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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: SU-014813

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the United States

NATIONAL CLINICAL TRIAL NO.: NCT00322517

PROTOCOL NO.: A6191007

PROTOCOL TITLE: A Phase 2 Study of the Efficacy and Safety of SU-014813 in Subjects with Metastatic Breast Cancer

Study Center(s): Germany (3), Italy (4), Netherlands (2), United Kingdom (4), United States (3).

Study Initiation and Completion Dates: 11 April 2006 to 09 July 2009

Phase of Development: Phase 2

Study Objective(s): Primary: To determine the antitumor efficacy of single agent SU-014813 at a dose of 100 mg orally (PO) once daily (QD) in subjects with metastatic breast cancer (MBC).

Secondary:

- To assess onset and duration of tumor control and 1-year survival rate;
- To evaluate the safety of SU-014813;
- To assess subject-reported outcomes;
- To determine SU-014813 plasma trough concentration (C_{trough}) and to explore the relationship between C_{trough} and efficacy, safety, and biomarkers;
- To explore the correlations of cancer biomarkers with treatment-related outcomes.

METHODS

Study Design: This was an open-label, uncontrolled, 2-stage, multicenter, Phase 2 clinical trial evaluating the efficacy and safety of single-agent SU-014813 in subjects with MBC.

The sample size was determined using Simon's optimal design for Phase 2 studies. A

maximum of 66 evaluable metastatic breast cancer subjects were to be included in the study. Initially, 21 evaluable subjects were planned for evaluation for response (complete response[CR] or partial response [PR]) in Stage 1. Once 3 or more confirmed responses were documented, the study was to proceed to Stage 2 where 45 additional evaluable subjects were to be enrolled and treated, to a total sample size of 66 evaluable treated subjects. If 11 or more responses (CR or PR) were documented among these 66 evaluable subjects, the study was to be considered successful. All subjects received SU-014813 daily for up to 6 months, in the absence of any withdrawal criteria that would require discontinuation.

Early discontinuation of study treatment was required in cases of disease progression, unresolved SU-014813-associated toxicity, withdrawal of subject consent, the need for surgery or other anticancer therapy not specified in the protocol, or if it was deemed by the treating investigator to be in the subject's best interest. After completion of the study, subjects with clinical benefit, as judged by the investigator and upon discussion with the sponsor, could have been candidates for continuation of treatment beyond 6 months.

Number of Subjects (Planned and Analyzed): A total of 66 subjects were planned for enrollment; 90 subjects were screened and enrolled. Of these, 89 subjects were treated. A total of 78 subjects were analyzed for efficacy and 89 subjects were evaluated for AEs and 88 subjects were evaluated for laboratory data.

Diagnosis and Main Criteria for Inclusion: Subjects were enrolled if they were females at least 18 years old who had a histologically or cytologically proven diagnosis of metastatic breast adenocarcinoma that was not amenable to surgery, radiation, or combined modality therapy with curative intent. Subjects were to receive prior treatment with an anthracycline and a taxane, either concurrently or sequentially, in the adjuvant and/or advanced disease treatment settings and may have received as many as 2 other chemotherapy regimens in the advanced disease setting.

Study Treatment: All subjects received SU-014813 at the dose of 100 mg daily in repeated cycles of 21 days. SU-014813 was dispensed as hard gelatin capsules to be taken orally, every morning, on an empty stomach, 1 hour before breakfast or at least 2 hours after food intake. SU-014813 was dispensed to subjects to take home for self-administration. Dose escalation to 150 mg/day was permitted only in subjects who experienced Grade ≤1 nonhematologic or Grade ≤2 hematologic toxicity attributed to SU-014813 within the first 8 weeks of treatment. Dose reduction by 1 dose level may have been permitted after discussion between the sponsor and the investigator.

