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

PROTOCOL NO.: A6181113

PROTOCOL TITLE: An Explorative Study of the Tolerability of SU-011248 in Combination With Docetaxel and Trastuzumab as First-Line Treatment in Patients With Breast Cancer Over-Expressing HER-2

Study Centers: A total of 6 centers participated in this study (4 in Belgium and 2 in Italy).

Study Initiation and Final Completion Dates: 11 December 2006 to 28 September 2011

This study was terminated prematurely.

Phase of Development: Phase 1b

Study Objectives:

Primary Objective: To assess the tolerability of the combination of sunitinib malate (also referred to as SU-011248, henceforth will be referred to as sunitinib; 37.5 mg once daily [Schedule 2/1]) with docetaxel (75 mg/m^2 every 3 weeks) and trastuzumab (therapeutic dose) in subjects with advanced breast cancer (ABC) overexpressing human epidermal growth factor receptor-2 (HER-2).

Secondary Objectives:

- To assess preliminary antitumor activity of the combination;
- To determine trough plasma concentrations (C_{trough}) of sunitinib and its active metabolite SU-012662, plasma concentrations of docetaxel and serum concentrations of trastuzumab.

METHODS

Study Design:

This was an exploratory clinical study evaluating the tolerability and preliminary antitumor activity of sunitinib combined with docetaxel and trastuzumab in subjects with ABC. Eligible subjects had HER-2 overexpressing tumors (immunohistochemistry [IHC] 3+ or fluorescence in-situ hybridization [FISH]+) and had not received prior treatment for advanced disease. They could have received adjuvant therapy with standard chemotherapy

with or without trastuzumab, provided that they had relapsed ≥6 months since last dose of trastuzumab. Subjects who had received a taxane-based adjuvant therapy could have entered the study only if ≥12 months had elapsed since completion of their adjuvant chemotherapy.

The proposed combination of docetaxel/trastuzumab/sunitinib was to be studied in terms of safety and preliminary antitumor activity in a total of 25 subjects. Safety was analyzed with special attention to cardiac events. If no >1 subject out of the 25 enrolled in this study required discontinuation of trastuzumab or sunitinib or both due to clinical symptoms of cardiac failure, then the combination was considered suitable for being tested in a Phase 3 study in the same population.

Study treatment continued until a subject experienced disease progression (PD) that was documented according to Response Evaluation Criteria in Solid Tumors (RECIST), had occurrence of unacceptable toxicity, or withdrew consent. If the study treatment was discontinued for reasons other than PD, the subject was followed, and tumor assessments continued until PD, or until a new anticancer therapy was initiated, or until death, whichever occurred first.

If docetaxel was discontinued for reasons other than PD, treatment with sunitinib and trastuzumab may have continued until PD occurred or until a new anticancer treatment was initiated. In these cases, sunitinib was to be administered as a continuous regimen, with the provision of at least 1-week treatment rests inserted into the regimen as needed, or dose reductions, depending on individual tolerability. In addition, subjects experiencing good tolerability to sunitinib could have escalated the dose to 50 mg.

If PD occurred during treatment, docetaxel and sunitinib were to be discontinued and the Investigator was to select an alternative therapeutic option and discontinue trastuzumab.

Subjects could have continued treatment beyond the time of RECIST-defined progression at the discretion of the Investigator if the subject was perceived to be experiencing clinical benefit.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Protocol Activity	Screen	Study Treatment[a]							Post Treatment		
		Cycle 1[b]				Subsequent Cycles			End of Tx/ Withdrawal[d]	28-Day Post Tx[e]	Follow-Up[f]
	≤21 Days to Dosing	Day 1[c]	Day 2 (-2/+2)	Day 8 (-2/+2)	Day 15 (-2/+1)	Day 1	Day 2 (-2/+2)	Day 8 (-2/+2)			
Baseline documentation											
Informed consent[g]	X										
Medical/oncological history[h]	X										
Physical examination[i]	X	X				X			X	(X)	
Baseline signs/symptoms		X C1									
Laboratory studies											
Hematology[j]	X	X		X	X	X		X	X	(X)	
Blood chemistry	X	X				X			X	(X)	
Thyroid function testing (TSH)[k]	X										
Pregnancy test (as appropriate)[l]	X										
12-lead ECG[m]	X					X C3, then odd # cycles			X		
MUGA or ECHO[n]	X					X			X		
Study registration[o]	X										
Docetaxel infusion		X				X					
Trastuzumab infusion[p]		X		(X)	(X)	X		(X)			
Sunitinib capsule dosing[q]			X→	X→	X		X→	X→			
Tumor assessments											
CT or MRI scans[r]	X					X from C3 (every 6 weeks)			X		X
Other clinical assessments											
Adverse events[s]	X	X	X	X	X	X	X	X	X	X	
Study drug compliance[t]						X from C2			X		
Concomitant medications/treatments[u]	X	X	X	X	X	X	X	X	X	X	
Post treatment anti-cancer therapy										(X)	X
Special laboratory studies											
Trough sunitinib concentration (C_{trough})[v]					X C1,C2, C4,C6	X C2,C4,C6					
Docetaxel plasma levels[w]		X C1,C2,C4,C6									
3-Weekly trastuzumab plasma levels[x]		X C1,C2,C4,C6									
Weekly trastuzumab serum levels[x]		X C1,C2,C4,C6			X C1,C2, C4,C6						

