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# A Phase II Trial of Vorinostat (Suberoylanilide Hydroxamic Acid, -SAHA) in Metastatic Breast Cancer: A California Cancer Consortium Study

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## Abstract

**Purpose—**The primary goal of this trial was to determine the response rate of single-agent vorinostat in patients with metastatic breast cancer. The secondary goals included assessment of time to progression, evaluation of toxicities, and overall survival.

**Experimental Design—**From June 2005 to March 2006, fourteen patients received vorinostat, 200 mg orally, twice daily for 14 days of each 21 day cycle. Response and progression were evaluated using RECIST criteria.

**Results—**The median age for all patients was 60.5 years (range: 37–88). Eight patients were ER and/or PR positive, four were Her-2 positive. Sites of metastatic disease included brain, liver, lungs, bones, pelvis, pleura, chest wall, and distant lymph nodes. Patients received a median of 1.5 prior (range: 0–2) chemotherapeutic regimens for metastatic disease. Fatigue, nausea, diarrhea, and lymphopenia were the most frequent clinically significant adverse effects. The median number of cycles delivered was two (range: 1–20). There were no complete or partial responses and the study was terminated after the first stage, however 4 patients were observed with stable disease with time to progression of 4,8,9 and 14 months. The median number of months that patients received treatment on this study was 1.7 (range: 0.5–14).

**Conclusion—**While not meeting the RECIST response criteria for adequate single-agent activity, the observed tolerable toxicities and the potential for clinical benefit in terms of stable disease suggest that further assessment of vorinostat as a part of combination therapy with either chemotherapeutic or targeted agents in metastatic breast might be undertaken.

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## INTRODUCTION

More effective treatments for breast cancer are desperately needed. Epigenetic changes associated with the development and progression of cancer occur through a variety of mechanisms. Hypermethylation in the mammalian genome results in transcriptional repression[1]. Similarly, DNA that is wrapped around condensed, non-acetylated histones is transcriptionally inactive, whereas acetylation promotes transcriptional activity[2–4] The dynamic equilibrium between histone acetylation and deacetylation is regulated by histone acetyltransferases and histone deacetylases (HDACs)[5]. The HDACs exert their targeted action during post-translational acetylation of core nucleosomal histones, thereby regulating gene expression. The effect of HDAC inhibitors may vary depending on the specific experimental, or physiological environment. For example, HDAC inhibition causing decreased ERα expression can lead to a switch to agonist activity of partial antiestrogens, and such inhibiton can also sensitize ERα-negative breast cancer cells via upregulation of ER β activity. In general, data suggest that a decrease in histone acetylation may be associated with adverse outcome in human cancer [6, 7]. Because aberrant HDAC activity has been implicated in a variety of cancers, development of HDAC inhibitors is a rational approach to the design of targeted anticancer therapeutics.

Vorinostat (suberoylanilide hydroxamic acid) is a small molecule inhibitor of both class I and II HDAC enzymes with its main mechanisms of action in alterations of acetylating and downstream effects on apoptotic pathways[8]. Preclinical data has shown growth inhibition of MCF-7, MDA-MB 231, MDA-MB-435 and SKBr-3 breast cancer cell lines by inducing G1 and G2/M arrest and apoptosis[9]. In HER-2 – overexpressing breast cancer cell lines, in addition to dose-dependent facilitation of apoptosis, vorinostat induced acetylation of hsp90, leading to dissociation of HER-2 from the chaperone molecule, and resulting in polyubiquitylation and degradation of Her-2[10].

Phase I trials demonstrated that oral vorinostat administered as 200 mg twice daily, or 400 mg daily was well tolerated. Pharmacokinetic analysis suggested that the bioavailability of vorinostat ranged from 34.9% to 52.3% (only slightly improved with food), its half-life was 91–127 minutes with the duration of HDAC inhibition lasted ≥10 hours. The predominant toxicities included anorexia, fatigue, dehydration, diarrhea, and thrombocytopenia[11]. Vorinostat was recently approved by the US Food and Drug Administration in October 2006 for the treatment of advanced, refractory cutaneous T cell lymphoma[12].

