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

PROTOCOL NO.: A6181100

PROTOCOL TITLE: Exploratory Evaluation of a Sequential Administration of Docetaxel and SU011248 in Women With Advanced Breast Cancer

Study Centers: 3 centers took part in the study and enrolled subjects: 1 each in Italy, Belgium, and Sweden.

Study Initiation and Final Completion Dates: 25 July 2006 to 16 February 2009

Phase of Development: Phase 1b

Study Objectives:

Primary Objective: To characterize the pharmacokinetics (PK) of docetaxel and SU011248 (sunitinib) (and its metabolite, SU012662) according to the schedule adopted in the trial.

Secondary Objectives:

- To assess the tolerability of the combination of sunitinib given at 37.5 mg/day (Schedule 2/1) with docetaxel administered at 75 mg/m^2 every 3 weeks in ABC subjects who had relapsed after an anthracycline-based adjuvant regimen;

- To assess preliminary anti-tumor activity of the combination sunitinib/docetaxel**.**

METHODS

Study Design: This was an exploratory clinical trial evaluating the PK and the tolerability, as well as preliminary antitumor activity, of a sequential administration of docetaxel and sunitinib in subjects with unresectable locally recurrent or metastatic breast cancer. Eligible subjects had human epidermal growth factor receptor 2 (HER-2) negative disease that had relapsed after anthracycline-based chemotherapy in the adjuvant treatment setting. Subjects who had received a taxane as a component of their adjuvant anthracycline-based regimen might have entered the study only if ≥12 months had elapsed since completion of their adjuvant chemotherapy in order to avoid inclusion of subjects whose disease was refractory or resistant to taxane. Subjects eligible for enrollment had not received treatment for advanced disease other than hormonal therapies and were not candidates for curative therapies.

The proposed combination sunitinib plus docetaxel was planned to be studied in a total of 20 subjects. The goal was to have no less than 12 subjects evaluable for PK analysis. Subjects evaluable for PK had a full PK profile in Cycles 1 and 2 for sunitinib and docetaxel. Subjects not evaluable for PK were to be replaced. The trial began with the enrollment of 6 subjects. Since neither unusual toxicity nor drug-drug interaction was observed, subject accrual was continued, and the cohort was completed.

Treatment on study was administered in 3week cycles. Docetaxel was administered via intravenous (IV) infusion on Day 1 at a starting dose of 75 mg/m^2 every 3 weeks. Sunitinib was administered at 37.5 mg orally once daily for 2 weeks starting from Day 2 (Day 3 of Cycle 2 for subjects included in the PK study) every 3 weeks (2 weeks on, then 1 week off; Schedule 2/1). To further attempt to optimize the dosing schedule of this combination, docetaxel was administered on Day 1 and sunitinib dosing began on Day 2 in the present study. At the time of study design, this sequential administration was chosen to lower the possibility of any interaction between the 2 drugs and to minimize any overlapping toxicities that might occur between IV administered docetaxel and orally administered sunitinib.

In the first 12 subjects who were evaluable for PK, the PK study was conducted on Day 1 (docetaxel) and Day 2 (sunitinib) of Cycle 1 and Cycle 2. In Cycle 1, sunitinib was administered on Day 2 and ended on Day 15. In Cycle 2, sunitinib was administered on Day 3 and ended on Day 16. Therefore, Cycle 3 started on Day 23 to allow a washout period of 6 days before docetaxel dosing. The PK study in Cycles 1 and 2 allowed the comparison of the docetaxel PK curves with this schedule of administration and sunitinib given a day and 2 days after docetaxel. In the remaining subjects, sunitinib was always administered on Day 2.

Both drugs may have had dose interruption and/or dose reduction based on tolerability in Cycles ≥2, ie, docetaxel from 75 to 60 mg/m^2 and sunitinib from 37.5 to 25 mg/day. In subsequent cycles, intrapatient re-escalation of both drugs back to the previous dose level was permitted at the discretion of the Investigator in case of minimal treatment-related effects in the previous cycle. Subjects completing the first 2 cycles of treatment with minimal toxicities might have dose escalated sunitinib in the third cycle to 50 mg/day.

Since docetaxel is myelotoxic, the use of hematopoietic growth factors was permitted for treatment of Grade 4 neutropenia or febrile neutropenia in the first cycle and might have been used prophylactically after the first cycle.

Study treatment continued until progressive disease (PD) was documented according to the Response Evaluation Criteria in Solid Tumors (RECIST), occurrence of unacceptable toxicity, or withdrawal of subject consent. If the study treatment was discontinued for reasons other than PD, these subjects were followed up, and tumor assessment continued until PD or until the initiation of a subsequent anticancer therapy in absence of documented PD, or until death, whichever occurred first.

Docetaxel was administered until it was in the best interest of the subject to discontinue, as judged by the Investigator. At the time of permanent docetaxel discontinuation for reasons other than PD, treatment with sunitinib may have continued until PD occurred, if this was

clinically indicated, or a new anticancer treatment was initiated as per the Investigator's clinical judgment. In this case, sunitinib might have been administered on a continuous daily dosing schedule, with the provision of at least 1-week treatment interruptions as needed, and/or dose reduction, depending on individual tolerability. In addition, subjects experiencing good tolerability to sunitinib may have had their dose escalated to 50 mg.