Table 1. Schedule of Activities

( ) – if applicable.
C = cycle; CR = complete response; CRF = case report form; C_{trough} = trough plasma concentrations; CT = computed tomography; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PD = disease progression; PR = partial response; TSH = thyroid stimulating hormone; Tx = treatment.

a. Treatment With Sunitinib/Docetaxel: All assessments performed prior to dosing with docetaxel or sunitinib unless otherwise indicated. Acceptable time windows for performing each assessment described in the column headings.
   Cycle Duration: Each cycle lasts 3 weeks, unless cycle duration is prolonged due to toxicities. A maximum of 2-week delay 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 prompt discussion with the Sponsor. Subjects discontinuing treatment with docetaxel and continuing to receive sunitinib and/or trastuzumab may have subsequent clinic visits every 6 weeks (instead of 3 weeks), which must include tumor assessment, until PD.
b. Cycle 1: Only during the first cycle hematology checked and reported in the CRF every week as well as the adverse events.
c. Cycle 1 Day 1: Hematology, blood chemistry, and physical examination not required if acceptable screening assessment performed within 3 days prior to the start of treatment with trastuzumab and docetaxel.
d. End of Treatment/Withdrawal: These assessments 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.
e. 28-Day Post Treatment: Subjects who discontinued study drugs evaluated up to 28 days after last dose of study treatment. Adverse events followed up until all serious or study drug-related toxicities resolved or determined to be “chronic” or “stable”, whichever later.
f. Follow-Up: Subjects discontinuing study drugs for reasons other than PD may have subsequent clinic visits every 6 weeks, which included tumor assessment, until PD or a subsequent anti-cancer therapy. A tumor assessment mandatory before initiating a new anti-tumor therapy.
g. Informed Consent: Obtained prior to undergoing any study specific procedure and occurs prior to the 21-day Screening Period.
h. Medical/Oncologic History and Demographics: Included information on prior anti-tumor regimens (dose and duration of administration) and relapse date.
i. Physical Examination: 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).
j. Hematology: The nadir of hematologic parameters after docetaxel administration captured and reported in the CRF. The window for hematology testing: -2/+2 days.
k. Thyroid Function Testing (TSH): Completed at Screening and repeated during the study if clinically indicated.
l. Pregnancy Test: The test performed at least 3 days before study treatment.
m. 12-Lead ECG: At Baseline, on Day 1 Cycle 3 and subsequent odd cycles, and at the End of Treatment. Additional ECGs performed as clinically indicated and performed 2 weeks following sunitinib intrasubject dose adjustment. Three consecutive 12-lead ECGs performed approximately 2 minutes apart to determine the mean corrected QT (QTc) interval. The ECGs performed at the same time of day (eg, in the morning) and time matched (±1 hour). If the mean QTc interval prolonged (>500 msec), then the ECGs re-read by a cariologist at the site for confirmation.
n. MUGA or ECHO: At Baseline, on Day 1 of each cycle, and at the End of Treatment. Additional assessments performed as clinically indicated. Acceptable time window for performing MUGA or ECHO is ±7 days.
o. Study Registration: Subjects registered with the Sponsor prior to being considered enrolled on the study.

Table 1. Schedule of Activities

p. Trastuzumab Administration: Two schedules allowed:
Weekly Schedule: Loading dose of 4 mg/kg over 90 minutes on Day 1 followed by weekly maintenance doses of 2 mg/kg as 30-minute infusions if the initial loading dose was well tolerated on Days 1, 8, 15.
Every -3-Week Schedule: Loading dose of 8 mg/kg over 90 minutes on Day 1 followed by maintenance doses of 6 mg/kg as 90-minute infusions. The administration of 6 mg/kg repeated on Day 1 every 3 weeks.

q. Sunitinib Administration: Sunitinib administered from Day 2 to Day 15 (2 weeks) of every cycle followed by 1-week rest.

r. Tumor Imaging: CT or MRI scan of known areas of disease performed at Screening. During study, tumor imaging studies follow known areas of disease, and other areas whenever disease progression suspected. Tumor assessment repeated every 6 weeks starting from the end of Cycle 2 (Day 1 Cycle 3). In case of a PR or CR confirmatory tumor assessment performed 4 weeks after initial documentation of response. Allowable window for tumor imaging studies: +/-7 days.

s. Adverse Events: Subjects 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 determined to be “chronic” or “stable”, whichever later. Serious adverse events monitored and reported from the time that the subject provides informed consent.

t. Study Drug Compliance: The sunitinib bottle(s) including any unused capsules returned to the clinic for drug accountability.

u. Concomitant Medications and Treatments: Concomitant medications and treatments recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.

v. Trough Drug Concentration (sunitinib and SU012662) Determination: Blood samples (2 mL) collected before dosing during Cycles 1 (D15), 2 (D1, D15), 4 (D1, D15), 6 (D1, D15).

w. Docetaxel Plasma Levels: Blood samples (5 mL) collected at the end of infusion during Cycles 1 (D1), 2 (D1), 4 (D1), 6 (D1).

x. Trastuzumab Serum Levels: Blood samples (5 mL) collected before dosing as follows:
Weekly Trastuzumab: During Cycles 1 (D1, D15), 2 (D1, D15), 4 (D1, D15), 6 (D1, D15);
3-Weekly Trastuzumab: During Cycles 1 (D1), 2 (D1), 4 (D1), 6 (D1).

Number of Subjects (Planned and Analyzed): There were 25 subjects planned for this study. A total of 26 subjects (16 in Belgium and 10 in Italy) were assigned to study treatment and 25 subjects were treated and analyzed. One subject was enrolled, but never received treatment.

