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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00243503

PROTOCOL NO.: A6181067

PROTOCOL TITLE: A Phase 2 Efficacy and Safety Study of SU011248 in Combination with Trastuzumab as Treatment for Metastatic Disease in Patients with Breast Cancer

Study Centers: The study was conducted at 4 centers in Belgium (2 centers did not randomize subjects), 3 centers in Canada, 3 centers in France, 3 centers in Spain, and 15 centers in USA (9 centers did not randomize subjects)

Study Initiation and Completion Dates: 24 February 2006 to 20 July 2010

Phase of Development: Phase 2

Study Objectives:

Primary

- To estimate the objective response rate (ORR) for the combination of trastuzumab and sunitinib in locally recurrent or metastatic breast cancer (BC).

Secondary

- To evaluate the safety and tolerability of sunitinib administered in combination with trastuzumab in this subject population.
- To assess measures of duration of tumor control and survival.
- To assess patient reported outcomes.
- To determine sunitinib and SU-012662 (active metabolite of sunitinib) plasma trough concentrations (C_{trough}) in combination with trastuzumab and to potentially explore the relationship between C_{trough} and efficacy, and safety.

METHODS

Study Design: This Phase 2 clinical study evaluated the activity and safety of trastuzumab administered in combination with sunitinib in subjects with locally recurrent or metastatic BC. Approximately 53 subjects were planned to be enrolled into this study.

Treatment on study was administered in 4-week cycles. Trastuzumab was administered weekly (loading 4 mg/kg followed by weekly 2 mg/kg) or every 3 weeks (loading 8 mg/kg followed by 6 mg/kg every 3 weeks). Sunitinib dosing began with 37.5 mg by oral capsule once daily in a continuous regimen. Subjects experiencing dose-limiting toxicity attributed to sunitinib had 1-week off-treatment periods inserted into the regimen as needed and could have had their dose reduced. Subjects completing 2 cycles (8 weeks) of treatment with minimal treatment-related effects could have had their dose escalated to 50 mg daily in the third cycle. Subsequent cycles could have had further dose titration depending upon individual tolerability.

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 have been based on achievement of maximum benefit or tolerability issues). If either trastuzumab or sunitinib were discontinued for reasons other than progressive disease (PD), subjects could have continued to receive the remaining agent until PD. Subjects discontinuing both agents prior to PD were followed for tumor assessment until PD, until the initiation of a subsequent anti-cancer therapy in the absence of documented PD, or until death, whichever occurred first. Subjects could have also continued to receive single-agent sunitinib beyond the time of RECIST-defined progression at the discretion of the investigator if the subject was perceived to be experiencing clinical benefit. Treatment on study was planned to continue for up to 18 months; subjects requiring continued access following 18 months were offered sunitinib on a separate protocol.

Number of Subjects (Planned and Analyzed): Approximately 53 subjects were planned to be enrolled into this study; 60 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion: Subjects with histologically or cytologically proven diagnosis of BC with evidence of unresectable, locally recurrent, or metastatic disease. Disease was to have been measurable as per RECIST and Human Epidermal growth factor Receptor 2 (HER2) positive. Prior treatment with trastuzumab and/or lapatinib in the neoadjuvant, adjuvant or metastatic disease setting was permitted.

Study Treatment: Trastuzumab was administered intravenously starting on Cycle 1 Day 1. Self-administration of sunitinib capsules took place on an outpatient basis except on days when pharmacokinetic (PK) sampling was conducted. Capsules were to be taken once daily in the morning without regard to meals.

Efficacy Evaluations: The determination of anti-tumor efficacy was based on objective tumor assessments made according to the RECIST system of unidimensional evaluation. The primary efficacy endpoint was ORR, defined as the percent of subjects with confirmed

complete response (CR) or confirmed partial response (PR) according to the RECIST, relative to all subjects who were enrolled in the study with a measurable disease at baseline and treated with the combination at any time. Secondary endpoints included duration of response (DR), clinical benefit rate (CBR), progression-free survival (PFS), time-to-tumor progression (TTP), probability of survival at 1 year, and overall survival (OS).

