Cycle 2 Day 1 (p-value =0.0290), while IGF1R + CTC were significantly lower in the standard-of-care arm at Cycle 1 Day 15 (p-value =0.0236) and Cycle 3 Day 1 (p-value =0.0460) when compared to the sunitinib arm.

In the standard-of-care arm, subjects having < median CTC at Baseline experienced prolonged PFS, whereas no PFS difference was seen in the sunitinib arm.

Safety Results: The overall adverse experience is summarized for the AT population by treatment arm in Table 11. Most subjects (99.1% versus 96.1% subjects on sunitinib versus standard-of-care regimen, respectively) experienced AEs. Serious AEs (SAEs), deaths on study (deaths on study treatment or within 28 days of the last dose of study treatment), and permanent discontinuations due to AEs appeared to be more common on sunitinib (SAEs: 36.4% versus 20.4%; deaths on study: 20.9% versus 3.9%; discontinuations due to AEs: 31.8% versus 4.9%). Twenty-three (20.9%) versus 4 subjects (3.9%) on sunitinib versus standard-of-care regimen, respectively, died on treatment.

Table 11. Overall Adverse Event Experience (As-Treated Population)

Variable	Sunitinib (N=110)	Standard-of-Care (N=103)
Subjects with at least 1 adverse event	109 (99.1)	99 (96.1)
Subjects with at least 1 serious adverse event	40 (36.4)	21 (20.4)
Subjects with at least 1 treatment-related adverse event[a]	106 (96.4)	90 (87.4)
Related to sunitinib	106 (96.4)	0 (0.0)
Related to standard-of-care treatment	1 (0.9)	90 (87.4)
Related to sunitinib and standard-of-care treatment	1 (0.9)	0 (0.0)
Subjects with at least 1 treatment-related serious adverse event[a]	16 (14.5)	5 (4.9)
Related to sunitinib	16 (14.5)	0 (0.0)
Related to standard-of-care treatment	0 (0.0)	5 (4.9)
Subjects who had adverse event with action taken of sunitinib permanently withdrawn	35 (31.8)	0 (0.0)
Subjects who had adverse event with action taken of standard-of-care treatment permanently withdrawn	0 (0.0)	5 (4.9)
Subjects who died[b]	96 (87.3)	19 (8.4)
On-study deaths[c]	23 (20.9)	4 (3.9)
Follow-up deaths[d]	73 (66.4)	15 (14.6)

Adverse events and serious adverse events are not separated out.
AT = as treated; N = number of subjects.
a. "Treatment-related" included AEs with causality.
b. Only no crossover deaths were summarized.
c. Deaths that occurred after the first dose date, but within 28 days after the last dose date.
d. Deaths occurred more than 28 days after the last dose date.

Treatment-Emergent Adverse Events: The treatment-emergent AEs (TEAEs) reported in ≥5% subjects on either treatment arm are summarized in Table 12. The most common AEs in the sunitinib arm were nausea, diarrhea, fatigue, and neutropenia. The most common AEs in the standard-of-care regimen arm were nausea and vomiting, palmar-plantar erythrodysesthesia syndrome, and neutropenia.

Table 12. Treatment-Emergent Adverse Events (All Causality) Reported in ≥5% of Subjects (As-Treated Population)

