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Phase I/II trial of non-cytotoxic suramin in combination with weekly paclitaxel in metastatic breast cancer treated with prior taxanes

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Abstract

Purpose—Suramin, a polysulfonated naphthylurea, inhibits the actions of polypeptide growth factors including acidic and basic fibroblast growth factors (aFGF and bFGF), which confer broad spectrum chemotherapy resistance. We hypothesized that suramin at non-cytotoxic doses in combination with weekly paclitaxel would be well tolerated and demonstrate anti-tumor activity.

Methods—Women with metastatic breast cancer who had been previously treated with a taxane in the adjuvant or metastatic setting were eligible. The primary objective of the phase I was to determine the dose of intravenous (IV) weekly suramin that resulted in plasma concentrations between 10 and 50 $\mu\text{mol/l}$ over 8–48 h (or the target range) in combination with IV 80 mg/m^2 of weekly paclitaxel. The primary objective of the phase II trial was to determine the anti-tumor activity of the dosing regimen defined in phase I. Therapy was continued until disease progression or development of unacceptable toxicity.

Results—Thirty-one patients were enrolled (9: phase I; 22: phase II). In phase I, no dose-limiting toxicities were observed. Pharmacokinetics during the first cycle showed suramin concentrations within the target range for 21 of 24 weekly treatments (88 %). In phase II, the objective response rate (ORR) was 23 % (95 % CI 8–45 %), the median progression-free survival was 3.4 months (95 % CI 2.1–4.9 months), and the median overall survival was 11.2 months (95 % CI 6.6–16.0 months).

Conclusions—Non-cytotoxic doses of suramin in combination with weekly paclitaxel were well tolerated. The efficacy was below the pre-specified criteria required to justify further investigation.

Keywords

Suramin; Paclitaxel; Metastatic; breast cancer; Phase I; Phase II

Introduction

Resistance to chemotherapy is mediated by a number of factors including extracellular polypeptide growth factors such as acidic and basic fibroblast growth factors (aFGF and bFGF) [1]. Higher expression of bFGF is associated with resistance to the taxanes, anthracyclines, and anti-metabolites [2]. Suramin, a polysulfonated naphthylurea, inhibits multiple growth factors including aFGF, bFGF and at doses that are non-cytotoxic, suramin reverses FGF-induced drug resistance and enhances the anti-tumor activity of chemotherapies with diverse chemical structures and biological mechanisms in both cultured cells and in tumor-bearing animals [1, 3, 4].

Paclitaxel, in the taxane family of tubulin stabilizing agents, is one of the most active drugs in metastatic breast cancer. Based on preclinical evidence that non-cytotoxic suramin improves the efficacy of paclitaxel and enhances the in vivo antitumor activity of paclitaxel in human breast xenografts compared with paclitaxel alone [4, 5], we hypothesized that the combination of low non-cytotoxic doses suramin with weekly paclitaxel would be active and well tolerated in women with metastatic breast cancer. To test this hypothesis, a phase I/II trial of non-cytotoxic suramin in combination with paclitaxel in women with metastatic disease was undertaken in women who had previously received a taxane in either the adjuvant or metastatic setting.

The primary objective of the phase I trial was to determine the dose of IV weekly suramin in combination with IV 80 mg/m² of weekly paclitaxel that would result in suramin plasma concentrations of 10–50 µM for 8–48 h; over this range, suramin is not cytotoxic and modulates the FGFs. The primary objective of the phase II trial was the objective response rate, and the secondary end points were toxicities of the combination, progression-free and overall survival, and evaluation of pretreatment plasma bFGF levels.