Diagnosis and Main Criteria for Inclusion:

Subjects with breast cancer having evidence of unresectable, locally recurrent, or metastatic disease; with tumors over-expressing HER-2, and subjects who were a candidate for treatment with docetaxel/trastuzumab were included in the study.

Subjects with histology of inflammatory carcinoma and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN), concomitant with alkaline phosphatase >2.5 × ULN, were excluded from the study.

Study Treatment:

Subjects were registered sequentially as the study was a single-arm study.

Treatment on study was administered in 3-week cycles. Docetaxel was administered intravenously (IV) on Day 1 at a starting dose of 75 mg/m^2 every 3 weeks. Trastuzumab was administered IV weekly starting on Day 1 (loading dose of 4 mg/kg followed by a weekly dose of 2 mg/kg) or every 3 weeks starting on Day 1 (loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks). Sunitinib was administered orally starting from Day 2 to 15 every 3 weeks (Schedule 2/1). The starting dose of sunitinib was 37.5 mg daily.

Docetaxel and sunitinib doses could have been reduced based on tolerability in Cycles ≥2, (ie, docetaxel from 75 to 60 mg/m^2 and sunitinib from 37.5 to 25 mg once daily). In subsequent cycles, intrasubject re-escalation of both drugs back to the previous dose level was permitted at the discretion of the Investigator and considering the subject's clinical status.

Trastuzumab was administered at the indicated doses without dosage modification. Trastuzumab was interrupted only if predefined specific events occurred. A minimum of 6 subjects were to receive the trastuzumab weekly schedule and a minimum of 6 subjects were to receive the every 3 weeks schedule.

Since docetaxel is myelotoxic, the use of hematopoietic growth factors was permitted.

Drug interaction studies have not been performed with trastuzumab. A specific pharmacokinetic (PK) interaction study was not conducted during this study. However, a series of PK samplings were drawn in order to check the plasma levels of sunitinib and docetaxel, and the serum levels of trastuzumab at specific time points during the study.

Efficacy, Pharmacokinetic and Safety Endpoints:

Primary Endpoint:

- Safety profile characterized by type, incidence, severity, timing, seriousness, and relatedness of adverse events (AEs), and laboratory abnormalities.

Secondary Endpoints:

- Progression-free survival (PFS);
- Objective response rate (ORR);
- Duration of response (DR);
- C_{trough} of sunitinib, its metabolite SU012662, and total drug (sunitinib + SU012662);
- Plasma levels of docetaxel and serum levels of trastuzumab.

Safety Evaluations: Safety evaluations included evaluation of AEs, clinical laboratory safety assessments, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, 12-lead electrocardiograms (ECGs), and echocardiogram (ECHO) or multigated acquisition scans (MUGA) to measure left ventricular ejection fraction (LVEF).

Statistical Methods:

Analysis sets:

The intent-to-treat (ITT) population and safety analysis set included all subjects enrolled in the study who received at least 1 dose of study drug. The ITT population was analyzed for PFS. The per protocol population was analyzed for objective response and included all subjects who received at least 1 dose of sunitinib and had at least a tumor assessment postbaseline. The PK analysis set included the ITT population of subjects who had completed sampling for PK profiles for sunitinib, docetaxel, and trastuzumab and had been documented to be compliant with the concomitant medications requirements.

Efficacy:

Due to the exploratory nature of the study, no imputations of missing data were done. No confirmatory inferential analyses were planned. The number and percent of subjects achieving objective response (complete response [CR] or partial response [PR]) were summarized along with the corresponding 95% exact confidence interval (CI), as well as the number and percent of subjects achieving clinical benefit response (CR, PR, or stable disease for at least 24 weeks). PFS and duration of response were summarized using the Kaplan-Meier method. Duration of response was calculated only for those subjects with an objective response (PR or CR).

Pharmacokinetics:

Summary descriptive statistics, figures, and listings of plasma concentrations by cycle and day were provided for sunitinib, SU-012662, total drug, trastuzumab, and docetaxel. All concentrations which were below the limits of quantitation were set to 0 prior to computation of descriptive statistics. For comparison purposes, the arithmetic mean values for C_{trough} of sunitinib, SU-012662, and total drug when sunitinib was administered with docetaxel and trastuzumab were compared to the historical control values when sunitinib was administered alone. The mean values for end-of-infusion docetaxel concentrations (ie, maximum plasma concentrations [C_{max}]) when administered with trastuzumab and sunitinib were compared to end-of-infusion docetaxel concentration when docetaxel was administered alone. The values for trough trastuzumab concentrations when administered with docetaxel and sunitinib were compared to historical control mean value when trastuzumab was administered alone.

Safety:

Safety data were evaluated using descriptive statistics.

RESULTS

Subject Disposition and Demography:

Disposition:

A summary of subject disposition is provided in Table 2.

A total of 26 subjects were assigned to study treatment and 25 subjects were treated. One subject was enrolled, but never received treatment.

Table 2. Subject Disposition

Number of Subjects	Sunitinib + Docetaxel + Trastuzumab	Docetaxel + Trastuzumab	Total
Assigned to study treatment	25	1	26
Treated	24	1	25
Discontinued	24	1	25
Died	0	1	1
Related to study drug			
Adverse event	2	0	2
Not related to study drug			
Objective progression or relapse	14	0	14
Other	7	0	7
Subject refused continued treatment for reason other than adverse event	1	0	1

Only discontinuations from the full study are summarized in this table.
One subject was assigned to sunitinib + docetaxel + trastuzumab but she died before taking sunitinib.