Outcomes Research and Pharmacokinetic Evaluations: Patient-reported outcomes (PROs) were assessed using the self-administered, validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the breast cancer module BR23 questionnaires.

Trough blood samples were obtained on Day 1 of Cycles 3 and 5 for analysis of sunitinib and its active metabolite SU-012662.

Safety Evaluations: Adverse events (AEs) were recorded throughout the study. Clinical laboratory tests included hematology, blood chemistry, thyroid function, electrolyte levels, and serum or urine pregnancy test (for women of childbearing potential). Other safety measures included physical examination, Eastern Cooperative Oncology Group performance status (ECOG PS), vital signs, 12-lead electrocardiogram (ECG), and a multigated acquisition (MUGA) scan or echocardiogram for an assessment of left ventricular ejection fraction (LVEF).

Statistical Methods: Efficacy analyses were conducted on the intent-to-treat (ITT) population, which consisted of subjects treated with the combination at any time. The number and percent of subjects achieving objective response (OR) (CR or PR) were summarized along with the corresponding exact two-sided 95% confidence interval (CI) calculated using a method based on the F distribution. A 13% improvement in the historical ORR from 20% for subjects treated with trastuzumab to 33% for subjects treated with trastuzumab plus sunitinib was expected for this study. The study was designed to test the null hypothesis that the true historical ORR was no different from that of the combination (trastuzumab plus sunitinib) versus the alternative hypothesis that trastuzumab plus sunitinib had a higher ORR by checking if the lower bound of the 95% CI of ORR of the combination was larger than 13%. The CBR was summarized along with the corresponding exact two-sided 95% CI calculated using a method based on the F distribution. Time-to-event endpoints, including TTP, PFS, OS, and DR were summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event time and two-sided 95% CI for the median were provided for each endpoint. The 1-year survival probability was estimated using the Kaplan-Meier method and a two-sided 95% CI for the log [-log(1-year survival probability)] was calculated using a normal approximation and then back transformed to give a CI for the 1-year survival probability itself.

Descriptive information was provided on the symptom scales for the EORTC-QLQ C30 and BR23 and on functioning scales and global quality of life (EORTC-C30) at each assessment. Descriptive statistics were generated. The proportions of subjects who reported at least a 10-point improvement (ie, 10% of the possible range of 100) in certain PRO domains and symptoms as compared with the baseline (pre-treatment) scores was reported.

Summary descriptive statistics, figures, and listings of plasma concentrations by cycle and day were presented for sunitinib, SU-012662, and Total Drug. For comparison purposes, the geometric mean values for trough concentrations (C_{trough}) of sunitinib, SU-012662, and Total Drug when sunitinib was administered with trastuzumab were compared to the historical control values when sunitinib was administered alone.

PK-evaluable subjects on Day 1 of Cycle 3 and Day 1 of Cycle 5 were each divided into 2 PK subgroups: those with C_{trough} values < the median C_{trough} value and those equal or above the C_{trough} value. Summary statistics of incidence of AEs asthenia, hypertension, ejection fraction decreased, leukopenia, neutropenia, thrombocytopenia, and lymphopenia by maximum Common Toxicity Criteria for Adverse Events (CTCAE) Grade and for all Grades combined during Cycles 1-4 for both PK subgroups at each visit were generated. In addition, the Pearson correlation coefficients between the percent change in the lab values for absolute neutophil count (ANC), thrombocyte count, lymphocyte count, leukocyte count, LVEF, systolic BP, and diastolic BP with total drug C_{trough} values were calculated with respect to each PK visit. Finally, the summary statistics for the rate of stable disease, ORR, and CBR, PFS, and OS were provided for both PK subgroups at each PK visit.