Based on promising activity noted in preclinical studies, we set out to conduct a phase II study of single-agent vorinostat in patients with metastatic breast cancer (MBC). The primary endpoint in this trial was to estimate the objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST).

## Materials and Methods

### Patient eligibility

Patients with histologically or cytologically confirmed stage IV MBC were eligible. Patients must have had measurable disease by RECIST criteria. Prior adjuvant therapy, any number of courses of hormonal therapy, and up to 2 lines of prior chemotherapy for MBC (including trastuzumab-containing regimens in Her-2 positive patients), and prior radiation treatment were allowed. Patients must have been ≥ 18 years old, and an estimated life expectancy of ≥ 6 months and an Eastern Cooperative Group (ECOG) performance score of 0–2. Required baseline hematologic and metabolic requirements also included an absolute neutrophil count of ≥ 1,000/μl, platelets ≥ 100,000/μl, serum creatinine ≤ 1.6 mg/dl or a calculated measured creatinine clearance ≥ 60 ml/min, total bilirubin le; 2 mg/dl, and serum aspartate and alanine

transaminases ≤ 3 times the institutional upper limit of normal. Patients with known, stable, treated brain metastases, who had not received steroids for at least two months, were eligible. Women of child-bearing potential were required to use adequate contraception prior to study entry and for the duration of study participation. All patients were required to understand and voluntarily sign the informed consent forms approved by the institutional review boards. Exclusion criteria included having received chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study. Patients with uncontrolled intercurrent illness and pregnancy were excluded. As a precaution, a list of drugs or substances with the potential to affect selected P450 isoenzymes were provided to all participating clinicians due to potential suppression of the P450 system by vorinostat.

The study was approved by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), Bethesda, MD.

## Treatment Plan

Vorinostat, 200 mg orally twice daily, was administered for the first 14 days of each 21 day cycle. Treatment was continued unless either disease progression was determined, the patient requested to be withdrawn from the study, or excessive toxicity was noted. All subjects were asked to keep a diary and to return all medication bottles with unused medication. Pill counts were done to verify doses taken.

In anticipation of nausea, prochlorperazine, 10 mg orally every 8 hours, or ondansetron ODT, 8 mg every 12 hours, was prescribed as needed. Diarrhea was treated promptly with appropriate supportive care, including loperamide.

## Patient evaluation

Pre-treatment evaluation included a complete medical history, with details of prior treatments, physical examination, ECOG performance status, hematologic and biochemical profiles, serum pregnancy test as indicated, a 12-lead electrocardiogram as indicated, and tumor target assessment with appropriate radiographic examinations. When feasible, tumor biopsies of metastatic sites were also performed.

During the first cycle, patients were evaluated weekly for toxicity. During subsequent courses of treatment, a physical evaluation and laboratory assessment (serum chemistry and hemogram) were performed every 3 weeks. Toxicity was assessed at the beginning of each cycle and as clinically indicated using the NCI Common Terminology Criteria for Adverse Events (CTCAE version 3.0) scale. Reasons for dose delay or dose modifications were recorded.

## Response evaluation

Tumor assessments were carried out every 2 cycles (every 6 weeks), unless earlier evaluations were clinically indicated. Responses were described according to RECIST criteria. Radiographic response review occurred at two levels: measurement of tumors at each institution was undertaken by the clinical investigator in addition to the standard radiology report. A central radiology review of any observed objective response was to be subsequently performed by the response review committee of the California Cancer Consortium.

## Toxicity evaluation and dose modifications

Vorinostat was to be held for ≥ grade 3 toxicity (or ≥ grade 2 diarrhea) until the toxicity resolved to ≤ grade 1. The drug was then restarted at a 25% dose reduction (by reducing the

morning dose from 200 mg to 100 mg). A second ≥ grade 3 toxicity (≥ grade 2 for diarrhea) resulted in a 50% dose reduction (100 mg twice daily). A third episode of ≥ grade 3 toxicity (≥ grade 2 for diarrhea), or any incidence of ≥ grade 3 toxicity (or ≥ grade 2 diarrhea) that did not resolve to ≤ grade 1 in < 21 days resulted in discontinuation of vorinostat.