System Organ Class MedDRA (v14.0) Preferred Term	Sunitinib n (%)	Standard-of-Care n (%)
Number of subjects evaluable for adverse events	110	103
Number (%) of subjects with adverse events	109 (99.1)	98 (95.1)
Blood and lymphatic system disorders	56 (50.9)	35 (34.0)
Anaemia	15 (13.6)	17 (16.5)
Leukopenia	24 (21.8)	8 (7.8)
Neutropenia	34 (30.9)	24 (23.3)
Thrombocytopenia	27 (24.5)	7 (6.8)
Endocrine disorders	15 (13.6)	4 (3.9)
Hypothyroidism	15 (13.6)	3 (2.9)
Eye disorders	21 (19.1)	11 (10.7)
Conjunctivitis	6 (5.5)	3 (2.9)
Periorbital oedema	6 (5.5)	1 (1.0)
Gastrointestinal disorders	91 (82.7)	63 (61.2)
Abdominal pain	12 (10.9)	8 (7.8)
Abdominal pain upper	10 (9.1)	5 (4.9)
Constipation	13 (11.8)	17 (16.5)
Diarrhoea	50 (45.5)	26 (25.2)
Dry mouth	6 (5.5)	3 (2.9)
Dyspepsia	19 (17.3)	6 (5.8)
Gastrooesophageal reflux disease	6 (5.5)	1 (1.0)
Nausea	52 (47.3)	36 (35.0)
Oral pain	7 (6.4)	0
Stomatitis	15 (13.6)	6 (5.8)
Vomiting	26 (23.6)	17 (16.5)
General disorders and administration site conditions	90 (81.8)	69 (67.0)
Asthenia	32 (29.1)	15 (14.6)
Chest pain	9 (8.2)	7 (6.8)
Fatigue	41 (37.3)	38 (36.9)
Mucosal inflammation	30 (27.3)	16 (15.5)
Oedema peripheral	7 (6.4)	7 (6.8)
Pyrexia	9 (8.2)	17 (16.5)
Investigations	40 (36.4)	17 (16.5)
Alanine aminotransferase increased	6 (5.5)	5 (4.9)
Aspartate aminotransferase increased	8 (7.3)	5 (4.9)
Blood alkaline phosphatase increased	6 (5.5)	0
Platelet count decreased	14 (12.7)	1 (1.0)
Weight decreased	12 (10.9)	3 (2.9)
White blood cell count decreased	6 (5.5)	3 (2.9)
Metabolism and nutrition disorders	39 (35.5)	27 (26.2)
Decreased appetite	29 (26.4)	12 (11.7)
Hypokalaemia	5 (4.5)	6 (5.8)
Musculoskeletal and connective tissue disorders	56 (50.9)	37 (35.9)
Arthralgia	9 (8.2)	2 (1.9)
Back pain	12 (10.9)	9 (8.7)
Musculoskeletal chest pain	12 (10.9)	6 (5.8)
Musculoskeletal pain	7 (6.4)	9 (8.7)
Neck pain	8 (7.3)	4 (3.9)
Pain in extremity	19 (17.3)	9 (8.7)
Nervous system disorders	45 (40.9)	34 (33.0)
Dizziness	6 (5.5)	6 (5.8)
Dysgeusia	23 (20.9)	5 (4.9)
Headache	19 (17.3)	13 (12.6)
Psychiatric disorders	16 (14.5)	14 (13.6)
Anxiety	9 (8.2)	4 (3.9)
Insomnia	7 (6.4)	10 (9.7)
Reproductive system and breast disorders	17 (15.5)	5 (4.9)

Table 12. Treatment-Emergent Adverse Events (All Causality) Reported in ≥5% of Subjects (As-Treated Population)

System Organ Class MedDRA (v14.0) Preferred Term	Sunitinib n (%)	Standard-of-Care n (%)
Breast pain	7 (6.4)	5 (4.9)
Respiratory, thoracic and mediastinal disorders	48 (43.6)	30 (29.1)
Cough	19 (17.3)	13 (12.6)
Dyspnoea	25 (22.7)	13 (12.6)
Epistaxis	11 (10.0)	4 (3.9)
Pleural effusion	6 (5.5)	5 (4.9)
Skin and subcutaneous tissue disorders	69 (62.7)	41 (39.8)
Alopecia	4 (3.6)	6 (5.8)
Dry skin	7 (6.4)	1 (1.0)
Erythema	11 (10.0)	3 (2.9)
Palmar-plantar erythrodysaesthesia syndrome	27 (24.5)	27 (26.2)
Pruritus	7 (6.4)	2 (1.9)
Rash	10 (9.1)	1 (1.0)
Skin discolouration	18 (16.4)	0
Vascular disorders	40 (36.4)	23 (22.3)
Hypertension	26 (23.6)	4 (3.9)
Lymphoedema	4 (3.6)	7 (6.8)

Subjects are only counted once per treatment for each row.
Excludes events that occurred prior to dosing or after subjects crossed over from standard-of-care to Sunitinib.
MedDRA (v14.0) coding dictionary applied.
MedDRA (v14.0) = Medical Dictionary for Regulatory Activities (version 14.0); n = number of subjects with adverse events.