Efficacy Evaluations: The primary endpoint was the overall confirmed objective response rate (ORR), defined as the proportion of subjects with confirmed CR or PR according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0). The determination of antitumor activity was based on objective tumor assessments made according to the RECIST system of unidimensional evaluation.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

Pharmacokinetic Measurements: Blood samples for the measurement of SU-014813 plasma concentrations were collected before dosing on Days 1 and 21 of Cycle 1, Day 15 of subsequent cycles (>1), and at the end of treatment. Except for the predose sample on Day 1 of Cycle 1, all predose samples were to be collected within 15 minutes before the next dose. All pharmacokinetic (PK) samples were analyzed for SU-014813 using a validated bioanalytical method.

Pharmacodynamic Measurements: In addition to standard assessments of disease activity, the biological activity of study medication was measured by biological markers. Biological marker studies were performed on peripheral blood and plasma by looking at ribonucleic acid (RNA) expression of certain genes in circulating peripheral blood cells and also screening plasma for changes in expression of proteins which could be altered in response to therapy. Any changes observed in these parameters were correlated with duration of dosing, drug plasma levels and changes in other parameters of activity as assessed by standard imaging studies. Biomarker samples were collected at the same time as selected PK samples for the purpose of PK-pharmacodynamic (PD) correlation. Plasma for assessment of soluble proteins was collected before dosing on Days 1 and 21 of Cycle 1 and on Day 15 of subsequent cycles throughout the study. Blood samples for evaluation of circulating endothelial cells (CECs) were also collected. CECs and their progenitors (CEPs) were also evaluated by culture assays.

Patient-reported outcomes: Patient-reported outcomes were evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and the breast cancer module (BR23). These measures were administered at Baseline (Cycle 1 Day 1), on Day 1 of each subsequent cycle, and at end of treatment.

Safety Evaluations: Adverse events (AEs) were recorded at each study visit to include the type, incidence, timing, seriousness, relatedness, and severity of AEs (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0).

Clinically significant laboratory abnormalities were also to be captured as AEs. Baseline tumor-related signs and symptoms were recorded as AEs during the trial if they worsened in severity or increased in frequency. Safety laboratory assessments included hematology, chemistry, coagulation, urinalysis, and serum or urine pregnancy tests.

Hematology and blood chemistry samples were taken at Screening and each study visit during treatment and at End of Treatment. Coagulation test samples were taken at Screening and on Day 1 of each treatment cycle. Urinalysis and pregnancy tests were performed only at Screening. Safety evaluations also included physical examinations collected at Screening, Day 21 of Cycle 1, and Day 1 of each subsequent cycle, as well as at End of Treatment.

Physical examinations included, but were not limited to, assessments of general appearance and examinations of known and suspected sites of disease. Eastern Cooperative Oncology Group (ECOG) performance status was assessed, as well as body weight and vital signs

(body temperature, blood pressure [sitting or supine position], and heart rate), which were performed at each visit; 12-lead electrocardiograms (ECGs) were performed at Screening and then again on Day 1 of Cycle 3, if applicable. To evaluate adrenal gland function, adrenocorticotropin hormone (ACTH) stimulation tests were performed at Screening and again on Day15 (-3/+0) of each odd- numbered cycle. If the results of any tests were abnormal (as defined as a serum cortisol value ≤18 µg/dL 30 minutes after the ACTH stimulation test) then the repeat test was to be performed prior to the start of SU-014813 treatment on the next cycle. If the ACTH stimulation test at the end of study/withdrawal visit test was abnormal then the test was to be repeated at the 28- day follow up visit.