Patients and methods

Eligibility

Histologically confirmed stage IIIB or IV metastatic breast cancer and the following: age 18 years; eastern cooperative oncology group (ECOG) performance status of 0–2; prior paclitaxel or other taxanes (i.e., docetaxel) in either the adjuvant or metastatic setting; 3 weeks from completion of prior chemotherapy, radiation therapy or surgery; white blood cell count 3,000/µl; absolute neutrophil count 1,000/µl; platelets 100,000/µl, and hemoglobin level 9.0 g/dl; total serum bilirubin level <1.5 times institutional upper normal limits; aspartate amino transaminase and alanine amino transaminase <2.5 times upper normal limits; serum creatinine <1.5 mg/dl or calculated creatinine clearance 50 ml/min; no brain metastases or leptomeningeal disease; no history of hypersensitivity to cremophor EL; no other malignancy in the past 5 years with the exception of basal cell cancer or carcinoma in situ of the cervix; no other investigational drug use and not pregnant or lactating. In addition, patients were eligible for the phase II trial if they received 2 prior chemotherapy regimens for stage IIIB or IV disease and had measurable disease according to RECIST criteria [6].

The treatment protocol and informed consent documents were approved by the Cancer Therapy Evaluation Program at the National Cancer Institute and the Institutional Review Boards at The James Cancer Hospital and Cleveland Clinic. Patients gave written informed consent according to the federal and institutional guidelines before treatment.

Study design, dosage, and dose modifications

The phase I study was conducted in the James Cancer Hospital Clinical Treatment Unit, and the phase II trial was conducted in the outpatient settings at James Cancer Hospital and the Cleveland Clinic. Paclitaxel was administered at a dose of 80 mg/m² IV on days 1, 8, 15, and 21 of a 28-day treatment cycle in combination with suramin dose determined by a nomogram [7]. Patients continued to receive therapy until disease progression or development of unacceptable toxicity.

Suramin was supplied by the National Cancer Institute, division of cancer treatment and evaluation (CTEP), in sterile 600 mg 10-ml vials. The vials were reconstituted with sterile water, resulting in a 100 mg/ml solution. The desired dose was additionally diluted in 0.9 % sodium chloride or 5 % dextrose in water. Suramin was administered by IV infusion over 30 min, 4 h prior to IV 60 min paclitaxel infusion. The target dose was calculated to yield plasma concentrations between 10 and 50 µM over approximately 8–48 h.

Commercially available paclitaxel was obtained in 30 mg (5 ml), 100 mg (16.7 ml), and 300 mg (50 ml) vials and was prepared according to the manufacturer's directions in glass or polyolefin containers diluted in 0.9 % sodium chloride or 500–1,000 ml of 5 % dextrose. The paclitaxel was infused over 1 h. Premedications given 30 min prior to the start of the paclitaxel infusion were 50 mg IV of diphenhydramine and 20 mg IV of famotidine; dexamethasone 20 mg was administered orally at 12 and 6 h prior to the paclitaxel infusion.

In the phase I trial, dose adjustments were based on the pharmacokinetics of suramin and for dose-limiting toxicity. The goal was to achieve the target suramin plasma level of 10–50 µM in 5 of 6 patients, as long as no dose-limiting toxicity was observed in more than 1 of 6 patients. Dose-limiting toxicities during treatment cycle 1 were defined as follows: any grade 3 or higher non-hematologic toxicity or any grade 4 hematologic toxicity excluding asymptomatic grade 4 neutropenia (ANC < 500/ul) for durations less than 7 days. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Additionally, failure to complete all planned treatment during cycle 1 for reasons other than disease progression or voluntary withdrawal was considered a dose-limiting toxicity.

In the phase II trial, paclitaxel was dose reduced from 80 to 70 mg/m² for febrile neutropenia and for neutropenia lasting greater than 7 days. Neurotoxicity prompted dose reductions in suramin and paclitaxel. For grade 1, no dose reductions were permitted; for grade 2, suramin was administered at 75 % and no dose reduction of paclitaxel; for grade 3, suramin 50 % and paclitaxel reduced from 80 to 70 mg/m²; and for grade 4, the treatment was discontinued. Treatment was discontinued if there was recurrence of grade 2 neuropathy or higher after dose reduction.