If PD occurred during treatment with the combination of sunitinib plus docetaxel, then both drugs were discontinued, and the Investigator decided about a more suitable therapeutic option.

Table 1. Schedule of Assessments

Protocol Activities	Screening	Study Treatment[a]							Post-Treatment		
		Cycle 1[b]				Cycle 2[c]			End of Tx/ Withdrawal[f]	28-day Post Tx[g]	Follow-Up[h]
	≤21 Days Prior to Dosing	Day 1[d]	Day 2	Day 7-10 (-2/+2)[e]	Day 15 (-2/+1)	Day 1	Day 3	Day 7-10 (-2/+2)			
Baseline documentation											
Informed consent[i]	X										
Medical/oncological history[j]	X										
Physical examination[k]	X	X				X			X	(X)	
Baseline signs/symptoms		X C1									
Laboratory studies											
Hematology	X	X		X	X	X		X	X	(X)	
Blood chemistry	X	X				X			X	(X)	
Pregnancy test (as appropriate)[l]	X										
12-lead ECG[m]	X				X				X		
MUGA or ECHO[n]	X								X		
Study registration[o]	X										
Docetaxel infusion		X									
Sunitinib capsule dosing[p]			X→ Days 2→15	X→	X		X→ Days C2 3→16	X→			
Tumor assessments											
CT or MRI scans[q]	X					X Every 6 weeks from C2			X		X
Other clinical assessments											
Adverse events[r]	X	X	X	X	X	X	X	X	X	X	
Study drug compliance[s]						X from C2			X		
Concomitant medications/treatments[t]	X	X	X	X	X	X	X	X	X	X	
Post sunitinib/docetaxel anticancer therapy										(X)	X
Special laboratory studies											

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	≤21 Days Prior to Dosing	Day 1[d]	Day 2	Day 7-10 (-2/+2)[e]	Day 15 (-2/+1)	Day 1	Day 3	Day 7-10 (-2/+2)			
Docetaxel PK evaluation[u]		X Profile				X Profile					
Sunitinib PK evaluation[u]			X Profile				X Profile				
Trough sunitinib concentration (C_{trough})[v]					X	X					

( ) – if applicable

AEs = adverse events; C1 = Cycle 1; C2 = Cycle 2; CR = complete response; Ctrough = trough concentration; CRF = case report form; CT = computerized tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; PK = pharmacokinetics; PR = partial response; PD = progressive disease; Tx = treatment.

a. All assessments were performed prior to dosing with docetaxel or sunitinib unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings.
Each cycle lasted 3 weeks with the exception of Cycle 2, which lasted until Day 23 to allow for PK profile of docetaxel without any possible effect of sunitinib. This occurred only in women participating in the PK study. A maximum of 2-week delay due to toxicities was allowed for docetaxel, and maximum acceptable interval between last and next sunitinib administrations due to persistent toxicity attributable to sunitinib or delay in docetaxel administration was 3 weeks. Longer delays prompted discussion with the Sponsor. Subjects discontinuing treatment with docetaxel and continuing to receive sunitinib may have had subsequent clinic visits every 6 weeks (instead of 3 weeks), which included tumor assessment, until PD.

b. Only during the first cycle, hematology was checked and reported in the CRF every week as well as the AEs.

c. Only for women participating in the PK study, in Cycle 2 sunitinib was dosed on Day 3, and ended on Day 16. Cycle 3 started on Day 23.

d. Hematology, blood chemistry, and physical examination were not required if acceptable screening assessment was performed within 3 days prior to the start of treatment with docetaxel.

e. The nadir of hematologic parameters after docetaxel administration must have been captured and reported in the CRF.

f. These assessments were obtained if not completed during the last week on study with the following exceptions: during the last 6 weeks on study for radiological tumor assessments; during the last 3 weeks on study for ECG; during the last 3 weeks on study for ECHO or MUGA scan.

g. Subjects who discontinued study drugs were evaluated up to 28 days after last dose of study treatment. Adverse events were followed up until all serious or study drug-related toxicities resolved or were determined to be “chronic” or “stable”, whichever was later.

h. Subjects discontinuing both sunitinib and docetaxel for reasons other than PD may have had subsequent clinic visits every 6 weeks, which included tumor assessment, until PD or a subsequent anticancer therapy. A tumor assessment was mandatory before initiating a new antitumor therapy.

i. Must have been obtained prior to undergoing any study specific procedure and may have occurred prior to the 21-day screening period.

j. Included information on prior antitumor regimens (dose and duration of administration) and relapse date.

k. Examination of major body systems, ECOG performance status, body weight, height (at Screening visit only), and vital signs (temperature, blood pressure, heart rate, respiratory rate).

l. The test was performed at least 3 days before study treatment.

m. Three consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine the mean QTc interval. The ECGs were performed in the morning and