Treatment-Emergent Treatment-Related Adverse Events: The treatment-related TEAEs are summarized in Table 13. The most common treatment-related AEs in the sunitinib arm were diarrhea (42.7%), nausea (40.0%), fatigue (30.9%), neutropenia (30.0%), and asthenia (27.3%). The most common treatment-related AEs in the standard-of-care regimen arm were nausea (31.1%), palmar-plantar erythrodysesthesia syndrome (27.2%), fatigue (24.3%), neutropenia (22.3%), and diarrhea (21.4%).

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

Preferred Term	Sunitinib (N=110)		Standard-of-Care (N=103)	
	Number (%) Subjects	Number of Events	Number (%) Subjects	Number of Events
Any treatment-related adverse event	106 (96.4)	1334	90 (87.4)	650
Nausea	44 (40.0)	77	32 (31.1)	58
Diarrhea	47 (42.7)	108	22 (21.4)	43
Fatigue	34 (30.9)	52	25 (24.3)	43
Neutropenia	33 (30.0)	94	23 (22.3)	55
Palmar-plantar erythrodysesthesia syndrome	26 (23.6)	50	28 (27.2)	75
Mucosal inflammation	29 (26.4)	42	16 (15.5)	22
Asthenia	30 (27.3)	53	12 (11.7)	23
Thrombocytopenia	26 (23.6)	62	7 (6.8)	14
Vomiting	18 (16.4)	44	13 (12.6)	15
Decreased appetite	22 (20.0)	25	8 (7.8)	10
Leukopenia	22 (20.0)	63	8 (7.8)	30
Anemia	14 (12.7)	21	15 (14.6)	28
Dysgeusia	22 (20.0)	33	5 (4.9)	6
Hypertension	24 (21.8)	49	1 (1.0)	1
Stomatitis	14 (12.7)	17	6 (5.8)	12
Dyspepsia	14 (12.7)	18	4 (3.9)	4
Headache	11 (10.0)	14	7 (6.8)	8
Skin discoloration	18 (16.4)	19	0 (0.0)	0
Constipation	9 (8.2)	9	8 (7.8)	9
Pain in extremity	14 (12.7)	23	2 (1.9)	2
Platelet count decreased	14 (12.7)	39	1 (1.0)	1
Hypothyroidism	14 (12.7)	17	0 (0.0)	0
Epistaxis	10 (9.1)	16	3 (2.9)	3
Abdominal pain upper	8 (7.3)	9	4 (3.9)	4
Dyspnea	10 (9.1)	13	2 (1.9)	2
Pyrexia	2 (1.8)	2	10 (9.7)	13

Adverse events and serious adverse events are not separated out.
MedDRA (v14.0) coding dictionary applied.
MedDRA (v14.0) = Medical Dictionary for Regulatory Activities (version 14.0); N = number of subjects in each treatment arm; n = number of subjects with adverse events.

Severity of Adverse Events as per CTCAE Criteria: Six (5.5%) versus 13 subjects (12.6%) on sunitinib versus standard-of-care, respectively, experienced AEs with a maximum severity of Grade 4, and 53 (48.2%) versus 34 subjects (33.0%) experienced AEs with a maximum severity of Grade 3. Grade 3 or 4 AEs experienced by greater than 5% subjects on sunitinib included neutropenia, thrombocytopenia, leucopenia, asthenia, disease progression, dyspnea, and fatigue. Most notably, Grade 3 or 4 neutropenia was reported in 20.9% versus 11.7% subjects on sunitinib versus standard-of-care, respectively. The Grade 3 or 4 AEs experienced by greater than 5% subjects on standard-of-care were neutropenia (10.7%) and palmar-plantar erythrodysesthesia syndrome (5.8%).

Treatment-Emergent Serious Adverse Events (All Causality): All SAEs, including deaths, are summarized in Table 14.

Table 14. Treatment-Emergent Serious Adverse Events - All Causality (As-Treated Population)