Study assessments

Pretreatment evaluations included a history and physical examination, ECOG performance status, complete blood count (CBC), serum chemistries, coagulation profile, urinalysis, electrocardiogram and radiological imaging with computed tomography (CT), and bone scans all within 4 weeks prior to study initiation. Women of childbearing potential had urine or serum pregnancy test prior to therapy initiation. During chemotherapy, evaluations included physical examination with performance status assessment on day 1 of treatment cycles; weekly laboratory studies included CBC with differential and serum chemistries; and imaging of the target lesions was completed every 2 cycles for women enrolled in the phase II. RECIST version 1.0 was used to define objective responses [6].

Calculation of suramin doses

The dose of suramin (mg) was calculated, using a dosing nomogram (i.e., dose equals the product of “FACTOR” and the squared value of the body surface area of a patient) to yield the target concentration range of 10–50 μM from 8 to 48 h (Supplemental Table 1). The value of FACTOR for the first dose was 125. The value of FACTOR for subsequent doses was calculated based on the time elapsed since the previous treatment. The first three patients enrolled on the study used an earlier version of the nomogram; the remaining patients in the phase I and II trial used the final version previously reported [7].

Suramin pharmacokinetics

Blood samples were obtained from the arm contralateral to the site of drug infusion and placed in heparinized tubes. For the assessment of suramin pharmacokinetics, different sampling schedules were used in the phase I and phase II trials. For patients in phase I, a total of 16 samples (pretreatment, and 0.16, 0.33, 0.5, 1, 1.5, 2, 3, 4.5, 5.5, 9, 12, 15, 24, 48, and 72 h after initiation of suramin infusion) were collected during the first and fourth weeks of cycle 1. For subsequent cycles, 3 samples were collected (pretreatment, 3 and 4.5 h after treatment initiation). For patients in phase II trial, a total of 6 samples were collected during the first and fourth weeks of cycle 1 (pretreatment, and 0.5, 3, 4.5, 5.5, and 6 h after treatment initiation), and 3 samples were collected in subsequent cycles (pretreatment, and 3 and 4.5 h after treatment initiation). Samples were analyzed for suramin concentrations using a previously described high-performance liquid chromatography method² and for bFGF levels (see correlatives section).

Drug concentrations at these time points in the phase I patients were estimated by fitting a three-compartment open model with multiple dosing (WinNonlin, Pharsight, Mountain View, CA, USA) to the concentration–time profiles [7]. Suramin concentrations (actual measurements) were compared in patients on the phase I and II trials at the same time points (pretreatment, 0.5, 3, 4.5, and 5.5 h for the first and fourth weekly treatment in cycle 1, and pretreatment, 3 and 4.5 h for the first weekly treatment of the remaining cycles).

Correlative studies for bFGF

Pretreatment plasma bFGF concentrations were evaluated on all patients. All plasma samples were analyzed for bFGF concentrations using an Enzyme-Linked ImmunoSorbent Assay kit (Oncogene, Cambridge, MA, USA), following the manufacturer’s instructions. The antibody was a murine monoclonal anti-bFGF antibody conjugated with horseradish peroxidase. The lower detection limit of the assay was 2.5 pg/ml.

Statistical methods and analysis

The primary end point of the phase I trial was to determine the dosing nomogram yielding the target suramin plasma level of 10–50 μM in 5 of 6 patients, as long as dose-limiting toxicity was not seen in more than 1 of 6 patients. The primary end point of the phase II trial was the overall response rate. With 28 patients in the phase II portion, there was 83 % power to detect an improvement in overall response from 30 to 50 % with a Type I error rate of 10 %. Thus, to warrant further study, this study required at least 12 (43 %) observed responses. The overall response rate and the 95 % exact Clopper-Pearson confidence interval were calculated. Progression-free (PFS) and overall survival (OS) estimates were calculated using the Kaplan–Meier method. PFS was measured from the date on-study until the date of progression or death, whichever came first, censoring those alive and progression-free. There were no DLTs in Phase I. Seven patients (3 in phase I and 4 in phase II) went off-study due to toxicity and received other types of chemotherapy; these were censored for PFS at the date off-study. OS was defined as the date from on-study until the date of death,

censoring those alive at last follow-up. Pretreatment bFGF levels and the relationship to response were tested in the phase II cohort using the nonparametric Kruskal–Wallace test.