An overall summary of subject disposition is provided in Table 3.

Table 3. Overall Summary of Subject Disposition

	Sunitinib + Docetaxel + Trastuzumab
Subjects enrolled	26
Intent-to-treat population[a], N	25
Maximum cycles started, n (%)	
1	3 (12.0)
2	1 (4.0)
3	1 (4.0)
5	3 (12.0)
6	1 (4.0)
12	3 (12.0)
13	2 (8.0)
16	1 (4.0)
17	1 (4.0)
18	1 (4.0)
20	2 (8.0)
21	2 (8.0)
27	2 (8.0)
53	1 (4.0)
64	1 (4.0)

N/n = number of subjects.

a. This population included all subjects enrolled in the study who received at least 1 dose of study medication (sunitinib, docetaxel, or trastuzumab).

Discontinuations:

A summary of discontinuations from sunitinib, docetaxel, and trastuzumab is provided in Table 4.

Table 4. Discontinuations From Sunitinib, Docetaxel, and Trastuzumab

Number of Subjects	Sunitinib + Docetaxel + Trastuzumab	Docetaxel + Trastuzumab	Total
Discontinued from sunitinib	24	NA	24
Related to study drug			
Adverse event	9		9
Not related to study drug			
Global deterioration of health status	1		1
Objective progression or relapse	11		11
Other[a]	1		1
Subject refused continued treatment for reason other than adverse event	2		2
Discontinued from docetaxel	24	1	25
Related to study drug			
Adverse event	5	0	5
Not related to study drug			
Adverse event	1	1	2
Global deterioration of health status	1	0	1
Objective progression or relapse	4	0	4
Other[b]	12	0	12
Subject refused continued treatment for reason other than adverse event	1	0	1
Discontinued from trastuzumab	24	1	25
Related to study drug			
Adverse event	0	1	1
Not related to study drug			
Adverse event	2	0	2
Global deterioration of health status	1	0	1
Objective progression or relapse	14	0	14
Other[c]	4	0	4
Subject refused continued treatment for reason other than adverse event	3	0	3

NA = not applicable; PI = Principal Investigator.
a. Other = subject rolled over to another study.
b. Other = usual practice (9 subjects) and PI decision (3 subjects).
c. Other = Sponsor's decision (2 subjects), subject rolled over to another study, and PI wanted to combine trastuzumab with capecitabine.

Demographic Characteristics:

A summary of demographic characteristics is provided in Table 5.

Table 5. Demographic Characteristics

	Sunitinib + Docetaxel + Trastuzumab (N=24)	Docetaxel + Trastuzumab (N=1)	Total (N=25)
Gender, n			
Female	24	1	25
Age (years)			
18-44	4	0	4
45-64	12	1	13
≥65	8	0	8
Mean (SD)	57.0 (13.1)	59.0 (0.0)	57.0 (12.8)
Range	34-83	59-59	34-83
Race, n			
White	23	1	24
Black	1	0	1
Weight (kg)			
Mean (SD)	65.1 (14.8)	53.0 (0)	64.6 (14.7)
Range	43.6-101.5	53.0-53.0	43.6-101.5
Height (cm)			
Mean (SD)	161.5 (6.7)	147.0 (0.0)	160.9 (7.1)
Range	149.0-172.0	147.0-147.0	147.0-172.0

n/N = number of subjects; SD = standard deviation.

Baseline Characteristics:

A summary of baseline characteristics is provided in Table 6.

Table 6. Baseline Characteristics

	Sunitinib + Docetaxel + Trastuzumab (N=24)	Docetaxel + Trastuzumab (N=1)	Total (N=25)
Primary diagnosis			
(MedDRA [v14.0] preferred term)			
Breast cancer recurrent	1	0	1
Duration since first diagnosis (years)[a]			
Mean	4.25	0	4.25
Range	4.25-4.25	0	4.25-4.25
Breast cancer metastatic	23	1	24
Duration since first diagnosis (years)[a]			
Mean	4.13	0.02	3.96
Range	0.02-19.21	0.02-0.02	0.02-19.21
Estrogen receptor			
Negative	12 (50.0)	0	12 (48.0)
Positive	12 (50.0)	1 (100.0)	13 (52.0)
Progesterone receptor			
Negative	16 (66.7)	0	16 (64.0)
Positive	7 (29.2)	1 (100.0)	8 (32.0)
Unknown	1 (4.2)	0	1 (4.0)
HER-2 FISH			
Not done	6 (25.0)	0	6 (24.0)
Positive	18 (75.0)	1 (100.0)	19 (76.0)
HER-2 CISH			
Not done	21 (87.5)	1 (100.0)	22 (88.0)
Positive	3 (12.5)	0	3 (12.0)
HER-2 IHC			
2+	1 (4.2)	0	1 (4.0)
3+	20 (83.3)	1 (100.0)	21 (84.0)
Not done	3 (12.5)	0	3 (12.0)
Overall HER-2[b]			
Positive	24 (100.0)	1 (100.0)	25 (100.0)

CISH = chromogenic in-situ hybridization; FISH = fluorescence in-situ hybridization; HER-2 = human epidermal growth factor receptor-2; IHC = immunohistochemistry; MedDRA = Medical Dictionary for Regulatory Activities; v = version.

a. Duration (years) from first diagnosis to Day 1 of study.

b. Overall HER-2 was defined as:
Positive if HER-2 FISH/CISH = positive or (HER-2 FISH/CISH not negative and HER-2 IHC =3+);
Negative if HER-2 FISH/CISH = negative or (HER-2 FISH/CISH not positive and HER-2 IHC =0 or 1+).