System Organ Class MedDRA Preferred Term	Sunitinib (N=110)		Standard–of-Care (N=103)		Total (N=213)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any serious adverse event	40 (36.4)	107	21 (20.4)	45	61 (28.6)	152
Blood and lymphatic system disorders	6 (5.5)	14	3 (2.9)	3	9 (4.2)	17
Anaemia	3 (2.7)	3	0 (0.0)	0	3 (1.4)	3
Disseminated intravascular coagulation	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Febrile neutropenia	2 (1.8)	2	2 (1.9)	2	4 (1.9)	4
Leukopenia	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Pancytopenia	1 (0.9)	6	0 (0.0)	0	1 (0.5)	6
Thrombocytopenia	2 (1.8)	2	0 (0.0)	0	2 (0.9)	2
Cardiac disorders	4 (3.6)	6	2 (1.9)	3	6 (2.8)	9
Atrial fibrillation	1 (0.9)	1	1 (1.0)	1	2 (0.9)	2
Cardiac arrest	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Cardiac failure	1 (0.9)	2	0 (0.0)	0	1 (0.5)	2
Cardiopulmonary failure	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Myocardial ischaemia	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Supraventricular tachycardia	0 (0.0)	0	1 (1.0)	2	1 (0.5)	2
Gastrointestinal disorders	10 (9.1)	14	4 (3.9)	7	14 (6.6)	21
Abdominal pain	4 (3.6)	4	1 (1.0)	1	5 (2.3)	5
Abdominal pain lower	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Abdominal pain upper	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Ascites	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Constipation	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Faeces discoloured	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Gastritis	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Mouth ulceration	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Nausea	1 (0.9)	1	2 (1.9)	2	3 (1.4)	3
Pancreatitis	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Vomiting	2 (1.8)	2	3 (2.9)	3	5 (2.3)	5
General disorders and administration site conditions	18 (16.4)	24	5 (4.9)	6	23 (10.8)	30
Asthenia	4 (3.6)	4	1 (1.0)	1	5 (2.3)	5
Axillary pain	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Disease progression	16 (14.5)	16	3 (2.9)	3	19 (8.9)	19
Fatigue	2 (1.8)	2	0 (0.0)	0	2 (0.9)	2
Hyperthermia	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Mucosal inflammation	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Pyrexia	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Hepatobiliary disorders	1 (0.9)	2	1 (1.0)	1	2 (0.9)	3
Acute hepatic failure	1 (0.9)	2	0 (0.0)	0	1 (0.5)	2
Liver disorder	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Infections and infestations	3 (2.7)	3	3 (2.9)	4	6 (2.8)	7
Bronchopneumonia	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Neutropenic sepsis	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Pyelonephritis	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Staphylococcal infection	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Urinary tract infection	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Urosepsis	1 (0.9)	1	1 (1.0)	1	2 (0.9)	2
Injury, poisoning and procedural complications	1 (0.9)	1	1 (1.0)	1	2 (0.9)	2
Concussion	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Femur fracture	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Investigations	1 (0.9)	3	0 (0.0)	0	1 (0.5)	3

Table 14. Treatment-Emergent Serious Adverse Events - All Causality (As-Treated Population)

System Organ Class MedDRA Preferred Term	Sunitinib (N=110)		Standard–of-Care (N=103)		Total (N=213)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Blood bilirubin increased	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Blood creatinine increased	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Lipase increased	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Metabolism and nutrition disorders	1 (0.9)	1	1 (1.0)	1	2 (0.9)	2
Failure to thrive	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Hyperglycaemia	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Musculoskeletal and connective tissue disorders	2 (1.8)	2	1 (1.0)	1	3 (1.4)	3
Back pain	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Bone pain	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Neck pain	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.8)	2	0 (0.0)	0	2 (0.9)	2
Lymphangiosis carcinomatosa	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Malignant pleural effusion	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Nervous system disorders	3 (2.7)	3	3 (2.9)	3	6 (2.8)	6
Headache	2 (1.8)	2	0 (0.0)	0	2 (0.9)	2
Ischaemic stroke	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Migraine	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Presyncope	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Transient ischaemic attack	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Psychiatric disorders	2 (1.8)	4	1 (1.0)	1	3 (1.4)	5
Agitation	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Confusional state	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Depression	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Hallucination, visual	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Suicide attempt	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Renal and urinary disorders	1 (0.9)	1	1 (1.0)	1	2 (0.9)	2
Cystitis haemorrhagic	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Hydronephrosis	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Reproductive system and breast disorders	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Breast pain	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Respiratory, thoracic and mediastinal disorders	12 (10.9)	21	6 (5.8)	10	18 (8.5)	31
Asthma	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Dyspnoea	5 (4.5)	5	1 (1.0)	2	6 (2.8)	7
Dyspnoea exertional	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Haemoptysis	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Hydrothorax	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1
Hypoxia	1 (0.9)	1	1 (1.0)	3	2 (0.9)	4
Lung infiltration	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Pleural effusion	3 (2.7)	3	3 (2.9)	3	6 (2.8)	6
Pleuritic pain	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Pneumothorax	3 (2.7)	4	0 (0.0)	0	3 (1.4)	4
Pulmonary embolism	3 (2.7)	4	0 (0.0)	0	3 (1.4)	4
Surgical and medical procedures	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Ureteral stent insertion	1 (0.9)	1	0 (0.0)	0	1 (0.5)	1
Vascular disorders	4 (3.6)	4	3 (2.9)	3	7 (3.3)	7
Deep vein thrombosis	0 (0.0)	0	1 (1.0)	1	1 (0.5)	1