Results

Patient characteristics

Between April 2003 and June 2007, 31 women with metastatic breast cancer were enrolled. Baseline patient characteristics are described in Table 1. Nine patients were enrolled in phase I and 22 in phase II. The median age was 56 (range 35–73) and median ECOG was 0 (range 0–2). All patients had received prior taxanes, either in the adjuvant (26 %) or in metastatic setting (52 %), or in both (23 %). Fourteen (64 %) patients in the phase II trial had received a prior taxane in the metastatic setting. Of these, 2 had discontinued taxane treatment for toxicity and 12 for progressive disease. The majority of patients on the phase II study had received one (48 %) or two (32 %) prior chemotherapy regimens.

Treatment

Nine patients completed 22 treatment cycles in the phase I study and 21 patients completed 63 cycles in the phase II study. One patient started but did not complete the first cycle of treatment due to progressive disease. The median number of cycles that was completed was 2 (range 1–8 cycles). As illustrated in Fig. 1, all 9 patients in Phase I trial received the same suramin loading dose, which yielded a peak concentration of about 90 μM at the end of the 30-min infusion, declining to about 50 μM at 4.5–5.5 h, and subsequently to about 15 μM at 48 h. Doses for subsequent treatments (administered 7 days after the previous treatment) were calculated with a FACTOR value of 45 for the first 3 patients on the phase I trial and a FACTOR value of 39 for the remaining 6 patients (using the final nomogram). Pharmacokinetic studies during the first cycle of these patients (24 treatments) showed suramin concentrations within the target range of 10–50 μM over 8–48 h in 21 treatments (88 %). The remaining 3 treatments were received by a single patient, exhibiting 48 h concentrations of 4–5 μM . This result is similar to the results of other suramin trials, where the target concentrations were achieved in 90 % of patients [7–10].

A total of 22 phase II patients were treated on the final dosing nomogram. Their measured plasma concentrations at 5 time points (i.e., pretreatment, 0.5, 3, 4.5, and 5.5 h) were comparable to the concentrations in the 6 phase I patients treated on the same nomogram.

Toxicities

All treatment-related adverse events are reported in Table 2. There were no dose-limiting toxicities in the phase I study. The majority of treatment-related toxicities were grade 1 and 2. Grade 3 and 4 neutropenia occurred in 10 and 3 % of patients, respectively. The most common grade 3 and 4 non-hematologic toxicity was fatigue (19 %). Only 2 (6 %) developed grade 3 neuropathy (1 sensory and 1 motor). Both had prior taxane exposure. Although there were no deaths attributable to toxicity, one patient subsequently died within 30 days of coming off trial for progressive disease due to complications of Acute Respiratory Distress Syndrome (ARDS).

The toxicities that led to dose reduction or dose delays in paclitaxel and/or suramin included grade 3 fatigue ($n = 2$), grade 2 neuropathy ($n = 5$), neutropenia ($n = 1$), and pneumonia ($n = 1$). Seven (23 %) patients (phase I: $n = 3$; phase II: $n = 4$) discontinued treatment due to toxicities, with five discontinuing due to grade 3 or recurrent grade 2 neuropathy.

Efficacy

Efficacy results for the Phase II portion are shown in Table 3. Twenty-two phase II patients were evaluated in the intent-to-treat analysis. Over half (55 %) of the phase II patients had previously progressed within 6 months while being treated with a taxane for metastatic disease. These patients were considered taxane-refractory. There were no complete responses; 5 patients had partial response (PR) and the overall response rate was 23 % (95 % CI 8–45 %). Two of the patients with PR progressed during cycle 3. A total of 9 (41 %) patients had stable disease (SD), with 7 patients (32 %) SD for a duration of at least 8 weeks. Of the taxane-refractory patients, two (17 %) achieved a PR and six others (50 %) achieved SD. Response rates in patients with triple-negative breast cancer were 2 PR (25 %), 1 SD (13 %), and 5 PD (63 %). Response rates in patients with endocrine positive breast cancer were 3 PR (21 %), 8 SD (57 %), and 3 PD (21 %). Response rates between the two groups were not significantly different ($p = 0.11$). As shown in Fig. 2, the median PFS for all treated patients in the phase II study was 3.4 months (95 % CI 2.1–4.9 months) and the median OS was 11.2 months (95 % CI 6.6–16.0 months).