Statistical Methods: The sample size was determined by the optimal 2-stage Simon design, allowing early stopping in the first cycle if efficacy was inadequate. This design was used to test the null hypothesis that the true ORR was ≤10% (not clinically meaningful) versus the alternative hypothesis that the true response rate was ≥25%. With a significance level of 0.05 and a power of 90% (beta=0.1), a total of 66 evaluable subjects were required to assess the ORR. Twenty-one evaluable subjects were enrolled in Stage 1. If ≤2 objective tumor responses were observed in the first 21 evaluable subjects, the trial was to be terminated and the alternative hypothesis that the true response rate is ≥25% was to be rejected. However, if ≥3 objective tumor responses were observed in the first 21 evaluable subjects, the study was to be expanded to enroll a total of 66 evaluable subjects (45 new evaluable subjects to be enrolled into Stage 2). At the end of the study, if ≥11 objective tumor responses were observed, then the null hypothesis that the true response probability was ≤10% was to be rejected and further investigations of SU-014813 in this subject population would be warranted.

Two study populations were assessed:

- An as-treated population (full analysis set [FAS]); including all subjects enrolled in the study who received at least 1 dose of study medication. This population was employed in evaluating subject characteristics, treatment administration, efficacy endpoints, and safety at the time of the final analysis.

- An evaluable subject population (EAS); this group consisted of all eligible subjects receiving at least 3 weeks of treatment, who had measurable disease at Baseline and had at least 1 on-study assessment of response made by the investigator. This population was employed in evaluation of efficacy endpoints. Primary analysis of efficacy was based on the evaluable subject population.

Subject characteristics, treatment administration/compliance, efficacy endpoints, safety parameters, and SU-014813 C_{trough} were summarized by descriptive statistics. Data were also displayed graphically, where appropriate. The proportion of subjects who achieved an objective tumor response (CR or PR) was computed with the corresponding 90% and 95% confidence intervals (CIs).

The Clinical Benefit rate (the proportion of subjects who achieved CR or PR, or prolonged stabilization of the disease [SD] ≥24 weeks) was also computed. Time-to-event endpoints (time to tumor progression and 1-year survival rate) were analyzed using Kaplan-Meier

methods. For subject reported outcomes, the EORTC QLQ-C30/BR23 data were handled and scored according to the EORTC QLQ-C30 Scoring Manual. At each assessment, descriptive statistics of the absolute scores and changes from Baseline (Cycle 1 Day 1) were calculated.

RESULTS

Subject Disposition and Demography: Subject disposition and datasets analyzed are summarized in Table 1.

Table 1. Subject Disposition and Evaluation Groups

	Number (%) of Subjects
Screened	90 (100%)
Assigned to Study Treatment	90 (100%)
Treated	89 (98.9%)
Completed	1 (1.1%)
Discontinued	88 (97.8%)
Death	1 (1.1%)
Related to Study Drug	78 (87.6%)
Adverse Event	13 (14.6%)
Lack of Efficacy	65 (73.0%)
Not Related to Study Drug	9 (10.1%)
Adverse Event	3 (3.4%)
Other	3 (3.4%)
Subject no longer willing to participate in study	3 (3.4%)
Analyzed for Efficacy	
Evaluable Set	78 (86.7%)
Analyzed for Safety	
Adverse Events	89 (98.9%)
Laboratory Data	88 (97.8%)

Discontinuations occurring outside of the lag period have been attributed to the last study treatment received.

All enrolled subjects were women who had metastatic breast cancer. Subject demographics are summarized in Table 2. Most subjects had Stage IV cancer (80 subjects; 89.9%) and had Baseline ECOG status of 0 (49 subjects [55.1%]) or 1 (37 subjects [41.6%]). Four subjects had Stage IV M1A cancer (4.5%). One subject (1.1%) had a Baseline ECOG status of 2; 2 (2.2%) subjects did not have a recorded Baseline score. Most subjects had a treatment history of prior surgery (95.5%) and/or radiation therapy (88.8%) and a majority had undergone 2 or 3 systemic treatment regimens (69.7%). The most frequently reported prior systemic therapies used by subjects were combinations of anthracyclines, taxanes, or other drugs (85/89; 95.5%). The most commonly reported current medical conditions were hypertension (16/89; 18.0%) and hypothyroidism (10/89; 11.2%).

