Cancer Chemother Pharmacol (2008) 62:149–157
DOI 10.1007/s00280-007-0585-6

ORIGINAL ARTICLE

Phase II trial of daily oral perillyl alcohol (NSC 641066) in treatment-refractory metastatic breast cancer

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Received: 18 May 2007 / Accepted: 30 August 2007 / Published online: 21 September 2007

Abstract
Purpose Perillyl alcohol (POH) is a naturally occurring lipid with preclinical activity against mammary carcinomas. We conducted a phase II multi-institutional study of oral POH administered four times daily in women with advanced treatment-refractory breast cancer.
Methods Eligible women were treated with POH four times daily at 1,200–1,500 mg m^{-2} $dose^{-1}$ on a 28-day cycle. Patients tolerating 1,200 mg m^{-2} day^{-1} four times daily after one cycle were dose-escalated to 1,500 mg/m^2. The primary endpoint was 1-year freedom-from-progression (FFP) rate. Secondary endpoints were response rate, tolerability and correlative evaluations.
Results Twenty-nine cycles of POH were administered to 14 women. Three patients were dose-escalated to 1,500 mg/m^2. Grade 1 and grade 2 gastrointestinal effects and fatigue were predominant toxicities. Of seven patients receiving up to one cycle, three stopped therapy due to intolerance. Only two patients received more than two cycles, with disease stabilization of 3 and 8 months. Thirteen patients were evaluable for response. One-year FFP rate was zero. No objective responses were seen. The median time to progression was 35 days (95% CI, 29–123 days). Median overall survival was 389 days (95% CI, 202–776 days). Pharmacokinetic parameters were similar to previous investigations. The ability to correlate plasma TGF-β1 levels with outcome was limited by lack of clinical benefit and inter- and intra-patient variability.
Conclusions Enrollment was suspended short of planned accrual because of lack of response and poor tolerance to POH. This regimen does not appear to provide benefit in advanced treatment-refractory breast carcinoma.

Keywords Breast cancer · Monoterpenes · Perillyl alcohol · Phase II

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Introduction

Jemal et al. estimate that breast cancer will account for 40,910 deaths in the United States in 2007 [27]. While the 5-year survival rate in breast cancer patients has improved over the last 30 years [27], the treatment of metastatic disease refractory to endocrine therapy, trastuzumab [47], paclitaxel [1], vinorelbine [43], docetaxel [51], gemcitabine [12] and capecitabine [9] remains a formidable challenge for scientists, clinicians and patients. Clearly, novel effective treatments are needed for patients with advanced, treatment-refractory breast cancer.

Monoterpenes are a class of natural compounds with activity against a wide range of tumor types in preclinical models including breast carcinoma [7, 11, 23, 24, 55]. Monoterpenes administered as part of daily chow to rats with chemically induced primary mammary carcinomas resulted in disappearance of the majority of tumors [23, 24]. Monoterpene-induced tumor regression was sustained as

long as monoterpene exposure continued. The mechanism of action of monoterpenes is not clearly defined. Several investigators have suggested cellular effects, such as G_1 block and the induction of apoptosis [7, 46]; biochemical effects, such isoprenylation inhibition [18, 40]; differential gene regulation, including over-expression of the mannose 6-phosphate/insulin-like growth factor-II receptor genes and the transforming growth factor (TGF)-β receptor genes [2]; and inhibition of angiogenesis [31].

Perillyl alcohol (NSC 641066, POH) is the prototypic monoterpene and has undergone National Cancer Institute (NCI)-sponsored preclinical testing, formulation and phase I and II clinical evaluation. Preclinical data on monoterpenes, including POH, suggest the possibility of a static anti-tumor effect [2, 7, 18, 24, 40, 46] with a plasma half-life such that multiple daily doses are required to assure steady-state plasma levels [23, 24]. Therefore, phase I studies with POH have involved three and four times daily dosing on a 4-week cycle. Phase I testing revealed mild to moderate toxicities, most commonly gastrointestinal symptoms and fatigue, with daily administration of an oral formulation [26, 41, 42]. Significant heterogeneity in the tolerability and pharmacokinetics of POH was seen between patients. Tumor shrinkage with prolonged stable disease was observed in patients with colorectal cancer (>2 years) and hormone refractory prostate cancer ($\geq$6 months) [41, 42]. The recommended phase II regimen from our phase I studies is 1,200–1,600 mg m^{-2} $dose^{-1}$ orally four times daily throughout a 28-day cycle [41, 42].