bFGF correlative studies

Plasma levels of bFGF were measured prior to beginning suramin treatment in all 22 patients on the phase II study. The median level was 7.1 pg/ml (range 0.0–23.5). Two patients did not express any pretreatment bFGF levels. There was no association between baseline bFGF levels and response ($p = 0.35$; data not shown).

Discussion

Suramin at therapeutic concentrations impacts a number of cancer-related pathways including inhibition of angiogenesis, phosphorylation of protein kinase C, and metabolism of glycosaminoglycan [11–13]. Clinical trials using suramin at concentrations of 100–300 μM as a single agent [14–16] or in combination with cytotoxic agents [17, 18] demonstrated significant toxicities with only modest efficacy. In breast cancer, suramin as a single agent at concentrations of 140 μM was associated with significant toxicity [19]. Based on these results, the U.S. Food and Drug Administration disapproved the use of suramin at therapeutic concentrations.

In contrast to the high concentrations of suramin needed for anti-tumor activity, much lower, non-cytotoxic doses of suramin ranging between 10 and 50 μM inhibit FGFs. Suramin at these low concentrations enhances the antitumor effects of various chemotherapeutic agents in a variety of tumor cell lines [1] and in several animal models including prostate [3], lung [20], bladder [21], and breast [4]. In breast cancer models, low-dose suramin enhanced the activity of paclitaxel in breast cancer xenografts with lung metastases compared with paclitaxel alone [4].

These promising preclinical results led to several early phase clinical trials evaluating non-cytotoxic suramin in combination with standard chemotherapy drugs in solid tumors [9, 10, 22, 23]. Suramin was well tolerated when combined with carboplatin and paclitaxel in patients with advanced stage non-small cell lung carcinomas [22]. Comparing the response rates in chemotherapy naïve and pretreated non-small cell lung cancer, patients did not show evidence of an apparent enhancement of response rates in patients who were chemotherapy naïve [9]. A phase I study of suramin in combination with docetaxel and gemcitabine therapy showed tolerability and encouraging anti-tumor activity [23], and randomized phase II trials are ongoing or being initiated in chemotherapy naïve and pretreated non-small lung cancer patients [24].

In this phase I/II trial, non-cytotoxic suramin in combination with weekly paclitaxel was well tolerated. One of the limitations of the trial was that the phase II enrollment did not meet its goal of twenty-eight patients. Trial enrollment was terminated early due to withdrawal of drug sponsorship by CTEP when only 22 patients were enrolled. Other limitations of this trial include the small sample size and heterogeneity of patient population in terms of prior treatment regimens. The objective response rate (ORR) attained in the 22 enrolled patients (23 %) did not provide enough evidence to reject the null hypothesis that the true response rate is less than or equal to 30 %.

When this trial was initially designed, there was limited data in response rates in a previously treated metastatic population. Single-agent paclitaxel in ECOG 2100 as first-line metastatic therapy had ORR of 21–22 % with no difference in responses in patients with or without taxanes therapy in the adjuvant setting [25, 26]. Trials with single-agent capecitabine in taxane-pretreated metastatic breast cancer women yielded ORR ranging 20–27 % [20, 27]. In a recent trial, ORR in heavily pre-treated, taxane-refractory patients treated with single-agent ixabepilone was only 12 % [28]. The patients in the ixabepilone trial had received prior anthracycline, and docetaxel or paclitaxel-based chemotherapy as their most recent chemotherapy, and experienced progression of disease on taxane therapy within 4 months of their last dose.