Efficacy and Pharmacokinetic Results:

Efficacy Results:

Best Overall Response:

A summary of best overall derived tumor response for the per protocol population is provided in Table 7.

Table 7. Best Overall Derived Tumor Response (Per Protocol Population)

	Sunitinib + Docetaxel + Trastuzumab (N=22)
Subjects with baseline assessment, n	22
Subjects with measurable disease at Baseline, n	22
Best confirmed response, n (%)	
Complete response	0
Partial response	16 (72.7)
Stable disease	5 (22.7)
Progressive disease	1 (4.5)
Not evaluable	0
Missing	0
Overall confirmed objective response rate (CR+PR), n (%)	16 (72.7)
95% CI (%)[a]	49.8, 89.3
Clinical benefit rate[b], n (%)	18 (81.8)
95% CI (%)[a]	59.7, 94.8
Duration of stable disease, n	
<3 months	3
≥3 months and <6 months	0
≥6 months	2

The per protocol population was defined as subjects taking at least a dose of sunitinib and reporting at least a tumor assessment postbaseline. Three subjects were excluded from the per protocol population.
CI = confidence interval; CR = complete response; N/n = number of subjects; PR = partial response; SD = stable disease.
a. Two-sided 95% CI from Exact Method based on the F distribution.
b. Clinical Benefit Rate was defined as the percent of subjects with CR, PR, or SD ≥24 weeks.

Results for the best overall investigator tumor response results were identical to the derived tumor response results.

Progression-Free Survival:

A summary of PFS for the ITT population is provided in Table 8.

Table 8. Summary of Progression-Free Survival[a] Based on Derived Assessment (Intent-to-Treat Population)

	Sunitinib + Docetaxel + Trastuzumab (N=25)
Subjects with baseline assessment, n	25
Subjects with measurable disease at Baseline, n	25
Subject progression/death status, n (%)	
Subject did not progress or die due to any cause	8 (32.0)
Subject did progress or die due to any cause	17 (68.0)
Progression-free survival time (weeks)[b]	
Quartile (95% CI)	
25%	36.3 (16.3, 58.4)
50% (median)	58.4 (37.0, 66.1)
75%	79.0 (58.9, 133.4)

CI = confidence interval; N/n = number of subjects; PFS = progression-free survival.

a. PFS 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.

b. PFS (weeks) = (first event date – first dose date +1)/7.

Duration of Response:

A summary of duration of response for the ITT population is provided in Table 9.

Table 9. Summary of Duration of Tumor Response[a] Based on Derived Assessment (Intent-to-Treat Population)

	Sunitinib + Docetaxel + Trastuzumab (N=25)
Subjects with a response, n	16
Tumor response status, n (%)	
Subjects with response who had not progressed or died due to any cause	2 (12.5)
Subjects with a response and subsequent progression or death due to any cause	14 (87.5)
Duration of tumor response (weeks)[b]	
Quartile (95% CI)	
25%	31.6 (13.3, 51.3)
50% (median)	51.3 (32.0, 60.1)
75%	67.3 (51.3, 130.4)

CI = confidence interval; CR = complete response; DR = duration of response; N/n = number of subjects; PR = partial response.

a. 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.

b. DR (weeks) = (the end date for DR – first subsequent confirmed CR or PR +1)/7.

Results for DR based on investigator assessment were identical.

Pharmacokinetic Results:

Sunitinib, SU-012662, and Total Drug Pharmacokinetics:

A summary of observed and dose-corrected trough plasma concentrations for sunitinib, SU-012662, and total drug on Day 15 of Cycles 1, 2, 4, and 6 when sunitinib was administered with docetaxel and trastuzumab is presented in Table 10.

Table 10. Summary of Observed and Dose-Corrected Trough Plasma Concentrations (C_{trough}) of Sunitinib, SU-012662, and Total Drug on Day 15 of Cycles 1, 2, 4, and 6 Following Administration of Sunitinib in Combination With Docetaxel and Trastuzumab

Day	Cycle	Arithmetic Mean (%CV) [Median]							
		Observed C_{trough}				Dose-Corrected[a] C_{trough}			
		n	Sunitinib (ng/mL)	SU-012662 (ng/mL)	Total Drug (ng/mL)	n	Sunitinib (ng/mL)	SU-012662 (ng/mL)	Total Drug (ng/mL)
15	1	19	40.2 (80) [39.4]	16.2 (75) [16.3]	56.3 (76) [52.9]	14	52.6 (54) [48.0]	20.9 (50) [22.0]	73.5 (49) [70.7]
	2	16	37.3 (83) [30.4]	14.4 (79) [11.0]	51.7 (80) [40.9]	10	52.3 (57) [45.8]	18.6 (66) [15.6]	70.9 (57) [60.0]
	4	16	43.2 (63) [39.2]	17.6 (63) [15.8]	60.8 (62) [55.3]	15	50.5 (53) [51.5]	20.4 (54) [21.5]	70.9 (51) [72.1]
	6	13	28.5 (74) [34.0]	11.5 (84) [11.1]	40.0 (75) [44.6]	8	42.9 (64) [43.2]	18.4 (66) [14.9]	61.2 (62) [63.8]

Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0.
CV = coefficient of variation; C_{trough} = trough plasma concentration; n = number of subjects with observations; total drug = sunitinib + SU-012662.

a. For dose-correction, the reference dose was 37.5 mg. Dose-corrected trough concentrations with 10 consecutive days of dosing at the same dose were included.