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Protocol Activities	Screening	Study Treatment[a]							Post-Treatment		
		Cycle 1[b]				Cycle 2[c]			End of Tx/ Withdrawal[f]	28-day Post Tx[g]	Follow-Up[h]
	≤21 Days Prior to Dosing	Day 1[d]	Day 2	Day 7-10 (-2/+2)[e]	Day 15 (-2/+1)	Day 1	Day 3	Day 7-10 (-2/+2)			

time matched (± 1 hour). If the mean QTc interval was prolonged (>500 msec), then the ECGs were re-read by a cardiologist at the site for confirmation. ECG was done on Day 15 of Cycle 1. Additional ECGs may have been performed as clinically indicated.

n. At Baseline and at the End of Treatment. Additional assessments may have been performed as clinically indicated. Acceptable time window for performing MUGA or ECHO was ±7 days.

o. Subjects were registered with the Sponsor prior to being considered enrolled on the study.

p. Sunitinib was administered from Day 2 to Day 15 (2 weeks) of every cycle followed by a 1-week off-treatment period. Sunitinib was taken once daily, in the morning, without regard to meals.

q. CT or MRI scan of known areas of disease was performed at Screening. During the study, tumor imaging studies were repeated at 6-week intervals to follow known areas of disease and to other areas whenever disease progression was suspected. In case of a PR or CR confirmatory tumor assessment was performed 4 weeks after initial documentation of response. Allowable window for tumor imaging studies was +/- 7 days.

r. Subjects were followed for adverse events from the first day of study treatment until at least 28 days after the last dose of study treatment, 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 that the subject provided informed consent as described in the protocol.

s. The sunitinib bottle(s) including any unused capsules were returned to the clinic for drug accountability.

t. Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.

u. Blood samples (2 mL for sunitinib and 5 mL for docetaxel) for PK profiles were collected during Cycles 1 and 2. PK profile for docetaxel:
Cycle 1 Day 1: predose, 0.5, 1 (just before infusion ends), 1.5, 2, 3, 4, 6, and 8 hours postdose; Day 2: 24 and 32 hours postdose; Day 3: 48 hours postdose.
Cycle 2 Day 1: predose, 0.5, 1 (just before infusion ends), 1.5, 2, 3, 4, 6, and 8 hours postdose; Day 2: 24 and 32 hours postdose; Day 3: 48 hours postdose.
PK profile for sunitinib: Cycle 1 Day 2: predose, 1, 2, 4, 6, 8, and 12 hours postdose; Day 3: 24 hours postdose; Cycle 2 Day 3: predose, 1, 2, 4, 6, 8, and 12 hours postdose; Day 4: 24 hours postdose.

v. Blood samples (2 mL) at predose on Day 15 (-2/+1) of C 1 (all subjects) and at predocetaxel on Day 1 of Cycle 2 (subjects participating in the PK study). All trough samples for sunitinib and SU012662 were collected approximately 24 hours after the last dose.

Number of Subjects (Planned and Analyzed): The planned number of subjects was 20. A total of 22 subjects entered (10 in Italy, 6 each in Belgium and Sweden) and were treated in this study.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were females who were 18 years of age or older and had histologically or cytologically proven diagnosis of breast cancer with evidence of unresectable locally recurrent or metastatic disease. Subjects must had to be a candidate for the treatment of breast cancer. Subjects with HER-2 positive breast cancer and inflammatory breast cancer, and who were on prior chemotherapy in the advanced disease setting were excluded from the study.

Study Treatment:

Docetaxel: Docetaxel was administered via IV infusion at the starting dose of 75 mg/m^2 every 3 weeks. The total docetaxel dose was administered on Day 1 of each cycle as a 1-hour IV infusion. The dose of docetaxel was calculated using body surface area (mg/m^2). Docetaxel is commercially available; locally obtained commercial supplies of docetaxel were used.

Sunitinib: Sunitinib was administered orally for 2 weeks every 3 weeks (2 weeks on, then 1 week off; Schedule 2/1), starting on Day 2 (Day 3 in Cycle 2 only for those subjects who were included in the PK study). The sunitinib starting dose was 37.5 mg daily. Sunitinib L-malate salt was supplied 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.

Efficacy, Pharmacokinetic and Safety Endpoints:

Primary Endpoint:

- PK parameters of docetaxel, sunitinib and its active metabolite SU012662.

Secondary Endpoints:

- Type, incidence, severity, timing, seriousness, and relatedness of adverse events (AEs), and laboratory abnormalities;
- Progression-free survival (PFS);
- Objective response rate (ORR);
- Clinical benefit rate (CBR, percent of subjects experiencing complete response [CR], partial response [PR] or stable disease [SD] for at least 24 weeks);
- Duration of response (DR).

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead electrocardiograms (ECGs), AEs, and safety laboratory tests.

Statistical Methods:

Analysis Sets:

Intent-to-Treat (ITT) Population: This population included all subjects enrolled in the study who received at least 1 dose of study medication (sunitinib or docetaxel). This was the primary population for evaluating all efficacy endpoints as well as subject characteristics. Subjects who did not have a baseline assessment of disease were excluded from the analyses of PFS, ORR, and DR.

Evaluable Set for Pharmacokinetic Analyses: The evaluable set for the purpose of PK evaluation was the ITT population of subjects who had completed sampling for PK profiles for both sunitinib and docetaxel.