## Specimen procurement for correlative studies

When feasible, specimens from tumor blocks and/or slides from the tissue were to be obtained at the time of the original diagnosis, at the time of diagnosis of metastatic disease, during treatment at day 14, and at the time the patient discontinued treatment. All formalin-preserved and fresh-frozen specimens were shipped to a designated consortium laboratory and to Merck laboratories. Gene expression profiling for exploratory assessment was carried out by Merck Research laboratories/Rosetta Inpharmatics (MRL/Rosetta)[13]

The gene expression profiling from tumor tissues was performed by James S. Hardwick, PhD, at Oncology Molecular Profiling, Merck Research Laboratories in West Point, PA. However, only 5 specimens -all pre-treatment- were suitable for such assessment due to a variety of logistical factors. Microarray analysis was performed on samples from these five patients (3 with prolonged stable disease, and 2 who progressed rapidly on vorinostat therapy). RNA isolated from tumor cells macrodissected from the pre-therapy biopsies was used to generate mRNA expression profiles with custom Agilent microarrays. Agilent microarrays employ a two-channel competitive hybridization technology where mRNA abundance in an experimental sample (the individual breast tumor biopsy specimens) is measured relative to a reference RNA pool. The reference RNA pool used for this project was the ‘Universal Human Reference RNA’ that is available commercially through Agilent Technologies.

## Statistical Analysis

To evaluate the response rate (confirmed complete and partial response) of MBC patients to vorinostat, a two-stage Simon optimum design was used. Patients who completed at least two cycles of therapy, terminated treatment due to toxicity, or who progressed prior to completion of two cycles of therapy, were evaluable for response and included in decisions regarding early termination of the study. The design provides for the probability of falsely declaring a regimen with a 5% response rate as warranting further study of 0.10 (alpha error) and the probability of correctly declaring an agent with a 20% response rate as warranting further study of 0.90 (power). The planned first-stage target accrual was 12 patients evaluable for response. If no responses were observed, accrual would be discontinued with the conclusion that oral single-agent vorinostat was not adequately promising for further study as a single agent. Secondary endpoints include overall and progression-free (time to progression or death) survival, using Kaplan-Meier estimates.

Gene expression in the rapidly progressing patients was compared to those having prolonged stable disease using Significance Analysis of Microarrays (SAM) analysis[14]. SAM computes a modulated t-statistic for each gene, which measures the statistical strength between expression and the explanatory grouping. After repeated permutations of the data, SAM tests whether there are any significant statistical associations between the gene expression values and the qualitative categories. SAM also features a tuning value which directly influences the false-discovery rate. In SAM, we specified two-class, unpaired analyses with a false discovery rate (FDR) rate of 5%. SAM analysis was followed by an search through Oncomine[1] database to compare to previous observations.

# RESULTS

## Patient Characteristics

Patient characteristics are summarized in Table 1. From June 2005 to March 2006, 14 female patients with measurable MBC were enrolled. Two patients did not complete two cycles of treatment but were included for toxicity assessment and intent to treat analysis. The median age was 60.5 years (range 37–88). Tumors from 6 patients (43%) were ER/PR negative and 10 (71%) were HER-2 non-over-expressing at diagnosis. Metastatic sites included: brain (having stable disease post-treatment), lungs, liver, bones, pleura, pelvis, chest wall and distant lymph nodes. One-half (50%) of the patients had previously received two lines of standard chemotherapy for MBC.

## Efficacy

In this two-stage Phase II trial, with a first stage of accrual of 12 evaluable patients, there was no confirmed response observed. As a result, it was decided by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) not to proceed to complete stage II, nor to amend the trial to focus on a different endpoint such as clinical benefit inclusive of stable disease, or time to progression.

All patients enrolled were evaluable for response. The median time on therapy was 1.7 months (range 1.2–9.0). Stable disease was observed in 4 (29%) patients with a median progression-free survival of 8.5 months (range 4–14 months). The median progression-free survival was 2.6 months (95% CI 1.4-NR), and the median overall survival was 24 months (95% CI 17.4-NR) for the fourteen patients. Overall survival at 12 months was 71% (95% CI 51%–100%).