AEs (all causalities and treatment-related) and serious adverse events (SAEs) were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Deaths were summarized by time period (on-treatment versus during follow-up) and cause of death. Deaths that occurred within 28 days after the last dose of study treatment were defined as on-treatment deaths. For hematology and chemistry tests, descriptive statistics were provided for each test result and for change from baseline by visit. Hematology results were graded according to the National Cancer Institute CTCAE Version 3.0. A shift summary of baseline grade by maximum CTCAE grade and cycle was presented. Vital signs data were summarized and presented categorically. ECOG PS data were summarized. ECG data were summarized and the frequency of subjects who experienced QTc interval prolongation was displayed by category according to CTCAE Version 3.0 Grades 1, 2, and 3/4. MUGA scan results were summarized.

RESULTS

Subject Disposition and Demography: Sixty subjects were enrolled in the study and 2 subjects completed and went onto the continuation protocol. The most common reason for discontinuation was lack of efficacy (44 subjects, 73.3%). Three subjects were enrolled under Protocol Amendment 1 in the trastuzumab/placebo arm, and discontinued prior to implementation of Protocol Amendment 2; consequently, these subjects received only trastuzumab.

Mean age was 55 years (range 31-81 years), and most subjects (55 subjects, 91.7%) were white. All subjects had ECOG PS of 0 or 1 at baseline. There were 33 subjects (55.0%) who were estrogen receptor positive and 22 subjects (36.7%) who were progesterone receptor positive. All subjects were HER2 positive.

Most subjects, 58 subjects (96.7%), had metastatic breast cancer; the other 2 subjects had locally recurrent breast cancer. Most subjects (43 subjects, 71.7%) had received prior

treatment with either an anthracycline based regimen plus trastuzumab or lapatinib (26 subjects, 43.3%), anthracycline only (11 subjects, 18.3%), trastuzumab only (4 subjects, 6.7%), or lapatinib only (2 subjects, 3.3%), while 16 subjects (26.7%) were naïve to treatment, ie, had not prior chemotherapeutic, trastuzumab or lapatinib treatment. Prior radiation therapy, hormonal therapy, and cancer surgery had been experienced by 38 subjects (63.3%), 31 subjects (51.7%), and 59 subjects (98.3%), respectively.

Efficacy Results: The primary efficacy endpoint was ORR; this was 36.8% (95% CI: 24.4%, 50.7%) (Table 1). Since the lower bound of the 95% CI of ORR for the combination was greater than 13%, the null hypothesis that the ORR of the combination was no different from the historical ORR was rejected. ORR was greater for subjects who were treatment-naïve or who only received prior adjuvant therapy (44.1%) compared to those with prior first-line treatment (26.1%).

Table 1. Summary of Best Overall Investigator Tumor Response (Intent-to-Treat Population)

	Trastuzumab + Sunitinib		
Variable	**All Subjects**	**No Prior Treatment or Adjuvant Treatment**	**Prior First Line Treatment**
Subjects with Baseline Assessments	57	34	23
Subjects with Measurable Disease at Baseline	57	34	23
Best Overall Response, number (%) of subjects			
Complete Response (CR)	2 (3.5)	2 (5.9)	0
Partial Response (PR)	19 (33.3)	13 (38.2)	6 (26.1)
Stable Disease	21 (36.8)	10 (29.4)	11 (47.8)
Progressive Disease	13 (22.8)	8 (23.5)	5 (21.7)
Not Evaluable	2 (3.5)	1 (2.9)	1 (4.3)
Overall Confirmed Objective Response Rate (CR+PR)			
Number (%) of Subjects	21 (36.8)	15 (44.1)	6 (26.1)
95% Exact Confidence Interval (%)[a]	(24.4, 50.7)	(27.2, 62.1)	(10.2, 48.4)
Clinical Benefit Rate[b]			
Number (%) of Subjects	32 (56.1)	20 (58.8)	12 (52.2)
95% Exact Confidence Interval (%)[a]	(42.4, 69.3)	(40.7, 75.4)	(30.6, 73.2)
Duration of Stable Disease, number (%) of subjects			
≥14 weeks and <24 weeks	5 (8.8)	1 (2.9)	4 (17.4)
≥24 weeks	11 (19.3)	5 (14.7)	6 (26.1)

[a] Two—sided 95% confidence interval from Exact Method based on the F Distribution.
[b] The percent of subjects with complete response, partial response or stable disease ≥24 weeks.