Safety Population: The safety population included all subjects enrolled in the study who received at least 1 dose of study medication (sunitinib or docetaxel).

Pharmacokinetics: Analysis of C_{trough} of sunitinib, SU012662 and total drug (sunitinib+SU12662) were summarized for each subject. Plasma sunitinib/SU012662 and docetaxel concentrations were measured using validated methods.

Efficacy (Antitumor Activity): Due to the exploratory nature of this study, no imputation of missing data was done. No confirmatory inferential analyses were planned. The set of subjects to be analyzed for objective response was all subjects with measurable disease at baseline, receiving at least 1 dose of sunitinib with a response assessment made by the Investigator. The number and percentage of subjects achieving objective response (CR or PR) were summarized along with the corresponding 95% exact confidence interval (CI), as well as the number and percentage of subjects achieving CBR (CR, PR, or SD for at least 24 weeks). PFS and DR were summarized using the Kaplan-Meier method. Duration of response was calculated only for those subjects with an objective response (PR or CR).

Safety: Safety data were analyzed using descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is provided in Table 2. A total of 22 subjects entered and were treated in this study. All 22 subjects discontinued the study. The most common reason for discontinuation from the study was disease progression, defined as either lack of efficacy (14 subjects) or disease progression (1 subject). Other reasons for discontinuation included AE (1 subject), other (3 subjects), and no longer willing to participate in study (2 subjects).

Table 2. Summary of Subject Disposition

Number of Subjects	Docetaxel + Sunitinib
Assigned to study treatment:	22
Treated	22
Completed	1[a]
Discontinued	21
Related to study drug	15
Adverse event	1[b]
Lack of efficacy	14
Not related to study drug	6
Other[c]	4
Subject no longer willing to participate in study	2

CRF = case report form; EOS = end of study.

a. EOS for 1 subject was indicated as completed in the CRF although this was not a per protocol reason for EOS. Therefore, the Investigator declared that the per protocol reason for EOS was subject withdrawn during active treatment period.

b. One subject discontinued due to an adverse event of cerebral hemorrhage.

c. Other reasons for discontinuation included: administration of hormonal therapy based on receptor status of the tumor, subject's request (2 subjects), disease progression (ie, lack of efficacy).

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

Table 3. Data Sets Analyzed

Number of Subjects	Docetaxel + Sunitinib
Analyzed for pharmacokinetics	13
Analyzed for efficacy	20
Analyzed for safety	22

A summary of demographic characteristics is provided in Table 4. There were 21 females and 1 male enrolled in this study. The mean age of subjects was 55.3 years (range, 35-72 years).

Table 4. Demographic Characteristics

Number (%) of Subjects	Docetaxel + Sunitinib (N=22)
Gender	
Male	1 (4.5)
Female	21 (95.5)
Age (years)	
<18	0
18-44	3 (13.6)
45-64	13 (59.1)
≥65	6 (27.3)
Mean	55.3
SD	10.0
Range	35-72
Race	
White	21 (95.5)
Black	1 (4.5)
Weight (kg)	
Mean	67.7
SD	12.5
Range	43.0-101.0
Height (cm)	
Mean	160.0
SD	7.8
Range	144.0-177.0

N = number of subjects; SD = standard deviation.

Efficacy and Pharmacokinetic Results:

Pharmacokinetic Results: Plasma PK parameter values and geometric mean (GM) ratios (paired observations) for sunitinib, SU012662, and total drug following administration of sunitinib on Cycle 1, Day 2 and Cycle 2, Day 3 (ie, 1 and 2 days after administration of docetaxel in the cycle) at the dose level studied (ie, sunitinib 37.5 mg on Schedule 2/1 with docetaxel 75 mg/m^2 every 3 weeks) are summarized in Table 5.

The respective GM ratios (ie, Cycle 1, Day 2/Cycle 2, Day 3) of maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24}) were 0.99 and 1.01, respectively, for sunitinib; 0.82 and 0.82, respectively, for SU012662; and 0.98 and 1.00, respectively for total drug.

The mean coefficient of variation (CV%) [median] trough plasma concentration for Cycle 1, Day 15 was 52.1(44%) [51.7] ng/mL for sunitinib, 21.8 (41%) [21.0] ng/mL for SU012662, and 73.8 (39%) [77.3] ng/mL for total drug.

The mean (CV%) [median] trough plasma concentration for Cycle 2, Day 1 was 5.00 (103%) [2.6] ng/mL for sunitinib, 4.88 (72%) [3.4] ng/mL for SU012662, and 9.87 (85%) [7.2] ng/mL for total drug.