Docetaxel Pharmacokinetics:

Docetaxel end-of-infusion concentration (ie, C_{max}) on Day 1 of Cycle 1 for 1 subject was identified as an outlier (ie, C_{max} was greater than mean +2 × standard deviation); therefore, the descriptive statistics for docetaxel on Day 1 of Cycle 1 were reported with and without the outlier subject.

A summary of observed and dose-corrected C_{max} plasma concentrations for docetaxel on Day 1 of Cycles 1, 2, 4, and 6 when docetaxel was administered with sunitinib and trastuzumab are presented in Table 11.

Table 11. Summary of Observed and Dose-Corrected End-of-Infusion Plasma Concentrations of Docetaxel on Day 1 of Cycles 1, 2, 4, and 6 Following Administration of Docetaxel in Combination With Sunitinib and Trastuzumab

Day	Cycle	Arithmetic Mean (%CV) [Median]			
		Observed C_{max}		Dose-Corrected[a] C_{max}	
		n	Docetaxel (ng/mL)	n	Docetaxel (ng/mL)
1	1	23	1117 (104) [668][b]	23	1117 (104) [668]
	2	19	1389 (91) [1060]	19	1459 (88) [1140]
	4	16	1317 (83) [1164]	16	1483 (86) [1301]
	6	15	1670 (97) [1810]	15	1771 (93) [1810]

CV = coefficient of variation; C_{max} = maximum plasma concentration which in this study was represented by the end-of-infusion concentration; n = number of observations; N = number of subjects.

a. For dose-correction, the reference dose was the starting total dose for each subject at 75 mg/m^2.

b. Excluding the extreme outlier subject on Day 1 of Cycle 1 since the concentration value (ie, 66500 ng/mL) for this subject was significantly greater than the mean plus 2 times standard deviations and was inconsistent with the values at other visits for the same subject. The descriptive statistics (mean (%CV) [median]) when including the outlier value were 3841 ng/mL (349) [769 ng/mL] on Day 1 of Cycle 1.

Trastuzumab Pharmacokinetics:

The observed trastuzumab C_{trough} values at all visits were below (84 samples out of a total of 88 samples) or very close (3 samples out a total of 88 samples) to the lower limit of quantification for all subjects for which PK samples were collected, with the exception of only 1 sample with concentration value of 76.8 on Day 1 of Cycle 6. The observed levels (<20 μg/mL) were lower than the observed and simulated historical trough mean values for trastuzumab on both weekly and every 3 weeks schedules (ie, ~60-70 μg/mL) (Table 12).

Table 12. Summary of Trastuzumab Trough Plasma Concentrations by Time

Day	Cycle	Sunitinib + Docetaxel + Trastuzumab	
		n	Arithmetic Mean (%CV) [Median]
1	1	23	0.00 [0.00]
	2	20	0.00 [0.00]
	4	17	0.00 [0.00]
	6	16	4.80 (400.00) [0.00]
15	1	4	0.00 [0.00]
	2	5	8.68 (136.93) [0.00]
	4	2	0.00 [0.00]
	6	1	21.00 [21.00]

Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0.
CV = coefficient of variation; n = number of subjects with observations.

Safety Results:

Treatment-Emergent Adverse Events - All Causality and Treatment-Related:

Table 13 provides the incidence of all causality and treatment-related treatment-emergent AEs by system organ class and preferred term in >5% subjects in the sunitinib + docetaxel + trastuzumab group. There were no AEs reported in >5% subjects in the docetaxel + trastuzumab group.

Table 13. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	Sunitinib + Docetaxel + Trastuzumab		
	n (%)	n1	n2
Number (%) of subjects:			
Evaluable for adverse events	24	-	-
With adverse events	23 (95.8)	-	-
Blood and lymphatic system disorders	18 (75.0)	134	134
Anaemia	6 (25.0)	29	29
Febrile neutropenia	2 (8.3)	2	2
Leukopenia	6 (25.0)	18	18
Neutropenia	14 (58.3)	81	81
Thrombocytopenia	4 (16.7)	4	4
Eye disorders	7 (29.2)	8	7
Conjunctivitis	5 (20.8)	6	5
Lacrimation increased	2 (8.3)	2	2
Gastrointestinal disorders	20 (83.3)	94	83
Abdominal pain	4 (16.7)	5	4
Abdominal pain upper	7 (29.2)	10	9
Constipation	4 (16.7)	4	3
Diarrhoea	15 (62.5)	29	25
Dyspepsia	2 (8.3)	2	2
Haemorrhoids	3 (12.5)	3	2
Nausea	11 (45.8)	18	17
Stomatitis	7 (29.2)	16	16
Vomiting	7 (29.2)	7	5
General disorders and administration site conditions	20 (83.3)	70	56
Asthenia	4 (16.7)	6	4
Fatigue	15 (62.5)	36	33
Mucosal inflammation	4 (16.7)	4	4
Oedema	2 (8.3)	2	2
Oedema peripheral	6 (25.0)	7	5
Pyrexia	13 (54.2)	15	8
Immune system disorders	5 (20.8)	10	7
Drug hypersensitivity	3 (12.5)	8	6
Hypersensitivity	2 (8.3)	2	1
Infections and infestations	7 (29.2)	11	0
Bronchitis	2 (8.3)	2	0
Cystitis	2 (8.3)	2	0
Gastroenteritis viral	2 (8.3)	3	0
Pharyngitis	2 (8.3)	2	0
Sinusitis	2 (8.3)	2	0
Investigations	2 (8.3)	2	1
Weight decreased	2 (8.3)	2	1
Metabolism and nutrition disorders	6 (25.0)	13	10
Decreased appetite	6 (25.0)	13	10
Musculoskeletal and connective tissue disorders	13 (54.2)	34	26
Arthralgia	5 (20.8)	6	6
Back pain	6 (25.0)	6	2
Bone pain	3 (12.5)	4	1
Myalgia	8 (33.3)	18	17