Secondary efficacy endpoints were evaluated. Median DR was 25.6 weeks (95% CI: 22.4, 32.9 weeks). CBR was 56.1% (95% CI: 42.4%, 69.3%). A total of 48 subjects (84.2%) had a PFS event (progression or death) during the observation period; median PFS was 28 weeks (95% CI: 24.1, 31.3 weeks). Median TTP was 26.0 weeks (95% CI: 23.3, 31.1 weeks). A

total of 20 subjects (35.1%) died; median OS was not reached, and 1-year survival rate was 91.2% (95% CI: 80.2%, 96.3%).

Outcomes Research and Pharmacokinetic Results: Overall, PROs among subjects treated with sunitinib plus trastuzumab appear to be mixed, with some functional domains and symptoms improved during treatment while others worsened. Specifically, emotional function, pain, insomnia, breast and arm symptoms clinically improved. The most notable clinical worsening was in diarrhea.

Trough plasma concentrations (C_{trough}) of sunitinib, SU-012662, and Total Drug are summarized in Table 2. The geometric mean ratios (Day 1 of Cycle 3 from this study over Day 28 Cycle 1 for historical control data; sunitinib + trastuzumab/sunitinib alone) of C_{trough} were 0.90, 1.06, and 1.01 for sunitinib, SU-012662, and Total Drug, respectively.

Table 2. Summary of Observed and Dose-Corrected Trough Plasma Concentrations (C_{trough}) of Sunitinib, SU-012662, and Total Drug on Day 1 of Cycles 3 and 5 Following Administration of Sunitinib in Combination with Trastuzumab

		Arithmetic Mean (%CV) [Median]							
		Observed C_{trough}				Dose-corrected[a] C_{trough}			
Day	Cycle	n	Sunitinib (ng/mL)	SU-012662 (ng/mL)	Total Drug (ng/mL)	n	Sunitinib (ng/mL)	SU-012662 (ng/mL)	Total Drug (ng/mL)
1	3	29	45.7 (61) [51.1]	23.7 (68) [23.3]	69.3 (61) [74.5]	18	53.5 (52) [57.9]	26.7 (54) [25.0]	80.2 (50) [82.8]
	5	18	43.6 (52) [49.9]	20.8 (68) [19.3]	64.3 (55) [69.9]	13	55.0 (45) [58.1]	24.7 (51) [25.3]	79.7 (46) [83.9]

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

There appeared to be correlations (ranging from weak to strong) between a number of safety laboratory values (ANC, thrombocyte count, leukocyte count, lymphocyte count, LVEF, systolic BP, and diastolic BP) and drug plasma exposures. In addition, there appeared to be a relationship between drug exposures and anti-tumor response. Subjects with higher drug plasma exposures appeared to have greater ORR and PFS values as compared to those with lower drug plasma exposures.

Safety Results: Most subjects (59 subjects, 98.3%) had at least 1 AE, with most of these subjects (55 subjects, 96.5%) having an AE considered to be related to sunitinib (Table 3). AEs considered related to trastuzumab and to both sunitinib and trastuzumab were reported for 39 subjects (65.0%) and 26 subjects (45.6%), respectively.