Table 5. Summary of Sunitinib, SU012662 and Total Drug PK Parameters Following Administration of Sunitinib on Cycle 1, Day 2 and Cycle 2, Day 3 in Advanced Breast Cancer Subjects

Dose (Sunitinib|Docetaxel) Analyte Parameter	Mean (CV%) [Median] (Cycle 1, Day 2)	Mean (CV%) [Median] (Cycle 2, Day 3)	Geometric Mean Ratio (90% CI) (Cycle 1, Day 2/ Cycle 2, Day 3)
37.5 mg|75 mg/m^2, n=11[a]			
Sunitinib			
T_{max} (hr)	6.0 (4.0, 24.0)[b]	6.0 (2.0, 8.0)[b]	NA
C_{max} (ng/mL)	29.2 (27) [30.0]	29.5 (27) [30.9]	0.99 (0.80-1.22)
AUC_{24} (ng•hr/mL)	486 (27) [469]	480 (27) [483]	1.01 (0.83-1.24)
SU012662			
T_{max} (hr)	6.0 (2.0, 24.0)[b]	6.0 (4.0, 24.0)[b]	NA
C_{max} (ng/mL)	5.07 (47) [5.16]	5.91 (38) [5.07]	0.82 (0.60-1.12)
AUC_{24} (ng•hr/mL)	82.2 (40) [91.8]	96.9 (31) [91.2]	0.82 (0.62-1.07)
Total Drug			
T_{max} (hr)	6.0 (2.0, 24.0)[b]	6.0 (2.0, 8.0)[b]	NA
C_{max} (ng/mL)	34.1 (27) [36.5]	34.7 (26) [34.5]	0.98 (0.80-1.19)
AUC_{24} (ng•hr/mL)	569 (27) [561]	567 (26) [539]	1.00 (0.83-1.21)

Total Drug = sunitinib+SU012662.
AUC_{24} = area under plasma concentration-time curve from time 0 to 24 hours postdose; CI = confidence interval; C_{max} = maximum concentration; CV = coefficient of variation; hr = hours; n = number of subjects; NA = not applicable; PK = pharmacokinetic; T_{max} = time to maximum concentration.
a. Paired observations.
b. Median (minimum-maximum).

Docetaxel Pharmacokinetics: Summary of plasma PK parameter values and GM ratios (paired observations) for docetaxel following its administration on Cycle 1, Day 1 and Cycle 2, Day 1 (ie, 1 and 2 days prior to the first dose of sunitinib in the cycle) after IV infusion of docetaxel over approximately 1 hour at the dose level studied (ie, Sunitinib 37.5 mg on Schedule 2/1 + docetaxel 75 mg/m^2 every 3 weeks) are summarized in Table 6.

The respective geometric mean ratios (ie, Cycle 1, Day 1 / Cycle 2, Day 1) of C_{max}, AUC_{last}, and AUC_{inf} were 0.99, 0.96, and 0.95, respectively. The GM ratio for AUC_{24-48} following administration of docetaxel on Cycle 1, Day 1 and Cycle 2, Day 1 was 1.12, and represents the docetaxel plasma exposure ratio for docetaxel combined with sunitinib over docetaxel alone.

Table 6. Summary of Docetaxel Pharmacokinetic Parameters Following Intravenous Infusion of Docetaxel on Cycle 1, Day 1 and Cycle 2, Day 1

Dose (Sunitinib|Docetaxel) Analyte Parameter	Mean (CV%) [Median] (Cycle 1, Day 1)	Mean (CV%) [Median] (Cycle 2, Day 1)	Geometric Mean Ratio (90% CI) (Cycle 1, Day 1/ Cycle 2, Day 1)
37.5 mg|75 mg/m^2, n=10[a]			
Docetaxel			
T_{max} (hr)	0.7 (0.5, 1.0)[b]	0.8 (0.5, 1.0)[b]	NA
C_{max} (ng/mL)	2932 (31) [2775]	2955 (29) [2960]	0.99 (0.79-1.25)
AUC_{last} (ng•hr/mL)	3160 (21) [3193]	3304 (23) [3256]	0.96 (0.80-1.15)
AUC_{24-48} (ng•hr/mL)	249 (44) [211]	225 (43) [206]	1.12 (0.81-1.56)
AUC_{inf} (ng•hr/mL)	3501 (20) [3384][c]	3690 (21) [3671][c]	0.95 (0.79-1.14)
$t_{½}$ (hr)	23.0 (26) [23.3]	24.9 (43) [21.8]	NA
CL (L/hr)	37.4 (15) [37.0]	37.8 (25) [34.8]	1.00 (0.85-1.18)

AUC_{last} = area under plasma concentration-time curve from time 0 to the last measurable sampling time point; AUC_{inf} = area under plasma concentration-time curve from time 0 to infinity; AUC_{24-48} = area under plasma concentration-time curve from 24 hour to 48 hour postdose; CI = confidence interval; CL = total body clearance; C_{max} = maximum concentration; CV = coefficient of variation; NA = not applicable; n = number of subjects; $t_{½}$ = apparent elimination half-life; T_{max} = time to maximum concentration.

a. Paired observations.
b. For T_{max}, median and range are reported.
c. n=9.

Best Objective Response: A summary of best objective response based on Investigator assessments for the ITT population is provided in Table 7.

Out of 19 evaluable subjects with measurable disease, the best confirmed objective response was PR in 14 (73.7%) subjects and SD in 5 (26.3%) subjects. Notably, 5 of the 6 (83.3%) subjects with "triple-negative" disease achieved a confirmed PR, while 8 of 13 (61.5%) subjects with estrogen receptor positive (+/- progesterone receptor positive) disease achieved a confirmed PR.

The overall confirmed objective response (CR or PR) rate was 73.7%.