A total of 33 subjects (37.1%) had more than 2 sites of tumor involvement. The most frequently reported sites of tumor involvement were the liver (48.3%), lungs (42.7%), lymph nodes (30.3%), and bone (28.1%). Baseline demographics are summarized in Table 2.

Table 2. Demographics

Number (%) of Subjects	N=89
Age (years)	
<18	0
18-44	18 (20.2%)
45-64	58 (65.2%)
≥65	13 (14.6%)
Mean (SD)	52.7 (9.7)
Range	33-73
Race	
White	84 (94.4%)
Black	4 (4.5%)
Other	1 (1.1%)
Weight (kg)	
Mean (SD)	69.3 (15.5)
Range	36.0-121.5
n	84 (94.4%)
Height (cm)	
Mean (SD)	161.9 (7.8)
Range	139.0-179.0
n	85 (95.5%)

Abbreviations: n or N=number of subjects; SD=standard deviation

Efficacy Results:

Response Rate: Based on the evaluable-for-efficacy population (N=78), no subjects had a CR and 8 (10.3%) subjects had a PR to study drug; 23 (29.5%) subjects had stable disease/no response and 42 subjects (53.8%) had objective progression of their tumors. Thus, the ORR (CR + PR) was 8 (10.3%). A total of 62 (69.7%) subjects died due to disease progression. Based on the full analysis set (N=89), no subjects had a complete response and 8 (9.0%) subjects had a partial response to study drug; 27 subjects (30.3%) had stable disease/no response and 44 (49.4%) subjects had objective progression of their tumors.

Table 3 summarizes survival information for both the FAS population and the EAS population. The Clinical Benefit rate for the FAS population was 22.4% (20 subjects) and for the EAS population, it was 24.4% (19 subjects).

Table 3. Overall Survival

	FAS N=89 n	EAS N=78 n
Number of Deaths	65 (73.0%)	56 (71.8%)
Causes of death		
Disease under study	62 (69.7%)	53 (67.9%)
Study treatment toxicity	1 (1.1%)	1 (1.3%)
Unknown	1 (1.1%)	1(1.3%)
Other	1 (1.1%)	1(1.3%)
Number Censored	24 (27.0%)	22 (28.2%)
Reason for censorship		
In follow-up as of data cutoff	1 (1.1%)	1 (1.3%)
Lost to follow-up	23 (25.8%)	21 (26.9%)
Number of subjects with last contact date >1 year prior to data cutoff date	16 (18.0%)	14 (17.9%)
Survival probability at 1 year[a] (95% CI[b])	36.4% (26.4, 46.5)	37.7% (26.9, 48.6)
Kaplan-Meier Estimates of time to event (year)		
Quartiles (95% CI[c])		
25%	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)
50%	0.7 (0.5, 0.9)	0.7 (0.6, 0.9)
75%	1.4 (1.1, 2.0)	1.6 (1.2, 2.0)

Abbreviations: CI=confidence interval; n=number of subjects; FAS=full analysis set; EAS=efficacy analysis set

[a] Estimated from the Kaplan-Meier curve

[b] Calculated from the product-limit method

[c] Based on the Brookmeyer and Crowley method

The probability of being event free at 6 months was 25.4% (FAS); time to progression was 1.2 months (25% quartile), 2.6 months (50% quartile), and 6 months (75% quartile).

Pharmacokinetic, Pharmacodynamic, and/or Other Results:

PK Results: Measurable plasma trough concentrations were observed in all subjects on all PK collection days except at predose on Cycle 1/Day 1. Trough concentrations greater than the target therapeutic concentration of 100 ng/mL were routinely observed in the study.