Table 13. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	Sunitinib + Docetaxel + Trastuzumab		
	n (%)	n1	n2
Nervous system disorders	12 (50.0)	20	14
Dizziness	2 (8.3)	2	0
Dysgeusia	4 (16.7)	5	5
Headache	4 (16.7)	4	1
Paraesthesia	3 (12.5)	3	2
Peripheral sensory neuropathy	4 (16.7)	6	6
Respiratory, thoracic and mediastinal disorders	15 (62.5)	41	16
Cough	7 (29.2)	10	0
Dyspnoea	4 (16.7)	7	4
Epistaxis	9 (37.5)	15	12
Oropharyngeal pain	5 (20.8)	9	0
Skin and subcutaneous tissue disorders	10 (41.7)	29	21
Acne	2 (8.3)	2	1
Alopecia	6 (25.0)	7	7
Dermatitis	2 (8.3)	2	0
Hair colour changes	2 (8.3)	2	2
Palmar-plantar erythrodysaesthesia syndrome	6 (25.0)	6	6
Rash	5 (20.8)	8	3
Skin discolouration	2 (8.3)	2	2
Vascular disorders	8 (33.3)	12	9
Hypertension	6 (25.0)	10	7
Phlebitis	2 (8.3)	2	2

Except for 'n1' and 'n2' subjects 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, treatment-related.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events calculated using the corresponding gender count as denominator.
MedDRA (version 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities.

Serious Adverse Events:

Table 14 provides the incidence of all causality and treatment-related treatment-emergent SAEs by system organ class and preferred term in any treatment group.

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by:	Sunitinib + Docetaxel + Trastuzumab			Docetaxel + Trastuzumab		
System Organ Class and Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:						
Evaluable for adverse events	24	-	-	1	-	-
With adverse events	10 (41.7)	-	-	1 (100.0)	-	-
Blood and lymphatic system disorders	7 (29.2)	8	8	0	0	0
Febrile neutropenia	4 (16.7)	5	5	0	0	0
Neutropenia	3 (12.5)	3	3	0	0	0
Gastrointestinal disorders	4 (16.7)	5	5	0	0	0
Diarrhoea	1 (4.2)	1	1	0	0	0
Intestinal perforation	1 (4.2)	1	1	0	0	0
Rectal haemorrhage	1 (4.2)	1	1	0	0	0
Stomatitis	1 (4.2)	1	1	0	0	0
Vomiting	1 (4.2)	1	1	0	0	0
General disorders and administration site conditions	1 (4.2)	1	1	1 (100.0)	1	1
Fatigue	1 (4.2)	1	1	0	0	0
Multi-organ failure	0	0	0	1 (100.0)	1	1
Infections and infestations	3 (12.5)	4	4	0	0	0
Erysipelas	1 (4.2)	1	1	0	0	0
Pseudomembranous colitis	1 (4.2)	1	1	0	0	0
Sepsis	1 (4.2)	1	1	0	0	0
Viral infection	1 (4.2)	1	1	0	0	0
Musculoskeletal and connective tissue disorders	1 (4.2)	1	0	0	0	0
Pathological fracture	1 (4.2)	1	0	0	0	0
Nervous system disorders	1 (4.2)	1	1	0	0	0
Syncope	1 (4.2)	1	1	0	0	0
Psychiatric disorders	1 (4.2)	1	0	0	0	0
Anxiety	1 (4.2)	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (4.2)	1	0	1 (100.0)	1	1
Acute respiratory distress syndrome	0	0	0	1 (100.0)	1	1
Lung disorder	1 (4.2)	1	0	0	0	0

Except for 'n1' and 'n2', subjects 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, treatment-related.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events calculated using the corresponding gender count as denominator.
MedDRA (version 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities.

Permanent Discontinuations of Study Drugs Due to Adverse Events:

A listing of permanent discontinuations due to AEs is provided in Table 15.

The most common reasons for permanent discontinuation of study drug were fatigue and neutropenia (2 subjects each).