The CBR (CR, PR, or SD ≥24 weeks) rate was 89.5%.

Table 7. Summary of Best Objective Response Based on Investigator Assessments (Intent-to-Treat Population)

Variable	Investigator Assessment Docetaxel + Sunitinib (N=20)
Subjects with baseline assessments	20
Subjects with measurable disease at Baseline	19
Best objective response, n (%)[a]	
Complete response	0
Partial response	14 (73.7)
Stable disease [a]	5 (26.3)
Progressive disease	0
Not evaluable	0
Overall confirmed objective response (CR + PR)	
Rate, n (%)	14 (73.7)
95% exact CI[b]	48.8, 90.9
Clinical benefit response (CR + PR + SD ≥24 weeks)	
Rate, n (%)	17 (89.5)
95% exact CI[c]	66.9, 98.7
Duration of stable disease[d]	
≥3 months	4
≥6 months	3

CI = confidence interval; CR = complete response; F distribution = Fisher–Snedecor distribution: N = number of subjects; n = number of subjects with specified criteria; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease;

a. SD ≥24 weeks.
b. Calculated based on subjects with measurable disease at Baseline.
c. Two-sided CI from exact method based on F distribution.
d. Excludes subjects with a defined confirmed response.

Duration of Response: A summary of duration of response based on Investigator assessments for the ITT population is provided in Table 8.

A total of 14 subjects achieved an objective tumor response. The median duration of response for the subgroup of subjects with a confirmed objective response (CR+PR) was 28.7 weeks.

Table 8. Summary of Duration of Tumor Response Based on Investigator Assessments (Intent-to-Treat Population)

Variable	Investigator Assessment Docetaxel + Sunitinib (N=20)
Subjects with baseline assessments	20
Subjects with measurable disease at Baseline	19
Subjects with objective response	14 (73.7)
Tumor response status n (%)	
Subjects with a response who had not progressed or died due to any cause while on study	4 (28.6)
Subjects with a response and subsequent progression or death due to any cause while on study	10 (71.4)
Duration of tumor response (weeks)[a]	
Quartile (95% CI)	
25%	22.7 (18.4, 31.1)
50% (median)	28.7 (22.7, 69.6)
75%	69.6 (28.7, 69.9)

Duration of response was defined as the time from start of first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurred first. DR was calculated for the subgroup of subjects with objective disease response.
CR = complete response; DR = duration of response; PR = partial response; N = number of subjects; n = number of subjects with specified criteria.
a. DR (weeks) = (the end date for DR – first subsequent confirmed CR or PR + 1)/7.

Progression-Free Survival: A summary of PFS for the ITT population is provided in Table 9. The median PFS was 34.9 weeks for the ITT population. A total of 16 subjects (80.0%) had disease progression while on study. The remaining subjects did not experience disease progression nor death while on study.

Table 9. Summary of Progression-Free Survival Based on Investigator Assessments (Intent-to-Treat Population)

Variable	Investigator Assessments Docetaxel + Sunitinib (N=20)
Subjects with Baseline assessments[a]	20
Progression Status n (%)	
Subject did not progress or die due to any cause while on study	4 (20.0)
Subject did progress or die due to any cause while on study	16 (80.0)
Progression-Free Survival (weeks)[b]	
Quartile (95% CI)	
25%	27.6 (17.4, 30.3)
50% (median)	34.9 (28.1, 55.6)
75%	55.6 (34.9, 75.9)

Progression-free survival was defined as the time from the first dose of study treatment to the first documentation of objective tumor progression, or to death due to any cause, whichever occurred first.
CI = confidence interval; N = number of subjects; n = number of subjects with specified criteria; PFS = progression-free survival.
a. 20 subjects included 19 subjects with measurable disease and 1 subject with nonmeasurable disease.
b. PFS (weeks) = (first event date – first dose date + 1)/7.

Safety Results:

Overview of Adverse Events: An overview of treatment-emergent (all-causality and treatment-related) AEs is provided in Table 10.

Table 10. Overview of Treatment-Emergent (All-Causality and Treatment-Related) Adverse Events

Number of Subjects	All-Causality Docetaxel + Sunitinib (N=22)	Treatment-Related Docetaxel + Sunitinib (N=22)
Evaluable for AEs	22	22
Number of AEs	358	278
Subjects with AEs	22	22
Subjects with SAEs	11	8
Subjects with Grade 3 or 4 AEs	19	17
Subjects with Grade 5 AEs	0	0
Subjects discontinued due to AEs	3[a]	3[a]
Subjects with dose reduced due to AEs[b]	5	5
Subjects with temporary discontinuation due to AEs[b]	13	13

Except for the number of AEs, subjects are counted only once per treatment in each row.
Serious adverse events – according to the Investigators' assessments.
AE = adverse event; N = number of subjects; SAE = serious adverse event.

a. Includes 1 subject who discontinued the study because she was no longer willing to participate in the study, 1 subject who discontinued the study due to insufficient clinical response, and 1 subject who discontinued the study due to AE (cerebral hemorrhage).
b. Subject with reductions or interruptions due to sunitinib only.