Given the activity of POH against breast carcinoma in vitro and in vivo, the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center and the Wisconsin Oncology Network initiated a phase II study of POH in patients with metastatic, treatment-refractory breast cancer. The primary endpoint was 1-year freedom-from-progression (FFP) rate. Secondary endpoints were response rate, tolerability and correlative studies including pharmacokinetic analyses and comparison of plasma TGF-β1, a potential surrogate of the clinical activity of POH [28], with response.

Patients and methods

Patient selection

This study was open to women at least 18 years of age with metastatic breast cancer progressing through at least one chemotherapy regimen in the advanced setting. Adjuvant therapy did not meet this requirement. Additionally, women with estrogen receptor positive tumors must have had progressive disease during or after the use of endocrine therapy. Eligibility criteria included microscopic confirmation of breast cancer, an Eastern Cooperative Oncology Group performance status of $\leq$2, life expectancy of at least 12 weeks, recovery from toxicity of prior anti-cancer treatment, adequate major organ function (white blood count $\geq$4,000 mm^{-3}; absolute neutrophil count (ANC) $\geq$1,500 mm^{-3}; platelet count $\geq$100,000 mm^{-3}; total bilirubin $\leq$1.5 mg/dl; aspartate aminotransferase $\leq$2.0 times the upper institutional limit of normal; blood urea nitrogen (BUN) $\leq$30 mg% and creatinine $\leq$1.5 mg%), the ability to understand the investigational nature of the study and give informed consent, and at least one measurable disease site. Patients were ineligible if they had received endocrine or immunologic therapy within 2 weeks; cytotoxic chemotherapy or radiotherapy within 4 weeks; were pregnant or nursing; were of reproductive age and unwilling to use effective birth control; or had brain metastasis. Use of cholesterol-lowering agents, supplemental vitamins and other antioxidants was not permitted for enrolled patients. The Institutional Review Boards of participating sites approved this study.

Pretreatment evaluation and follow-up studies

Baseline evaluations, required within 2 weeks prior to first protocol treatment, included physical exam with weight, assessment of performance status and dimensional assessment of measurable lesions. Laboratory studies required within 2 weeks prior to initial treatment included complete blood count (CBC) with differential cell count, urinalysis, serum electrolytes, BUN, serum creatinine, serum calcium, serum phosphorus, uric acid, alkaline phosphatase, aspartate transaminase (AST), lactate dehydrogenase (LDH) and total bilirubin. CBC with differential count, BUN, creatinine, serum calcium, serum phosphorus, uric acid, alkaline phosphatase, AST, LDH and total bilirubin were evaluated weekly during cycle 1, then every 2 weeks for the first 6 months and, thereafter, every 4 weeks. The latter schedule was also applied upon dose escalation. Plasma TGF-β1 levels were drawn on selected patients enrolled at the University of Wisconsin, Madison at baseline, weekly during cycle 1, biweekly during cycle 2 and then on day 1 of subsequent cycles.

Drug administration and dose modifications

Perillyl alcohol was supplied as soft gelatin capsules containing 250 mg of POH and 250 mg of soybean oil by the Pharmaceutical Management Branch, Cancer Therapy Evaluation Program (CTEP), NCI.

Perillyl alcohol was administered orally continuously on a 28-day cycle as 1,200 mg m^{-2} $dose^{-1}$ four times daily at approximately 6-h intervals. As the capsule amount of POH was 250 mg, the calculated dose was rounded up or down

by this increment to achieve the final dose. Patients maintained a drug diary that was reviewed monthly by the site investigator.