Table 14. Treatment-Emergent Serious Adverse Events - All Causality (As-Treated Population)

System Organ Class MedDRA Preferred Term	Sunitinib (N=110)		Standard–of-Care (N=103)		Total (N=213)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Hypertension	2 (1.8)	2	0 (0.0)	0	2 (0.9)	2
Hypotension	1 (0.9)	1	1 (1.0)	1	2 (0.9)	2
Thrombosis	1 (0.9)	1	1 (1.0)	1	2 (0.9)	2

% = (n/N) × 100
Standard-of-care (capecitabine, vinorelbine (oral or intravenous infusion), docetaxel, gemcitabine, or paclitaxel 175—200 or 80—90).
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment arm.

Treatment-Emergent Treatment-Related Serious Adverse Events: Table 15 presents a summary of treatment-related SAEs reported during the study. The only treatment-related SAE that was experienced by ≥2% subjects on sunitinib was asthenia.

Table 15. Treatment-Emergent Treatment-Related Serious Adverse Events (As-Treated Population)

Preferred Term	Sunitinib (N=110)		Standard-of-Care (N=103)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any treatment-related serious adverse event	16 (14.5)	33	5 (4.9)	7
Febrile neutropenia	2 (1.8)	2	2 (1.9)	2
Thrombocytopenia	2 (1.8)	2	0 (0.0)	0
Asthenia	3 (2.7)	3	0 (0.0)	0
Hypertension	2 (1.8)	2	0 (0.0)	0
Anemia	2 (1.8)	2	0 (0.0)	0
Vomiting	1 (0.9)	1	1 (1.0)	1
Pancytopenia	1 (0.9)	6	0 (0.0)	0
Cardiac failure	1 (0.9)	2	0 (0.0)	0
Abdominal pain lower	1 (0.9)	1	0 (0.0)	0
Feces discolored	1 (0.9)	1	0 (0.0)	0
Mouth ulceration	1 (0.9)	1	0 (0.0)	0
Fatigue	1 (0.9)	1	0 (0.0)	0
Mucosal inflammation	0 (0.0)	0	1 (1.0)	1
Acute hepatic failure	1 (0.9)	2	0 (0.0)	0
Neutropenic sepsis	0 (0.0)	0	1 (1.0)	1
Blood bilirubin increased	1 (0.9)	1	0 (0.0)	0
Blood creatine increased	1 (0.9)	1	0 (0.0)	0
Lipase increased	1 (0.9)	1	0 (0.0)	0
Failure to thrive	1 (0.9)	1	0 (0.0)	0
Headache	1 (0.9)	1	0 (0.0)	0
Migraine	1 (0.9)	1	0 (0.0)	0
Asthma	1 (0.9)	1	0 (0.0)	0
Cystitis hemorrhagic	0 (0.0)	0	1 (1.0)	1
Thrombosis	0 (0.0)	0	1 (1.0)	1

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

Permanent Discontinuations due to Adverse Events: AEs that led to discontinuation of study drug are summarized for sunitinib and the other study treatments in standard-of-care regimen in Table 16. AEs that led to discontinuation for more than 1 subject were disease progression

(8 subjects, 7.3%, versus 2 subjects, 1.0%, on sunitinib versus standard-of-care regimen, respectively), dyspnea (6, 5.5%, versus 0 subjects), asthenia (3, 2.7%, versus 0 subjects), fatigue (3, 2.7%, versus 1, 1.0%, subjects), palmar-plantar erythrodysesthesia syndrome (3, 2.7%, versus 0 subjects), oral pain (2, 1.8%, versus 0 subjects), thrombocytopenia (2, 1.8%, versus 0 subjects), and vomiting (1, 0.9%, versus 1, 1.0%, subjects).