Treatment-Emergent Non Serious Adverse Events (All Causalities) and Treatment-Related by System Organ Class and Preferred Term: A summary of treatment-emergent non serious AEs and treatment-related AEs by MedDRA system organ class (SOC) and preferred term (PT) reported is provided in Table 11.

Table 11. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v11.0) Preferred Term	Docetaxel + Sunitinib		
	n (%)	n1	n2
Number (%) of subjects:			
Evaluable for adverse events	22		
With adverse events	21 (95.5)		
Blood and lymphatic system disorders	11 (50.0)	25	25
Febrile neutropenia	2 (9.1)	2	2
Neutropenia	10 (45.5)	23	23
Eye disorders	8 (36.4)	11	9
Conjunctivitis	2 (9.1)	2	2
Lacrimation increased	3 (13.6)	4	3
Photopsia	2 (9.1)	2	2
Visual acuity reduced	2 (9.1)	3	2
Gastrointestinal disorders	20 (90.9)	122	113
Abdominal distension	2 (9.1)	2	2
Abdominal pain upper	7 (31.8)	10	8
Diarrhoea	13 (59.1)	41	39
Dyspepsia	7 (31.8)	13	10
Glossodynia	2 (9.1)	3	3
Haemorrhoids	2 (9.1)	2	1
Nausea	11 (50.0)	28	28
Oral pain	3 (13.6)	3	3
Stomatitis	11 (50.0)	16	16
Vomiting	4 (18.2)	4	3
General disorders and administration site conditions	19 (86.4)	91	73
Asthenia	6 (27.3)	12	12
Chest discomfort	3 (13.6)	8	2
Chest pain	4 (18.2)	10	7
Face oedema	2 (9.1)	4	3
Fatigue	10 (45.5)	22	19
Local swelling	2 (9.1)	6	5
Mucosal inflammation	9 (40.9)	14	14
Oedema peripheral	2 (9.1)	3	2
Pain	3 (13.6)	3	3
Pyrexia	7 (31.8)	9	6
Infections and infestations	8 (36.4)	14	1
Cystitis	2 (9.1)	4	0
Nasopharyngitis	6 (27.3)	10	1
Investigations	4 (18.2)	4	3
Alanine aminotransferase	2 (9.1)	2	1
Electrocardiogram QT prolonged	2 (9.1)	2	2
Metabolism and nutrition disorders	3 (13.6)	4	4
Anorexia	3 (13.6)	4	4
Musculoskeletal and connective tissue disorders	13 (59.1)	35	21
Arthralgia	4 (18.2)	4	2
Back pain	3 (13.6)	4	0
Bone pain	3 (13.6)	8	0
Myalgia	7 (31.8)	17	17
Pain in extremity	2 (9.1)	2	2
Nervous system disorders	10 (45.5)	40	29
Dizziness	4 (18.2)	5	4
Dysgeusia	6 (27.3)	7	6
Headache	8 (36.4)	17	8
Paraesthesia	2 (9.1)	2	2
Peripheral sensory neuropathy	5 (22.7)	9	9
Psychiatric disorders	4 (18.2)	6	1
Depression	3 (13.6)	3	1

Table 11. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All causalities) in >5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v11.0) Preferred Term	Docetaxel + Sunitinib n (%)	n1	n2
Insomnia	3 (13.6)	3	0
Respiratory, thoracic and mediastinal disorders	11 (50.0)	40	23
Cough	3 (13.6)	9	1
Dyspnoea	4 (18.2)	7	4
Epistaxis	6 (27.3)	13	11
Pharyngolaryngeal pain	7 (31.8)	11	7
Skin and subcutaneous tissue disorders	21 (95.5)	74	70
Alopecia	12 (54.5)	13	13
Dry skin	3 (13.6)	3	3
Night sweats	2 (9.1)	2	0
Palmar-plantar erythrodysaesthesia syndrome	11 (50.0)	34	34
Petechiae	2 (9.1)	2	0
Pruritus generalised	3 (13.6)	3	3
Rash	5 (22.7)	7	7
Skin exfoliation	2 (9.1)	2	2
Skin hyperpigmentation	2 (9.1)	2	2
Swelling face	3 (13.6)	6	6
Vascular disorders	4 (18.2)	7	7
Flushing	2 (9.1)	4	4
Hypertension	2 (9.1)	3	3

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: (optional): The number of occurrences of treatment emergent causally related to treatment adverse events.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (v11.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.

Serious Adverse Events: A summary of all SAEs treatment emergent (all causality) and treatment-related is provided in Table 12.