Table 3. Treatment-Emergent Adverse Events

	Trastuzumab + Sunitinib/Trastuzumab				
Number (%) of subjects	**All Causalities**	**Sunitinib Related**	**Trastuzumab Related**	**Sunitinib and Trastuzumab Related**	**Placebo Related**
Evaluable for AEs	60	57	60	57	6
Number of AEs	886	554	179	120	14
With AEs	59 (98.3)	55 (96.5)	39 (65.0)	26 (45.6)	4 (66.6)
With SAEs	25 (41.7)	18 (31.6)	4 (6.7)	4 (7.0)	0
With Grade 3 or 4 AEs	48 (80.0)	43 (75.4)	13 (21.7)	11 (19.3)	1 (16.7)
With Grade 5 AEs	1 (1.7)	1 (1.8)	1 (1.7)	1 (1.8)	0
Discontinued Study due to AEs	15 (25.0)	12 (21.1)	6 (10.0)	5 (8.8)	0
Discontinued Sunitinib due to AEs	18 (30.0)	15 (26.3)	6 (10.0)	5 (8.8)	0
Discontinued Trastuzumab due to AEs	15 (25.0)	11 (19.3)	8 (13.3)	6 (10.5)	0
Temporarily Discontinued Sunitinib due to AEs	43 (71.7)	37 (64.9)	10 (16.7)	8 (14.0)	0
Temporarily Discontinued Trastuzumab due to AEs	27 (45.0)	11 (19.3)	19 (31.7)	9 (15.8)	0
Dose Reduction of Sunitinib due to AEs	14 (23.3)	14 (24.6)	2 (3.3)	2 (3.5)	0
Dose Reduction of Trastuzumab due to AEs	4 (6.7)	3 (5.3)	1 (1.7)	1 (1.8)	0

AE = adverse event; SAE = serious adverse event; MedDRA = Medical Dictionary for Regulatory Activities
For each preferred term, AEs were counted only once for each subject
SAEs were according to the investigator's assessment (data source was case report form).
Three subjects only took trastuzumab.
MedDRA (v13.0) coding dictionary applied.

The most frequently reported AEs were diarrhea (36 subjects, 60.0%), asthenia (29 subjects, 48.3%), dysgeusia (27 subjects, 45.0%), and hypertension (26 subjects, 43.3%) (Table 4). Most subjects experienced a maximum Grade 3 AE (42 subjects, 70.0%), with 5 subjects (8.3%) experiencing a maximum Grade 4 AE. AEs were more frequently considered to be related to sunitinib than to trastuzumab.

Table 4. Treatment-Emergent Adverse Events (All Causalities) by Preferred Term (All Cycles) in ≥15% Subjects (Safety Population)

Number (%) of Subjects Preferred Term	Trastuzumab + Sunitinib/Trastuzumab (N=60)
Diarrhea	36 (60.0)
Asthenia	29 (48.3)
Dysgeusia	27 (45.0)
Hypertension	26 (43.3)
Mucosal inflammation	21 (35.0)
Vomiting	21 (35.0)
Dyspepsia	20 (33.3)
Epistaxis	20 (33.3)
Nausea	20 (33.3)
Fatigue	19 (31.7)
Headache	19 (31.7)
Thrombocytopenia	19 (31.7)
Decreased appetite	18 (30.0)
Neutropenia	17 (28.3)
Dry skin	15 (25.0)
Ejection fraction decreased	14 (23.3)
Yellow skin	13 (21.7)
Abdominal pain	11 (18.3)
Pyrexia	11 (18.3)
Weight decreased	11 (18.3)
Constipation	10 (16.7)
Left ventricular dysfunction	10 (16.7)
Palmar-plantar erythodysesthesia syndrome	10 (16.7)
Dyspnea	9 (15.0)
Insomnia	9 (15.0)
Rash	9 (15.0)

N = total number of subjects, MedDRA = Medical Dictionary for Regulatory Activities
Three subjects only took trastuzumab.
MedDRA (v13.0) coding dictionary applied.

One subject (1.7%) experienced a Grade 5 (fatal) AE: a 66-year-old female died on Day 90, 7 days after taking her last dose of sunitinib and 21 days after her last dose of trastuzumab (89 days since her first doses of sunitinib and trastuzumab on Day 1) due to cardiogenic shock and multiorgan failure. Both of these SAEs were considered to be related to sunitinib and trastuzumab. Another 22 subjects died during follow-up, due to disease under study.