Table 15. Permanent Discontinuations of Study Drugs Due to Adverse Events

Subject Gender/Age [Years]	Adverse Event (MedDRA [v14.0] Preferred Term)	Cycle Start[a]/ Stop[a]	Cycle Start Day[a]/Stop Day[a]	Start Day[b]/ Stop Day[b]	Grade	Outcome	Action Taken With: Sunitinib Trastuzumab Docetaxel	Causality
Sunitinib + Docetaxel + Trastuzumab								
F/69	Neutropenia	1/1	7/15	7/15	4	Resolved	Permanently discontinued Permanently discontinued Permanently discontinued	Docetaxel
	General physical health deterioration	1/1	7/28	7/[>28]	2	Still present	Permanently discontinued Permanently discontinued Permanently discontinued	Sunitinib/docetaxel
F/36	Fatigue	5/5	1/20	85/[>104]	3	Still present	Permanently discontinued Permanently discontinued Permanently discontinued	Sunitinib/docetaxel
F/47	Neutropenia	12/12	27/35	321/329	2	Resolved	Stopped temporarily Stopped temporarily Permanently discontinued	Sunitinib/docetaxel
F/70	Diarrhea	21/21	2/16	431/445	3	Resolved	Permanently discontinued No action taken No action taken	Sunitinib
F/69	Left ventricular dysfunction	10/12	22/1	227/263	2	Resolved	Permanently discontinued Stopped temporarily No action taken	Sunitinib/trastuzumab
	Peripheral sensory neuropathy	9/10	21/22	203/227	2	Resolved	No action taken No action taken Permanently discontinued	Docetaxel
F/69	Pathological fracture	5/5	17/25	122/130	3	Resolved	Permanently discontinued Permanently discontinued Permanently discontinued	Disease under study
F/83	Fatigue	1/5	8/15	8/[>113]	3	Still present	Permanently discontinued No action taken No action taken	Sunitinib/docetaxel
	Weight decreased	1/2	8/1	8/22	2	Resolved	Permanently discontinued No action taken No action taken	Sunitinib/docetaxel

Table 15. Permanent Discontinuations of Study Drugs Due to Adverse Events

Subject Gender/Age [Years]	Adverse Event (MedDRA [v14.0] Preferred Term)	Cycle Start[a]/ Stop[a]	Cycle Start Day[a]/Stop Day[a]	Start Day[b]/ Stop Day[b]	Grade	Outcome	Action Taken With: Sunitinib Trastuzumab Docetaxel	Causality
F/71	Asthenia	15/18	22/22	344/ [>457]	3	Still present	Permanently discontinued Stopped temporarily No action taken	Sunitinib
	Drug hypersensitivity	1/1	1/1	1/1	2	Resolved	No action taken No action taken Permanently discontinued	Docetaxel
F/54	Intestinal perforation	9/9	28/39	215/226	4	Resolved	Permanently discontinued No action taken Permanently discontinued	Sunitinib
F/69	Edema peripheral	8/21	12/8	158/ [>463]	1	Still present	Permanently discontinued No action taken No action taken	Sunitinib
F/63	Lethargy	1/1	3/7	3/7	3	Resolved	Permanently discontinued No action taken No action taken	Sunitinib
Docetaxel + Trastuzumab								
F/59	Multi-organ failure	1/1	16/22	16/22	5	Resolved	No action taken Permanently discontinued Permanently discontinued	Trastuzumab

F = female; ID = identification; MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Day relative to first day of each treatment period. First day of each treatment period = Day 1.
b. Day relative to start of study treatment. First day of study treatment = Day 1.

Deaths:

One (4.0%) subject died during the study, while on treatment.

One subject, a 59-year-old white female, received trastuzumab and docetaxel (subject did not receive sunitinib). She developed Grade 4 acute respiratory distress syndrome on Day 2 of Cycle 1. The subject developed multi-organ failure on Day 16 of Cycle 1 and died on Day 22.

Laboratory Evaluations:

The most frequently reported hematology laboratory abnormalities were decrease of absolute neutrophils and decrease of white blood cells (100% each). A common terminology criteria for adverse events (CTCAE) Grade 4 decrease of absolute neutrophils was reported in 79.2% of the subjects and a CTCAE Grade 4 decrease of white blood cells was reported in 44.0% of the subjects.

The median neutrophil nadir was 365/mm^3 and ranged from 10 to 3400/mm^3. The median number of days to neutrophil nadir was 8.5 days (range, 7 to 23 days).

The most frequently reported chemistry laboratory abnormalities were hyperglycemia (81.8%), elevated AST (62.5%), creatine kinase (60.0%), and elevated ALT (54.2%).

Vital Signs:

There were no clinically relevant changes in vital signs.

Electrocardiogram:

The maximum on-study corrected measure of the time between the start of the Q wave and the end of the T wave (QT interval) (Fridericia's formula [QTcF]) was Grade 1 in 1 (5.3%) subject. No subject had a CTCAE of Grade 2 or more.

ECOG Performance Status:

The maximum on-study ECOG performance status score was 1 in 16 (64.0%) subjects, 2 in 3 (12.0%) subjects, and 3 in 3 (12.0%) subjects. The maximum on-study ECOG performance status score was not evaluable in 1 (4.0%) subject.

Left Ventricular Ejection Fraction:

Two subjects had a LVEF lower than the lower limit of normal.

CONCLUSIONS:

- The combination of sunitinib (37.5 mg once daily [Schedule 2/1]) with docetaxel (75 mg/m^2 every 3 weeks) and trastuzumab (therapeutic dose) had an acceptable toxicity profile in subjects with ABC overexpressing HER-2;

- The combination of sunitinib (37.5 mg once daily [Schedule 2/1]) with docetaxel (75 mg/m^2 every 3 weeks) and trastuzumab (therapeutic dose) showed preliminary antitumor activity with a best overall ORR of 72.7% (16 of 22 subjects had PR) and a median PFS of 58.4 (95% CI, 37.0, 66.1) weeks;

- There were no clinically relevant changes in the PK of sunitinib or docetaxel when they were both administered together with trastuzumab as a triple combination in comparison to when each was administered alone. Although the plasma exposures to trastuzumab when administered with sunitinib and docetaxel appeared to be considerably lower than historical control plasma exposure values, the true cause of this lower exposure could not be ascertained. Future studies will need to be conducted to confirm this finding and identify the cause of potentially lower trastuzumab exposures when co-administered with sunitinib and/or docetaxel.