Three of four patients with stable disease (SD) had their original diagnosis of breast cancer made between 1993–1995, with the diagnosis of metastatic breast cancer in 2005, the fourth patient was originally diagnosed in 2002 (ER/PR/Her2neu negative) and recurred with mediastinal lymphadenopathy in 2005 (Table 2) who stayed on treatment for 20 cycles. One patient, having one prior chemotherapeutic regimen, progressed after 6 cycles of vorinostat. Two patients, who had two prior treatment regimens for metastatic disease, stayed on this study for 10 and 11 cycles respectively.

## Treatment

Fourteen patients received 66 cycles of vorinostat (range 1–20). The median number of treatment cycles to patients observed to have stable disease was 10.5 (range 6–20), and 2 cycles (range 1–20) in all patients. The reasons for treatment discontinuation included progressive disease in 11 patients, 1 patient did not receive the prescribed treatment due to lack of compliance, and 2 patients refused further treatment due to general symptoms and patient preference prior to 2 cycles. These two patients were replaced for evaluation of the response rate for interim analysis, but are included in this final report.

## Toxicity

Vorinostat was well tolerated in this population of patients. The major observed toxicities are illustrated in Table 3. As expected, nausea, fatigue and leucopenia were observed, with grade 3 fatigue reported in one patient. Two patients withdrew from the trial early, but were included in the analysis for toxicity. These patients requested discontinuation of treatment due to grade 2 nausea after cycle 1, however, one of these patients was observed to have progression of disease at the time of this evaluation. One patient stopped taking medication during cycle 3 because of malaise, and one patient required a 50% dosage reduction because of grade 3 fatigue, grade 2 diarrhea, and grade 2 anorexia. However, this patient went on to

receive a total of 10 cycles at 50% dose reduction. No treatment-related deaths occurred during the study.

### Preliminary Gene Expression Data

While limited to five pre-treatment tumor samples, we performed an exploratory analysis on gene expression using the Significance Analysis of Microarrays (SAM) algorithm. Our objective was to examine gene expression in the rapidly progressing patients compared to those having prolonged stable disease. We found that in one gene, dystonin (DST or BPAG1), a probe expression was 5.9-fold lower in the two rapidly progressing patients with a false discovery rate less than 5%. While we would not consider this a finding by itself, it was the initial signal that lead us to examine the available Oncomine database for the role of DST in other microarray studies as described in our discussion.

## DISCUSSION

Vorinostat is the first histone deactylase inhibitor approved for cancer indication by the US Food and Drug Administration for the treatment of advanced, refractory cutaneous T-cell lymphoma. It is currently being evaluated for potential activity in solid tumors. This trial is the first report for vorinostat activity as a single agent in patients with MBC. Kelly et al [15] treated 2 breast cancer patients in their phase I trial of oral vorinostat. Neither of these patients was reported to achieve an objective response or stabilization of disease. Rubin et al observed one case among 4 patients treated with MBC who achieved stable disease for greater than 15 months[16]

As targeted therapeutic agents come of age, it is becoming clear that the classic, RECIST-based assessment of tumor response may not be well-suited for drug screening. In this phase II, single-agent trial of vorinostat no RECIST-based responses were observed which resulted in stopping the trial at the first stage. However, 4 of 14 (29%) patients experienced a clinical benefit, having SD and a median time to disease progression of 8.5 (4–14) months. Adverse effects in these patients were tolerable. Although one can argue that the promising duration of SD was primarily observed in a less heavily pre-treated patient group, since these patients had a relatively long relapse-free interval from the time of their original diagnosis, the fact remains that clinically observable single-agent activity was associated with the use of this oral agent.

An increasing number of publications suggest that making therapeutic decisions based solely on RECIST criteria may be deficient. Our experience, and findings from clinical trials with other targeted agents, such as kinase inhibitors, highlights the need to modify both our clinical expectations [17] and our primary objectives regarding endpoints.