Table 12. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v11.0) Preferred Term	Docetaxel + Sunitinib		
	n (%)	n1	n2
Number (%) of subjects:			
Evaluable for adverse events	22		
With adverse events	11 (50.0)		
Blood and lymphatic system disorders	6 (27.3)	8	8
Febrile neutropenia	5 (22.7)	5	5
Leukopenia	1 (4.5)	1	1
Neutropenia	2 (9.1)	2	2
Gastrointestinal disorders	1 (4.5)	1	1
Stomatitis	1 (4.5)	1	1
General disorders and administration site conditions	2 (9.1)	2	1
Fatigue	1 (4.5)	1	1
Oedema peripheral	1 (4.5)	1	0
Hepatobiliary disorders	1 (4.5)	1	1
Jaundice	1 (4.5)	1	1
Musculoskeletal and connective tissue disorders	1 (4.5)	2	0
Back pain	1 (4.5)	1	0
Musculoskeletal pain	1 (4.5)	1	0
Nervous system disorders	2 (9.1)	4	4
Cerebral haemorrhage	1 (4.5)	1	1
Headache	1 (4.5)	3	3
Respiratory, thoracic and mediastinal disorders	1 (4.5)	1	0
Pleural effusion	1 (4.5)	1	0
Skin and subcutaneous tissue disorders	2 (9.1)	2	1
Palmar-plantar erythrodysaesthesia syndrome	1 (4.5)	1	1
Petechiae	1 (4.5)	1	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: The number of occurrences of treatment emergent causally related to treatment adverse events.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (v11.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.

Permanent Discontinuations due to Adverse Events: A summary of subjects who permanently discontinued sunitinib or docetaxel due to AEs is provided in Table 13. A total of 4 subjects permanently discontinued sunitinib or docetaxel due to an AE during the study.

Table 13. Permanent Discontinuations due to Adverse Events

Serial No.	Adverse Event (MedDRA Preferred Term)	Cycle Start/ Stop	Cycle Start Day/ Stop Day	Start Day[a]/ Stop Day	Grade	Outcome	Study Drug Action/Background Drug Action	Causality
1	Anemia	9/9	21/28	193/200	3	Resolved	Permanently discontinued No action taken	Sunitinib
	Anemia	9/9	28/40	200/212	2	Resolved	Permanently discontinued No action taken	Sunitinib
	Anemia	9/9	40/74	212/246	3	Resolved	Permanently discontinued No action taken	Sunitinib
2	Febrile neutropenia	1/1	9/10	9/10	3	Resolved	Permanently discontinued Permanently discontinued	Sunitinib/ docetaxel
3	Cerebral hemorrhage	1/1	29/32	29/32	2	Resolved	Permanently discontinued Permanently discontinued	Sunitinib
4	Dyspnea	17/18	2/29	360/408	2	Resolved	No action taken Permanently discontinued	Sunitinib/ docetaxel

MedDRA = Medical Dictionary for Regulatory Activities.
a. Day relative to start of study treatment. First day of study treatment = Day 1.

Dose Reductions or Temporary Discontinuations due to Adverse Events:

Sunitinib: At least 1 AE contributed to a dose reduction of sunitinib in 5 (22.7%) subjects during the study. The reasons for sunitinib dose reductions included Grade 2 mucositis (1 subject), Grade 4 neutropenia, Grade 1 bradycardia, and Grade 1 prolonged QTc interval (1 subject), Grade 2 rash (1 subject), Grade 3 febrile neutropenia and Grade 4 neutropenia (1 subject), and Grade 3 leukopenia (1 subject).

At least 1 AE contributed to an interruption (temporary discontinuation) of sunitinib dosing in 13 (59.1%) subjects during the study. The most common AEs for temporary discontinuation of sunitinib included hand-foot syndrome and neutropenia (5 subjects each), stomatitis (4 subjects), febrile neutropenia and fever (3 subjects each).

Docetaxel: At least 1 AE contributed to a dose reduction of docetaxel in 8 (36.4%) subjects during the study. Myelosuppression (neutropenia, febrile neutropenia) and fatigue were the most frequent reasons for docetaxel dose reduction.

Deaths: No deaths were reported in this study.

Laboratory Evaluations: The most frequently reported hematological abnormalities were leukopenia (100%), lymphopenia (100%), and neutropenia (95.5%). Neutropenia and febrile neutropenia were frequent reasons for dose reduction, temporary discontinuation, and permanent discontinuation of both sunitinib and docetaxel. Neutropenia, complicated or uncomplicated, had generally recovered in time for treatment in the subsequent cycle. A

total of 6 (27.3%) subjects had 7 events of moderate hypertension, defined as a systolic blood pressure >150 mm Hg or diastolic blood pressure >100 mm Hg. Only 1 subject had severe hypertension, defined as a diastolic blood pressure >110 mm Hg. Two subjects had ECG results reported as AEs (grade 1 QT interval prolongation); otherwise there were no clinically significant findings in ECG results. Left ventricular ejection fraction (LVEF) did not decrease below 50% in any subject during the study treatment. All subjects had a maximum recorded ECOG performance status of 0 or 1 at the end of the study.

CONCLUSIONS:

- There were no clinically significant changes in PK parameters for sunitinib and docetaxel, indicating absence of any drug-drug interactions following sequential dosing of docetaxel every 3 weeks and sunitinib on Schedule 2/1.

- The overall AE and laboratory profile of this combination in subjects with advanced breast cancer was generally acceptable and clinically manageable. Hematological toxicities, including grade 3/4 neutropenia, were adequately controlled with standard medical management.

- There was evidence of antitumor activity with this combination in advanced breast cancer subjects who had relapsed after an anthracycline-based adjuvant regimen, with an ORR of 73.7%, CBR rate of 89.5%, and a median PFS of 34.9 weeks.