The definition of taxane resistance varies across metastatic trials. In our study, 12 (55 %) phase II patients had previously experienced disease progression within 6 months during a prior taxane therapy (9 taxotere, 1 abraxane, 2 paclitaxel) for metastatic disease. Of these, 2 (17 %) achieved a PR. In addition, six (50 %) patients achieved disease stability. These numbers, although small, may be clinically relevant since patients with taxane-refractory MBC have limited treatment options. However, the overall median number of cycles was 2 and the short median progression-free survival of 3.4 months highlights the limited efficacy seen with this combination in this population. Table 4 summarizes response rates from several studies with paclitaxel in the metastatic setting. Note that it is difficult to draw comparisons across these studies given differences in prior taxane exposure and prior lines of therapy.

There was no correlation between pretreatment bFGF levels with response. The relatively small sample size may have limited the power to detect a significant correlation between serum FGF levels and response rates or toxicities. Intra-tumoral bFGF levels were not assessed because a method of assaying for them was developed after the trial closed [29].

Other biomarkers of taxane resistance are currently under investigation. Tumors that overexpress the microtubule associated protein tau are less sensitive to taxanes [30, 31]. Several other factors may be important in taxanes resistance pathways including class III β -tublins [32], and gene polymorphisms in ABCB1 [33] and CYP1B1 [34]. Additional studies are needed before these biomarkers can be incorporated into clinical decision making.

In conclusion, non-cytotoxic suramin in combination with weekly paclitaxel was a well-tolerated combination in patients with MBC previously treated with taxanes. The efficacy of suramin in combination with paclitaxel was below the pre-specified criteria required to justify further investigation.

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Fig. 1.

Suramin pharmacokinetics were evaluated to ensure that the suramin target plasma concentration range of 10–50 μM was maintained over 8–48 h. Three cohorts of 3 patients each were enrolled in the phase I trial. From *top to bottom*: *solid line*, 1st treatment for all patients ($n = 9$); *dashed line*, 4th treatment of cohort 1 ($n = 3$); *dotted line*, 4th treatment of cohorts 2 and 3 ($n = 6$). All 9 patients received a first-cycle suramin dose (in mg) of $125 \times \text{BSA}^2$. In order to maintain target plasma concentrations, the first cohort received subsequent doses of $45 \times \text{BSA}^2$, while cohorts 2 and 3 received $39 \times \text{BSA}^2$.

Fig. 2.

In the 22 patients enrolled in the phase II portion, median PFS was 3.4 months (95 % CI 2.1–4.9) and median OS was 11.2 months (6.6–16.0 months)

Table 1

Patient characteristics

Characteristics	All patients <i>n</i> = 31	Phase I <i>n</i> = 9	Phase II <i>n</i> = 22
Age, years			
Median	56	56	56
Range	35–73	44–73	35–70
Race			
White	27 (87)	8 (89)	19 (86)
African American	4 (13)	1 (11)	3 (14)
ECOG performance status			
0	16 (52)	5 (56)	11 (50)
1	12 (39)	4 (44)	8 (36)
2	3 (10)	0 (0)	3 (14)
Menopausal status			
Premenopausal	1 (3)	0 (0)	1 (5)
Postmenopausal	30 (97)	9 (100)	21 (95)
ER/PR/HER 2 neu status			
ER+ or PR+	20 (65)	6 (67)	14 (64)
HER2 neu+	0 (0)	0 (0)	0 (0)
Triple negative	11 (35)	3 (33)	8 (36)
No. of metastatic sites			
1	10 (32)	1 (11)	9 (41)
2	12 (39)	5 (56)	7 (32)
3	9 (29)	3 (33)	6 (27)
Sites of metastases			
Liver	15 (48)	3 (33)	12 (55)
Lung	16 (45)	6 (67)	10 (45)
Bone	17 (55)	6 (67)	11 (50)
Prior taxane therapy			
Paclitaxel	13 (42)	4 (44)	9 (41)
Docetaxel	15 (48)	5 (56)	10 (45)
Nab-paclitaxel	1 (3)	0 (0)	1 (5)
Paclitaxel and docetaxel	2 (6)	0 (0)	2 (9)
Prior chemotherapy (metastatic setting)			
0	5 (16)	5 (23)	0 (0)
1	14 (45)	10 (45)	4 (44)
2	10 (32)	7 (32)	3 (33)
3	2 (6)	0 (0)	2 (22)