PD Results: To assess the selectivity of SU-014813 for Class V/III targets in breast cancer patients, the effect of monotherapy on the plasma concentrations of soluble vascular endothelial growth factor receptor (sVEGFR)2, sVEGFR3 and sKIT were assessed in this study. SU-014813 decreased the plasma concentrations of sVEGFR2, sVEGFR3 and sKIT. Decreases were generally dose-dependent with suppression maintained on the continuous dosing regimen and rebound toward baseline observed during the "off" period on the 4/1 dosing regimen. Inhibition of all 3 soluble receptors indicated that SU-014813 acts a multitargeted Class V/III kinase inhibitor in breast cancer patients.

Safety Results: Fourteen subjects died during the study prior to the end of treatment. Deaths during the study were due to the following events: unknown (1 subjects), disease progression (7 subjects), cerebral hemorrhage (1 subject), pneumothorax (1 subject), multi

organ failure (1 subject), malignant pleural effusion (1 subject), gastrointestinal hemorrhage (1 subject), respiratory failure due to disease progression (1 subject). Two of these deaths (cerebral hemorrhage and gastrointestinal hemorrhage) were considered to be related to study drug by the investigator. Overall, 87 (97.8%) subjects experienced 1051 AEs during the study; 59 subjects (66.3%) experienced grade 3 or 4 AEs and 6 subjects (6.7%) experienced grade 5 AEs during the study. Grade 5 AEs included disease progression (2 subjects), gastrointestinal hemorrhage (1 subject), general physical health deterioration (1 subject), malignant pleural effusion (1 subject), and pneumothorax (1 subject).

Permanent discontinuations due to AEs were reported for 16 (17.9%) subjects. Thirteen of these subjects discontinued due to AEs that were considered by the investigator to be related to study drug. Temporary discontinuations due to AEs were reported by 48 subjects (53.9%). Discontinuations due to AEs are summarized in Table 4.

Table 4. Discontinuations Due to Adverse Events

Age/sex	MedDRA Preferred Term	Onset Day/Stop Day	Investigator Causality	CTC Grade/ Outcome
F/65	Electrocardiogram ST segment abnormal	18/40	Study drug	3/ resolved
F/67	Syncope	175/198	Study drug	4/ resolved
	Acute pulmonary edema	175/198	Study drug	4/ resolved
	Hypertension	175/198	Study drug	4/ resolved
F/64	Intestinal perforation	30/43	Study drug	4/ resolved
F/45	Pyrexia	10/[>16]	Other	2/ still present
F/53	Pulmonary embolism	69/[>78]	Study Drug	3/ still present
F/43	Dyspnoea	3/[>8]	Disease under study	3/ still present
F/55	Pneumothorax	116/[>116]	Disease under study	5/ still present
F/59	Nausea	280/290	Study drug	2/ resolved
	Vomiting	280/290	Study drug	2/ resolved
	Dizziness	284/290	Study drug	2/ resolved
F/48	Hypertension	19/21	Study drug	2/ resolved
F/56	Nausea	19/[>19]	Study drug	3/ still present
F/46	Ascites	232/[>232]	Study drug	3/ still present
F/39	Capillary leak syndrome	195/[>195]	Study drug	2/ still present
F/65	Mucosal inflammation	136/[>150]	Study drug	3/ still present
F/61	Polymyalgia rheumatica	98/[>131]	Study drug	3/ still present
F/47	Venoocclusive disease	92/[>92]	Study drug	4/ still present
F/60	Visual impairment	634/[>637]	Study drug	3/ still present

Abbreviations: F=female; MedDRA=Medical Dictionary for Regulatory Activities
Values in brackets are imputed from incomplete dates and times.