SAEs were experienced by 25 subjects (41.7%). SAEs experienced by ≥2% of subjects are summarized in Table 5; no SAE was reported for >5% of subjects. The most common SAE was thrombocytopenia, reported as an SAE for 3 subjects (5.0%); for each of these subjects, the SAE was considered to be related to sunitinib but not to trastuzumab.

Table 5. Serious Adverse Events by Preferred Term in ≥2% Subjects (All Causalities)

Number (%) of Subjects Preferred Term	Trastuzumab + Sunitinib/Trastuzumab (N=60)
Thrombocytopenia	3 (5.0)
Asthenia	2 (3.3)
Epistaxis	2 (3.3)
Febrile Neutropenia	2 (3.3)
Hypertension	2 (3.3)
Pancreatitis	2 (3.3)
Vomiting	2 (3.3)

N = total number of subjects; MedDRA = Medical Dictionary for Regulatory Activities
Data source was from case report form page.
Subjects were only counted once per treatment for each row.
Three subjects only took trastuzumab.
MedDRA (v13.0) coding dictionary applied.

Permanent discontinuations of sunitinib and/or trastuzumab due to AEs are listed in Table 6

Table 6. Permanent Discontinuations due to Adverse Events

Subject Age	MedDRA Preferred Term	Study Start Day/Stop Day[a]	Grade/ Outcome	Study Drug (s) Permanently Discontinued	Causality	SAE[b]
72	Pulmonary embolism	177/179	4/Resolved	S	S	Yes
43	Hypertension	192/207	3/Resolved	S/T	S	No
52	Thrombocytopenia	28/41	4/Resolved	S/T	S	Yes
	Epistaxis	27/33	3/Resolved	S/T	S	Yes
66	Cardiogenic shock	87/89	5/Resolved	S/T	S/T	Yes
	Multi-organ failure	87/89	4/Resolved	S/T	S/T	Yes
59	Decreased appetite	308/320	3/Resolved	S	S	No
75	Gastritis	254/274	1/Resolved	S	S	No
73	Anemia	43/[>63]	2/Still present[c]	S/T	S	No
	Thrombocytopenia	43/63	3/Resolved	S/T	S	Yes
	Diarrhea	43/49	2/Resolved	S/T	S	No
54	Left ventricular dysfunction	141/[>250]	2/Still present[c]	S/T	S/T	No
48	Pancreatitis	39/49	2/Resolved	S/T	S	Yes
51	Ejection fraction decreased	58/84	3/Resolved	S/T	T	No
54	Hypercalcemia	15/30	3/Resolved	S/T	Disease under study	Yes
61	Ejection fraction decreased	74/[>289]	3/Still present[c]	S/T	S/T	No
65	Cardiac failure acute	126/128	3/Resolved	S/T	S/T	Yes
31	Left ventricular dysfunction	139/217	2/Resolved	T	T	No
36	Left ventricular dysfunction	167/195	2/Resolved	T	S/T	No
61	Neutropenia	140/147	3/Resolved	S	S	No
37	Anal fistula	204/324	3/Resolved	S/T	S	Yes
74	Cardiac failure	80/102	3/Resolved	S	S/T	Yes
	Asthenia	80/102	3/Resolved	S	S/T	Yes
	Dyspnea	80/102	3/Resolved	S	S/T	Yes
	Left ventricular dysfunction	51/102	2/Resolved	T	S/T	No
39	Mastitis	112/[>112]	2/Still present[c]	S/T	Disease under study	No
69	Hypertension	41/92	3/Resolved	S	S	Yes

MedDRA = Medical Dictionary for Regulatory Activities; S = sunitinib; T =trastuzumab
[a] Day relative to start of study treatment. First day of study treatment = Day 1
[b] Serious adverse event per investigator assessment
[c] Event still present after continued follow-up
[ ] Days in brackets were imputed days derived from incomplete dates.
MedDRA (v13.0) coding dictionary applied.

Selected hematology parameters are summarized by maximum grade in Table 7. The most common parameter with Grade 3/4 abnormalities was neutrophils (absolute), with Grade 3 abnormalities reported for 9 subjects (15.0%) and Grade 4 abnormalities for 1 subject (1.7%).