Table 16. Summary of Adverse Events Leading to Discontinuation by Study Treatment (As-Treated Population)

Preferred Term	Treatment					
	Sunitinib (N=110) n (%)	Capecitabine (N=53)[a] n (%)	Vinorelbine (N=11)[a] n (%)	Docetaxel (N=6)[a] n (%)	Gemcitabine (N=32)[a] n (%)	Paclitaxel (N=4)[a] n (%)
Any adverse event leading to discontinuation	35 (31.8)	3 (2.9)	0 (0.0)	0 (0.0)	3 (2.9)	0 (0.0)
Disease progression	8 (7.3)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Dyspnea	6 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	3 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	3 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	3 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oral pain	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute hepatic failure	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bone pain	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast pain	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry mouth	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysgeusia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failure to thrive	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile neutropenia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperbilirubinemia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoesthesia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Jaundice	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphangiosis carcinomatosa	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mouth ulceration	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischemia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in extremity	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in jaw	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancytopenia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumothorax	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombosis	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tongue disorder	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Confusional state	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypercalcemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Paraesthesia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pleural effusion	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AT = as-treated; N = number of subjects in each group; n = number of subjects with adverse events.
a. The total number of subjects in the AT population (106) is used for determining percents.

Temporary Discontinuations or Dose Reduction due to Adverse Events: The most common (≥5 subjects on either arm) AEs leading to an interruption or reduction in dosing are summarized by treatment in Table 17. Overall, 81 (73.6%) versus 44 subjects (42.7%)

experienced AEs that led to a dose delay or reduction. On sunitinib these events included myelosuppressive (neutropenia, thrombocytopenia, platelet count decreased, and leucopenia), gastrointestinal (nausea, vomiting, diarrhea, and mucosal inflammation), cutaneous (palmar-plantar erythrodysesthesia syndrome), cardiovascular (hypertension), and constitutional (fatigue and asthenia) disorders. The AE most often leading to delays or reductions of standard-of-care was neutropenia.

Table 17. Summary of Adverse Events Leading to Temporary Discontinuation or Dose Reduction on Either Arm (AT Population)

		Standard-of-Care (N=103)[a]			
	Sunitinib (N=110) n (%)	**Capecitabine (N=53) n (%)**	**Vinorelbine (N=11) n (%)**	**Docetaxel (N=6) n (%)**	**Gemcitabine (N=32) n (%)**
Any dose delay or change due to adverse events	82 (74.5)	21 (20.4)	6 (5.8)	3 (2.9)	17 (16.5)
Neutropenia	23 (20.9)	1 (1.0)	4 (3.9)	0 (0.0)	8 (7.8)
Thrombocytopenia	14 (12.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)
Nausea	12 (10.9)	4 (3.9)	1 (1.0)	0 (0.0)	2 (1.9)
Platelet count decreased	11 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Palmar-plantar erythrodysesthesia syndrome	11 (10.0)	12 (11.7)	0 (0.0)	1 (1.0)	0 (0.0)
Hypertension	11 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	11 (10.0)	2 (1.9)	1 (1.0)	0 (0.0)	1 (1.0)
Leukopenia	9 (8.2)	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)
Diarrhea	9 (8.2)	5 (4.9)	0 (0.0)	0 (0.0)	1 (1.0)
Fatigue	9 (8.2)	4 (3.9)	0 (0.0)	0 (0.0)	1 (1.0)
Mucosal inflammation	7 (6.4)	2 (1.9)	0 (0.0)	1 (1.0)	0 (0.0)
Asthenia	7 (6.4)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)

Data not available for paclitaxel arm.
AT = as-treated; N = number of subjects in each treatment group; n = number of subjects with adverse events.
a. The total number of subjects on standard-of-care was used for percent. Three subjects (2.9%; 2 due to febrile neutropenia and 1 due to mucosal inflammation) on docetaxel and no subjects on paclitaxel had adverse events with an action of dose delay or change.