The most frequently reported treatment-emergent AEs (all cycles) were in the MedDRA system organ classes of Gastrointestinal Disorders (79 subjects; 88.8%) and General Disorders and Administration Site Conditions (63 subjects; 70.8%). The most frequently reported treatment-emergent AEs in >20% of subjects were nausea (64.0%), diarrhea (50.6%), vomiting (50.6%), fatigue (37.1%), anorexia (32.6%), dysgeusia (25.8%), mucosal inflammation (24.7%), and hypertension (24.7%), dyspnoea (20.2%), and headache (20.2%). AEs reported by at least 10% of subjects are summarized in Table 5

Serious adverse events were reported by 38 subjects (42.7%). Non-fatal SAEs reported during the study are summarized in Table 6**.**

Table 5. Treatment-Emergent Adverse Events Reported by >10% of Subjects by Preferred Term and Maximum CTCAE Grade (All Causalities)

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Adverse Event MedDRA Preferred Term	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)	Unknown/ Missing N (%)	Total N (%)
Nausea	40 (44.9%)	13 (14.6%)	4 (4.5%)	0 (0%)	0 (0%)	0 (0%)	57 (64.0%)
Diarrhea	25 (28.1%)	14 (15.7%)	6 (6.7%)	0 (0%)	0 (0%)	0 (0%)	45 (50.6%)
Vomiting	26 (29.2%)	17 (19.1%)	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)	45 (50.6%)
Fatigue	11 (12.4%)	17 (19.1%)	5 (5.6%)	0 (0%)	0 (0%)	0 (0%)	33 (37.1%)
Anorexia	18 (20.2%)	8 (9.0%)	3 (3.4%)	0 (0%)	0 (0%)	0 (0%)	29 (32.6%)
Dysgeusia	17 (19.1%)	5 (5.6%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	23 (25.8%)
Hypertension	7 (7.9%)	9 (10.1%)	5 (5.6%)	1 (1.1%)	0 (0%)	0 (0%)	22 (24.7%)
Mucosal Inflammation	13 (14.6%)	7 (7.9%)	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)	22 (24.7%)
Headache	12 (13.5%)	4 (4.5%)	1 (1.1%)	1 (1.1%)	0 (0%)	0 (0%)	18 (20.2%)
Dyspnoea	9 (10.1%)	6 (6.7%)	3 (3.4%)	0 (0%)	0 (0%)	0 (0%)	18 (20.2%)
Constipation	12 (13.5%)	4 (4.5%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	17 (19.1%)
Dyspepsia	15 (16.9%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	16 (18.0%)
Hair Color Changes	12 (13.5%)	2 (2.2%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	15 (16.9%)
Cough	8 (9.0%)	4 (4.5%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	13 (14.6%)
Neutropenia	0 (0%)	4 (4.5%)	7 (7.9%)	2 (2.2%)	0 (0%)	0 (0%)	13 (14.6%)
Pain in Extremity	7 (7.9%)	5 (5.6%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	13 (14.6%)
Palmar-Plantar Erythrodysaesthesia syndrome	9 (10.1%)	2 (2.2%)	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)	13 (14.6%)
Stomatitis	11 (12.4%)	1 (1.1%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	13 (14.6%)
Lethargy	9 (10.1%)	3 (3.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (13.5%)
Rash	9 (10.1%)	3 (3.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (13.5%)
Back Pain	7 (7.9%)	3 (3.4%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	11 (12.4%)
Chromaturia	11 (12.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (12.4%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; CTCAE=Common Terminology Criteria for Adverse Events
MedDRA coding dictionary v12.0 applied

Table 5. Treatment-Emergent Adverse Events Reported by >10% of Subjects by Preferred Term and Maximum CTCAE Grade (All Causalities)

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Adverse Event MedDRA Preferred Term	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)	Unknown/ Missing N (%)	Total N (%)
Abdominal Pain	9 (10.1%)	1 (1.1%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	11 (12.4%)
Asthenia	4 (4.5%)	5 (5.6%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	10 (11.2%)
Dizziness	9 (10.1%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (11.2%)
Leukopenia	0 (0%)	3 (3.4%)	7 (7.9%)	0 (0%)	0 (0%)	0 (0%)	10 (11.2%)
Thrombocytopenia	1 (1.1%)	4 (4.5%)	5 (5.6%)	0 (0%)	0 (0%)	0 (0%)	10 (11.2%)
Alopecia	7 (7.9%)	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (10.1%)
Dry Skin	9 (10.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (10.1%)
Yellow Skin	7 (7.9%)	2 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (10.1%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; CTCAE=Common Terminology Criteria for Adverse Events
MedDRA coding dictionary v12.0 applied