Three subjects (5.0%) had Grade 4 platelets. For most subjects with Grade 3/4 abnormalities, the parameter was Grade 0 at Baseline.

Table 7. Summary Results of Laboratories by Maximum CTCAE Grade (Hematology, All Cycles) (Safety Population)

Number (%) of Subjects	Trastuzumab + Sunitinib/Trastuzumab (N=60)				
Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hemoglobin	27 (45.0)	19 (31.7)	2 (3.3)	0	48 (80.0)
Lymphocytes (absolute)	19 (31.7)	17 (28.3)	6 (10.0)	1 (1.7)	43 (71.7)
Neutrophils (absolute)	13 (21.7)	23 (38.3)	9 (15.0)	1 (1.7)	46 (76.7)
Platelets	30 (50.0)	4 (6.7)	6 (10.0)	3 (5.0)	43 (71.7)
White blood cells	19 (31.7)	27 (45.0)	4 (6.7)	1 (1.7)	51 (85.0)

Source: Table 13.7.5.1
CTCAE = Common Terminology Criteria for Adverse Events; N = total number of subjects

The most common serum chemistry Grade 3/4 abnormalities were hyponatremia, with Grade 3 abnormalities reported for 5 subjects (8.3%) and abnormal alkaline phosphatase, with Grade 3 abnormalities for 3 subjects (5.1%) and Grade 4 abnormalities for 1 subject (1.7%). Single subjects also experienced Grade 4 abnormalities of creatinine, hypercalcemia, and hypocalcemia. For most subjects with Grade 3/4 abnormalities, the parameter was Grade 0 or 1 at Baseline.

The proportion of subjects with LVEF decline was greater for subjects who had received prior treatment with either trastuzumab plus anthracycline (50.0%) or anthracycline only (54.5%) compared to those who had received neither treatment (26.3%) or trastuzumab only (0%).

CONCLUSIONS:

- The ORR was 36.8% (95% CI: 24.4%, 50.7%). Since the lower bound of the 95% CI of ORR for the combination was greater than 13%, the null hypothesis that the ORR of the combination was no different from the historical ORR was rejected. ORR was greater for subjects who were treatment-naïve or who only received prior adjuvant therapy (44.1%) compared to those with prior first-line treatment (26.1%). Median DR was 25.6 weeks (95% CI: 22.4, 32.9 weeks).

- As well as the 21 subjects with an OR, 11 subjects had stable disease ≥24 weeks, resulting in a CBR of 56.1% (95% CI: 42.4%, 69.3%).

- Median PFS was 28 weeks (95% CI: 24.1, 31.3 weeks). Median OS was not reached.

- Sunitinib plus trastuzumab appeared to have an acceptable safety profile, with no new, unexpected AEs observed. One subject died on study due to cardiogenic shock that was considered to be related to study treatment (sunitinib and trastuzumab). The most frequently reported AEs, each of which was experienced by >40% of subjects, were diarrhea, asthenia, dysgeusia, and hypertension.

- The proportion of subjects with LVEF decline was greater for subjects who had received prior treatment with either trastuzumab plus anthracycline (50.0%) or anthracycline only (54.5%) compared to those who had received neither treatment (26.3%) or trastuzumab only (0%).

- Overall, PROs among subjects treated with sunitinib plus trastuzumab appear to be mixed, with some functional domains and symptoms improved during treatment while others worsened. Specifically, emotional function, pain, insomnia, breast and arm symptoms clinically improved. The most notable clinical worsening was in diarrhea.

- There were no clinically relevant changes in the PK of sunitinib when it was administered with trastuzumab in comparison to when sunitinib was administered alone. There appeared to be correlations between a number of key safety values (ANC, leukocyte count, LVEF, and systolic BP) and drug plasma exposures. In addition, there appeared to be a relationship between drug exposures and anti-tumor response. Subjects with higher drug plasma exposures appeared to have greater ORR and PFS values as compared to those with lower drug plasma exposures.