Perillyl alcohol was held upon patient request, for any grade ≥3 toxicity (as rated per the NCI Common Toxicity Criteria version 1.0 [34]) and for the following grade ≥2 toxicities: vomiting of ≥3 days duration, diarrhea of ≥3 days duration and creatinine. Once toxicities resolved to baseline, POH was resumed with a 25% dose reduction. However, patients with toxicities that did not resolve to baseline within 14 days of the drug being held were removed permanently from treatment. Patients without signs of the above toxicities during the initial 28 days of continuous POH were dose escalated by 25% to 1,500 mg/m^2. Supportive measures consistent with optimal patient care were provided throughout the study.

Disease assessment

Patients were evaluable for response if they (a) completed ≥4 weeks of therapy (interrupted or continuous); (b) were removed from treatment due to progressive disease (PD) before completing 4 weeks of therapy; and (c) were removed from treatment prior to the start of cycle 3, but at or after the beginning of cycle 1. In the latter case, patients were evaluated for response when treatment ended. Patients not completing 4 weeks of therapy for any other reason, including toxicity, were not evaluable for response. All patients treated on study were evaluable for toxicity.

Measurable tumor sites were assessed using World Health Organization criteria [33] within 2 weeks of initiating protocol treatment and then every two cycles while on treatment. Measurable disease was defined as any lesion for which two perpendicular diameters could be measured. Liver lesions were considered measurable when greater than 5 cm^2 by computed tomography. Disease sites previously irradiated were not considered measurable unless they demonstrated evidence of progression since completing radiotherapy. Complete response (CR) was defined as disappearance of all clinical and radiographic evidence of active tumor and disease-related symptoms for at least 4 weeks with stable performance status during this time. Partial response (PR) was defined as ≥50% reduction in the sum of the products of the perpendicular tumor diameters of all measurable lesions lasting at least 4 weeks without the simultaneous increase in the size of an individual lesion or the appearance of a new lesion. PD was defined as an increase of at least 25% in the size of any measurable lesion, or the appearance of a new lesion. Stable disease (SD) was defined as an assessment not meeting the criteria for PR, CR or PD for a minimum of 8 weeks.

Treatment was discontinued for the following reasons: progressive disease; change in health status rendering the patient unacceptable for further treatment in the judgment of the site investigator; withdrawn consent; or development of irreversible or life-threatening toxicity.

Pharmacokinetic analyses

In order to further characterize the pharmacokinetic parameters of POH and its major metabolites, perillic acid and dihydroperillic acid, blood samples were collected on day 1 of cycles 1 and 2 before administration of the first dose of POH and then at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 h post-administration of this dose. After collection, samples were cold centrifuged for 10 min at 2,000*g*. Thereafter, 2 ml plasma aliquots were stored at −70°C in Nunc tubes. Blood samples were to be collected for a subset of patients enrolled at the University of Wisconsin, Madison.

Analytical methods

Blood levels of POH, perillic acid and dihydroperillic acid were measured using the gas chromatographic method of Phillips et al. [35]. Assay standards were provided by the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis and Centers, NCI. For every single-dose concentration–time data set, pharmacokinetic parameters for perillic acid and dihydroperillic acid were determined by non-compartmental methods [20]. The area under the curve (AUC) for 0–6 h was evaluated using a linear trapezoidal rule. The C_{max} and t_{max} were determined by directly inspecting the data. The single-dose $t_{1/2}$ was evaluated by log–linear regression on the concentration–time curve's terminal portion. We used PKAnalyst (MicroMath Scientific Software, Salt Lake City, UT) and Sigma Stat (Jandel Scientific, San Rafael, CA) to determine the AUC and perform linear regression.