Table 6. Nonfatal Treatment-Emergent SAEs Reported During the Study

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Age	MedDRA Preferred Term	Onset Day	Investigator Causality	Outcome
48	Blood pressure increased	20	Related	Recovered
	Hypertensive crisis	22	Related	Recovered
65	Electrocardiogram ST segment abnormal	18	Related	Recovered
	Hypertensive crisis	18	Related	Recovered
	Hypertension	9	Related	Recovered
49	Blood pressure increased	31	Related	Recovered
62	Blood pressure increased	2	Related	Recovered
67	Pulmonary edema	175	Related	Recovered
	Syncope	175	Related	Recovered
	Hypertension	175	Related	Recovered
47	Chronic inflammatory demyelinating polyradiculoneuropathy	92	Related	Recovered with sequela
59	Pleural effusion	28	Unrelated	Recovered
54	Hypertensive crisis	19	Related	Recovered
	Epistaxis	19	Related	Recovered
	Headache	19	Related	Recovered
48	Encephalitis	103	Unrelated	Recovered
64	Pleural effusion	19	Unrelated	Recovered
	Intestinal perforation	30	Related	Recovered with sequela
57	Sepsis	NA	Related	Recovering
53	Pulmonary embolism	69	Related	Not recovered
50	Abdominal pain	11	Related	Recovered
55	Hemolytic anemia	39	Related	Not recovered
56	Wound infection	108	Unrelated	Recovering
56	Atrial fibrillation	106	Related	Recovered
	Nausea	116	Related	Unknown
	Vomiting	116	Related	Unknown
	Mucosal inflammation	116	Related	Unknown

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable

Table 6. Nonfatal Treatment-Emergent SAEs Reported During the Study

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Age	MedDRA Preferred Term	Onset Day	Investigator Causality	Outcome
60	Nausea	280	Related	Recovered
	Vomiting	280	Related	Recovered
	Dizziness	284	Related	Recovered
	Nausea	67	Related	Recovered
	Vomiting	67	Related	Recovered
	Lower respiratory tract infection	67	Unrelated	Recovered
48	Hypertension	6	Related	Recovered
	Headache	4	Related	Recovered
	Palpitations	4	Related	Recovered
	Hypertension	19	Related	Recovered
53	Central line infection	22	Unrelated	Recovered
73	Endocarditis bacterial	36	Unrelated	Recovered
46	Gastrointestinal hemorrhage	140	Related	Recovered
	Gastroenteritis	139	Related	Recovered
39	Pyelocaliectasis	64	Related	Recovered with sequela
	Pyelocaliectasis	178	Related	Recovered with sequela
	Capillary leak syndrome	195	Related	Unknown
	Urinary retention	195	Related	Unknown
65	Chills	49	Related	Recovered
	Erythema	49	Related	Recovered
	Edema peripheral	49	Unrelated	Recovered
	Pleural effusion	63	Unrelated	Recovered with sequela
	Productive cough	71	Unrelated	Recovered with sequela
	Dizziness	171	Unrelated	Recovered
	Nausea	171	Unrelated	Recovered
	Abdominal pain upper	171	Unrelated	Recovering
	Oesophageal candidiasis	175	Unrelated	Recovering