Table 2Toxicities ($n = 31$)

Adverse event	All grades	Grade 3	Grade 4
Hematologic			
Anemia	17 (55)	0 (0)	0 (0)
Leukopenia	14 (45)	3 (10)	2 (6)
Lymphopenia	11 (35)	7 (23)	0 (0)
Neutropenia	8 (26)	3 (10)	1 (3)
Febrile neutropenia	1 (3)	0 (0)	0 (0)
Thrombocytopenia	2 (6)	0 (0)	0 (0)
Non-hematologic			
Arthralgias	14 (45)	1 (3)	0 (0)
Myalgias	14 (45)	0 (0)	0 (0)
Neuropathy motor	5 (16)	1 (3)	0 (0)
Neuropathy sensory	26 (84)	1 (3)	0 (0)
Anorexia	15 (48)	2 (6)	0 (0)
Nausea	17 (55)	0 (0)	0 (0)
Vomiting	9 (29)	0 (0)	0 (0)
Diarrhea	15 (48)	3 (10)	0 (0)
Dyspnea	12 (39)	0 (0)	2 (6)
Fatigue	30 (97)	6 (19)	0 (0)
Hypocalcemia	2 (6)	0 (0)	0 (0)
Hypokalemia	3 (10)	1 (3)	0 (0)
Hyponatremia	2 (6)	1 (3)	0 (0)
Hypophosphatemia	1 (3)	0 (0)	0 (0)
Infection without neutropenia	12 (39)	2 (6)	0 (0)
Non-neutropenic fever	7 (23)	0 (0)	0 (0)
Rash	16 (52)	0 (0)	0 (0)
Renal insufficiency	5 (16)	0 (0)	1 (3)
Thrombosis	2 (6)	0 (0)	1 (3)

There was 1 patient with grade 5 acute respiratory distress (ARDS) within 30 days of study termination

Table 3

Phase II antitumor activity

Antitumor activity, <i>n</i> (%)	Phase II <i>N</i> = 22
Complete response	0 (0)
Partial response	5 (23)
Stable disease	9 (41)
Progressive disease	8 (36)
Objective response rate	5 (23, 95 % CI 8–45)
Median PFS, months	3.4
95 % CI	2.1–4.9
Median OS, months	11.2
95 % CI	6.6–16.0

PFS progress-free survival, *OS* overall survival, *CI* confidence interval

Weekly paclitaxel in women with metastatic breast cancer

Table 4

Regimen	Phase	# Prior chemo for mets	Prior taxane	Median cycles	ORR % (95 % CI)	Median PFS/TTP (months)
Paclitaxel (80 mg/m ²) + Suramin	II	2	Yes	2	23 (8–45)	3.4
Paclitaxel (80–108 mg/m ²) [35]	I	2	No	14	53 (34–72)	7.5
Paclitaxel (80 mg/m ²) [36]	II	2	No/yes ^b	4	22 (15–28)	4.7
Paclitaxel (90 mg/m ²) [37]	II	0	No	19	48 (35–61)	5
Paclitaxel (80 mg/m ²) ^a [38]	III	0	No	NA	42 (37–47)	9
Paclitaxel (90 mg/m ²) ^a [25]	III	0	No	NA	21	5.9

Chemo chemotherapy, *Mets* metastases, *PFS* progression-free survival, *TTP* time-to-progression, *NA* not available

^aResults described are for one treatment arm of a phase III randomized trial

^b25 % had received prior taxane therapy, majority in the metastatic setting