TGF-β1 plasma levels

Plasma level of TGF-β1 has been cited as a potential surrogate of the clinical activity of POH [28]. To compare these values with response, a plasma TGF-β1 level was drawn at baseline and then weekly for 4–8 weeks in patients enrolled at the University of Wisconsin, Madison. Measurement of plasma concentrations were made using a validated R&D Systems (Minneapolis, MN) Quantikine human TGF-β1 ELISA kit and read at 450 nm on a Molecular Dynamics Biolumin 960 plate reader.

Statistical considerations

Often, initial evaluations of novel agents in clinical breast cancer research are based on the ability of cytotoxic agents to induce tumor shrinkage (i.e., response rate) [2, 9, 19, 51].

However, response rate may not be a reasonable surrogate for cytostatic agents. Given the possible mechanisms of action of POH [2, 7, 18, 46], a clinically beneficial effect may manifest itself only as a static response (i.e., stable disease) in some patients. Because of this, the primary endpoint of this study focused on disease stabilization (FFP) rather than on response rate.

The regimens available at the time of study inception for second-line treatment of metastatic breast cancer had a 1-year FFP rate of <5% [22]. Based upon this, it was determined that the observed 1-year FFP rate in this study should significantly exceed 5% to justify further study of POH in metastatic breast cancer patients. Since patients in this study at the time the study protocol was written would likely not have a median life expectancy >12 months, this result would strongly imply a beneficial clinical effect worthy of further exploration. A target of 40 evaluable subjects was pursued. Due to clinical issues detailed later, study accrual was stopped after 14 patients were enrolled.

The study was originally designed so that a minimum of five out of 40 patients with 1-year FFP would be necessary to demonstrate a 1-year FFP rate significantly >5% at the usual one-sided 0.05 significance level. Power, with the original goal of 40 patients, was 80% to detect a true 1-year FFP rate of 17% or higher. There was a 90% chance that at least 12 1-year FFPs would occur if the true 1-year FFP rate was 20% or better. Thus, if POH had a modest effect (boosting overall disease stabilization rates, after accounting for toxicities and other dropouts, above about 15%) then this study should have detected it.

Results

Patient characteristics

Baseline characteristics of the 14 patients enrolled on this study are tabulated in Tables 1 and 2. All patients were female and ranged in age from 40 to 90 years, with a median age of 58 years. Nine patients were enrolled at the University of Wisconsin, Madison with the remainder enrolled through the Wisconsin Oncology Network. Most patients (10/14) had an ECOG performance status of one and were Caucasian (13/14). Measurable metastatic sites included liver (50%), lung (28.4%), lymph nodes (35.7%) and skin (14.3%). At enrollment, 11 patients (78.6%) had received more than two prior chemotherapy regimens, and half of patients had received two or more endocrine agents. The most prevalent prior chemotherapy regimens for any stage of disease were cyclophosphamide-methotrexate-5-fluorouracil (50%), paclitaxel (50%), docetaxel (42.9%), cyclophosphamide-doxorubicin-5-fluorouracil (35.7%), vinorelbine (28.6%), doxorubicin (21.4%) and doxorubicin-cyclophosphamide (21.4%). Only one patient had not received tamoxifen and half had received anastrazole. Three patients had received trastuzumab.

Table 1 Baseline patient characteristics ($N = 14$, all female)

Characteristic	Frequency	
	No.	%
Age, years		
Median	58	
Range	40–90	
ECOG performance status		
0	2	14.3
1	10	71.4
2	2	14.2
Race		
Caucasian, non-Hispanic	13	92.9
Hispanic	1	7.1
Metastatic sites		
Liver	7	50.0
Lung	4	28.4
Skin	2	14.3
Lymph node	5	35.7
ER and/or PR positive	10	71.4

ECOG Eastern cooperative oncology group, *ER* estrogen receptor, *PR* progesterone receptor

Table 2 Prior regimens used by the time of study entry in our patients ($n = 14$)

	Frequency	
	No.	%
Number of chemotherapy agents		
2	3	21.4
3	5	35.7
≥4	6	42.8
Endocrine agents		
0	1	7.1
1	6	42.9
≥2	7	50.0
Non-chemotherapy regimens		
Tamoxifen	13	92.9
Anastrazole	7	50.0
Megace	2	14.3
Trastuzumab	3	21.4

Perillyl alcohol administration and toxicity

Fourteen patients received a total of 29 cycles of POH. Only three patients' doses were escalated, based on tolerability

requirements, after one cycle of treatment to receive POH at 1,500 mg m^{-2} $dose^{-1}$ four times daily. Each of these three patients discontinued the study drug after the second cycle due to progressive disease.