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable

Table 6. Nonfatal Treatment-Emergent SAEs Reported During the Study

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Age	MedDRA Preferred Term	Onset Day	Investigator Causality	Outcome
68	Pyrexia	163	Related	Recovered
	Musculoskeletal pain	163	Related	Recovered
	Chills	163	Related	Recovered
	Erysipelas	163	Related	Recovered
	Herpes zoster	163	Related	Recovered
	Lymphoedema	163	Unrelated	Recovered
	Erysipelas	475	Related	Recovered
	Bone pain	541	Unrelated	Recovered
64	Headache	68	Unrelated	Recovered
	Gastroenteritis	68	Unrelated	Recovered
48	Pancreatitis	19	Unrelated	Recovered
45	Pericardial effusion malignant	29	Unrelated	Unknown
47	Venoocclusive disease	92	Related	Not recovered
	Intra-abdominal hemorrhage	109	Unrelated	Not recovered
50	Myocardial ischaemia	96	Unrelated	Recovering
	Dysphagia	197	Unrelated	Recovered
62	Visual impairment	634	Related	Not recovered
55	Portal vein thrombosis	48	Unrelated	Recovered

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable

Clinical laboratory results showed that most subjects maintained grade 1 or 2 hematology or blood chemistry values during the study. Shifts in hematology values of 2 or more common toxicity criteria (CTC) grades during any treatment cycle were observed as follows: hemoglobin (3 subjects), platelets (12 subjects), white blood cells (25 subjects), neutrophils (27 subjects), and lymphocytes (13 subjects).

Most subjects experienced grade 1 or 2 laboratory chemistry values. Shifts in chemistry values of 2 or more CTCAE grades (all cycles) were observed during the study. The laboratory parameters with the highest number of subjects with shifts of 2 or more CTCAE grades from Baseline were hypophosphatemia (17 subjects), AST (8 subjects), and hypocalcemia (7 subjects).

EORTC QLQ-C30 Outcomes: Mean functional scores at Baseline for the EORTC QLQ-C30 ranged from 73.29 to 84.40 with the highest Baseline score being for cognitive functioning. Mean symptom scores ranged from 7.26 to 36.32. The lowest symptom scores occurred for nausea and vomiting (7.26) and diarrhea (9.40). The highest mean symptom scores occurred for fatigue (36.32), pain (28.63), dyspnea (24.89), and insomnia (24.36).

Subject-reported outcomes using the EORTC QLQ-C30 questionnaire showed a small mean overall decrease from Baseline in all function scales, the greatest decrease was for Role Functioning (mean change from Baseline was -11.23). An overall mean increase from Baseline in symptoms was also observed with the largest increases being for symptoms of nausea, vomiting, appetite loss, and diarrhea.

Mean functional scores at Baseline for the EORTC QLQ-BR23 ranged from 65.37 to 83.99 with the highest Baseline score being for sexual functioning. Mean symptom scores ranged from 43.33 to 83.69. The lowest symptom scores occurred for upset by hair loss (43.33). The highest mean score occurred for breast symptoms (83.69).

Subject-reported outcomes using the EORTC QLQ-BR23 questionnaire showed a small mean overall decreases from Baseline in sexual enjoyment, future perspective, systemic therapy side effects, body image, and upset by hair loss.

CONCLUSION(S):

- The objective response rate (CR + PR) was 10.3% and the Clinical Benefit rate was 22.4%; time to tumor progression was 1.2 months (25% quartile), 2.6 months (50% quartile), and 6 months (75% quartile).

- Overall survival probability at 1 year was 36.4%; by 6 months, 75% of subjects had had an event of progression.

- Frequent AEs observed during treatment were related to gastrointestinal symptoms and discontinuations due to AEs were reported for 16 (17.9%) subjects.

- Patient-reported outcomes showed small mean decreases from Baseline values for functioning for both the EORTC QLQ-C30 and EORTC OLQ-BE23. The largest

increases from Baseline symptom scores were for diarrhea, nausea and vomiting, and fatigue.

- Plasma trough concentrations of SU-014813 greater than the target therapeutic concentration of 100 ng/mL were routinely observed in the study.

- Inhibition of the soluble receptors VEGFR2, sVEGFR3, and sKIT indicated that SU14813 acts a multitargeted Class V/III kinase inhibitor in breast cancer patients.