Deaths: Table 18 presents a summary of deaths during the study; this summary includes all subjects who died, regardless of when the death occurred after the last dose of study drug. Twenty-three (20.9%) versus 4 subjects (3.9%) died on treatment or within 28 days of their last dose of study medication. Twenty-one (91.3% on-study deaths) versus 4 deaths (100.0% on-study deaths) on study or within 28 days of treatment were due to progressive disease or to events considered as related to the underlying disease. One subject treated with sunitinib died during the study; this event was determined to be pneumothorax-related. One death occurred in a subject treated with sunitinib and was considered treatment-related.

Table 18. Summary of Deaths (As-Treated Population)

Treatment Group	Serial Number	Cause of Death	Days Since Last Dose	Relationship
Sunitinib	1	Progression of disease	9	Study disease
	2	Disseminated intravascular coagulation	8	Study disease
	3	Disease progression	8	Study disease
	4	Disease progression	2	Study disease
	5	Progression of disease	4	Study disease
	6	Progressive disease	22	Study disease
	7	Disease progression	23	Study disease
	8	Acute hepatic failure	13	Study drug
	9	Disease progression	13	Study disease
	10	Disease progression	14	Study disease
	11	Dyspnea	5	Study disease
	12	Disease progression	5	Study disease
	13	Disease progression	2	Study disease
	14	Carcinomatous lymphangitis = disease progression	20	Study disease
	15	Disease progression	22	Study disease
	16	Cardiac arrest	18	Study disease
	17	Pneumothorax	9	Other illness
	18	Disease progression	25	Study disease
	19	Fatal disease progression	5	Study disease
	20	Disease progression	2	Study disease
	21	Disease progression (fatal)	6	Study disease
	22	Disease progression	15	Study disease
	23	Fatal disease progression	28	Study disease
Standard-of-care	24	Hypoxia-disease progression	25	Study disease
	25	Disease progression	5	Study disease
	26	Disease progression	19	Study disease
	27	Disease progression	21	Study disease

Other Safety-Related Findings: Results for most hematology tests were highly variable. In general, there was a decline over time for absolute neutrophil count (with mean declines from Baseline up to 2.8×10^9/L), though the decrease was more pronounced on sunitinib (4.6 to 2.3 and 4.4 to 3.5×10^9/L on sunitinib versus standard-of-care, respectively). On sunitinib there was also a decline in monocytes (0.5 to 0.2 versus 0.5 to 0.5×10^9/L on standard-of-care), and platelets (276.9 to 155.0 versus 270.3 to 298.2×10^9/L). For all these measures, there did not appear to be a continued mean change during additional cycles beyond Cycle 1.

Results for most serum chemistry tests were highly variable. On sunitinib, there was a general increase from Baseline in liver function tests (alanine transaminase, aspartate transaminase, and alkaline phosphatase). There was little evidence of an increased frequency of shifts from Grade 2 or less to Grade 3 or greater for any serum chemistry variable.

There were no systematic changes in vital signs from Baseline. In general, for mean systolic blood pressure (BP), there appeared to be a modest increase from Baseline on sunitinib (up to 9.8 mmHg). Diastolic BP increased up to 7.5 mmHg on sunitinib.

There was no evidence of increased toxicity on sunitinib, relative to standard-of-care, with regard to cardiac function or thyroid function.

CONCLUSIONS:

- Sunitinib was not more effective than standard-of-care in subjects with previously treated, triple receptor negative (estrogen and progesterone receptors and HER2/neu), metastatic or locally recurrent BC, with a median PFS of 2.0 versus 2.7 months, respectively.

- The other efficacy endpoints OS, DR, and ORR were not improved with sunitinib.

- The steady state concentrations for sunitinib and its active metabolite were reached by Day 15 of Cycle 1 and did not show additional accumulations across different cycles.

- In comparison to Baseline levels, plasma VEGF-A levels were consistently elevated while plasma levels of VEGF-C, sVEGFR3 and sKIT were consistently reduced in response to sunitinib treatment. Similar changes in levels of these soluble proteins were not seen in the standard-of-care arm.

- The incidence of AEs fatigue, hand-foot syndrome, thrombocytopenia, and hypertension appeared to be higher in subjects with higher Total drug trough concentrations as compared to those with lower Total drug trough concentrations. However, there appeared to be no consistent trends or relationships between efficacy endpoints ORR, PFS, and OS with Total drug trough concentrations.

- In general the frequency of AEs, including SAEs, was higher on sunitinib than on standard-of-care. However, the AE and safety profiles of sunitinib were similar to what has been reported previously, including in the package insert.