While this study has yielded only very preliminary observation based on the small sample size in our gene array analysis, and highlights the difficulty in obtaining appropriate biopsy material both from pre- and post-treatment, a preliminary observation has been made. Dystonin was identified as a potential marker for tumor aggressiveness. We identified through Oncomine several previous microarray studies that evaluated the expression patterns of DST, including three in breast cancer. Lower DST expression was associated with higher tumor grades and breast cancer invasion in all of these reports. Schuetz et al have the most complete discussion of the potential role of DST in breast cancer. In addition to a microarray analysis, they found that that protein expression of DST is also decreased in IDC compared to DCIS[18]. It was hypothesized that DST is expressed inhemidesmosomes connecting epithelial cells to the basement membrane, and so the lower expression may be a contributing factor to invasiveness. Bergstraesser et al previously showed that invasive breast cancer cells do not express hemidesmosomes[19]. We are in the process of seeking to

best classify our tumor specimens (luminal A and B, basal, ERB/Her2, and normal) since the profiles need to be compared to an independent breast tumor data set. Our correlative finding agrees with the previous data suggests that DST could be a candidate gene marker for tumor aggressiveness. However, given the small sample size of this trial, the microarray data analysis with dystonin is served only as a hypothesis generating concept.

In summary, despite modest clinical benefit observed in this trial which diminishes enthusiasm as a single agent in this setting, its manageable toxicity and ease of administration, suggest vorinostat and its class should be further evaluated in the treatment of breast cancer as part of a combination therapy. Further assessment of vorinostat, in combination with paclitaxel and bevacizumab is currently ongoing in first-line MBC treatment (PHII-87 NCI #7703).

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**Table 1**

Patient Characteristics

| | |
|---|---|
| Number of patients (n) | 14 |
| Median age (range), years | 60.5 (37–89) |
| Hormone receptor status | |
| ER/PR status | |
| - positive | 8 |
| - negative | 6 |
| Her-2 status | |
| - positive | 4 |
| - negative | 10 |
| Metastatic sites | |
| Brain | 1 |
| Lung, liver, bones | 2 |
| Lung | 2 |
| Pelvic and chest wall | 1 |
| Bone | 1 |
| Liver and bone | 2 |
| Distant nodes | 2 |
| Pleura and bone | 1 |
| Distant node and bone | 1 |
| Liver | 1 |
| Prior line of systemic chemotherapy for MBC | |
| 0 | 2 |
| 1 | 5 |
| 2 | 7 |
| Prior systemic trastuzumab for MBC | 3 |

ER/PR: Estrogen Receptor/Progesterone Receptor, MBC:Metastatic Breast Cancer

**Table 2**

Characteristics of stable disease patients

| Patient | Sites of MBC | ER | PR | HER2 | Prior treatment for MBC | Cycles received on study |
|---|---|---|---|---|---|---|
| 1 | Lung, liver, bone | pos | neg | neg | 1 | 6 |
| 2 | Liver | neg | neg | pos | 2 | 11 |
| 3 | Bones | pos | pos | neg | 2 | 10 |
| 4 | Mediastinal nodes | neg | neg | neg | 0 | 20 |

MBC: Metastatic Breast Cancer, ER: Estrogen Receptor, PR: Progesterone Receptor

## Table 3

Treatment Related Toxicity

| | Grade 1–2 | Grade 3 | Grade 4 |
|---|---|---|---|
| Anorexia | 3 | | |
| Fatigue | 9* | 1 | |
| Diarrhea | 6 | | |
| Nausea/Vomiting | 10 | 1 | |
| Dyspepsia | 1 | | |
| Elevated LFT's | 10 | | |
| Dehydration | | 1 | |
| Hypokalemia | 2 | 1 | |
| Mucositis | 1 | | 1 |
| Lymphopenia | 8 | | 1 |
| Thrombocytopenia | 5 | 1 | |
| Leukopenia | 6 | | |
| Constipation | 2 | | |

LFT's: Liver Function Tests

*Two early withdrawals prior to response evaluation due to grade 2 nausea, fatigue and rapid progression of disease were observed.