Two patients received more than two cycles of POH. The first had predominately skin metastases and exhibited stable disease for eight cycles before disease progression. The second patient received three cycles prior to progressive disease. Five patients received two cycles of POH before tumor progression. The remaining seven patients received ≤1 cycle of therapy before being removed from treatment. Four of these were removed for progressive disease, whereas three stopped treatment due to intolerance. Among the patients with intolerance, one requested to end treatment after developing grade 2 fatigue, grade 2 dyspnea and grade 4 LDH with the first cycle. A second patient stopped treatment after grade 2 nausea, grade 2 eructation and grade 3 ANC developed. Both of the latter patients demonstrated progressive disease on exit study staging evaluations. A third withdrew consent 8 days into cycle 1 treatment with grade 4 dyspnea and grade 3 nausea and vomiting. No patient died on study.

Table 3 summarizes the maximal severity of toxicities observed in the 14 patients over 29 cycles. Toxicities are listed regardless of attribution status to POH. Most grade 3 and 4 toxicities were seen in cycle 1, including, for grade 3, nausea (1 patient); vomiting (1); alkaline phosphatase (2); aspartate transaminase (2); and, for grade 4, dyspnea (1) and lactate dehydrogenase (2).

Table 3 Maximal severity of toxicities per patient (n = 14) and type observed over 29 cycles

Classification[a]	Grade[a]			
	1	2	3	4
Pain			10	
Nausea and/or vomiting	2	4	1	
Bloating and indigestion	5	2		
Dyspnea		4	1	1
Fatigue			5	
Diarrhea	4	1		
Eructation	2	2		
Constipation	3			
Liver function tests	2		1	
Headache	2			
Fever	2			
Flatulence		2		
Hemoptysis			1	
ANC			1	

ANC Absolute neutrophil count

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 1.0

Overall, the predominant toxicities were gastrointestinal-related and fatigue. Almost all cycles were associated with gastrointestinal toxicity. These included nausea, eructation, epigastric pain/discomfort, constipation and diarrhea. Emesis occurred in only two patients. One-third of cycles were associated with grade 1 or 2 fatigue. Four patients had pulmonary toxicity. These patients had diffuse metastatic disease with known or suspected metastatic pulmonary involvement. Two patients described grade 2, and one patient described grade 3, dyspnea during their first or second cycle. One patient had grade 4 pulmonary toxicity (dyspnea and infiltrate) likely secondary to infection and unlikely caused by POH. One patient with rapidly progressive disease was observed to have a grade 3 transaminitis during cycle 1. Despite stopping the study drug, these parameters continued to worsen in a pattern consistent with progressive liver disease.

Patient outcome

Thirteen patients were considered evaluable for tumor response to POH (Table 4). The patient who withdrew due to toxicity 8 days into cycle 1 was censored for response. There were no partial or complete responses. Two patients demonstrated stable disease, over three and eight cycles. With a median follow up of 13.4 months (range 1.3–45.3 months), all study participants have died. The 1-year FFP rate was zero. The median time to progression (Fig. 1) was 35 days (95% CI, 29–123 days). Median overall survival (Fig. 1) was 389 days (95% CI, 202–776 days). Survival curves were estimated using the Kaplan–Meier method [29].

Pharmacokinetic analyses

Pharmacokinetic sampling of the main POH metabolites, perillic acid and dihydroperillic acid, were performed on day 1 of cycle 1 in three patients enrolled at the University of Wisconsin, Madison receiving protocol treatment at the initial dose level of 1,200 mg/m^2. Perillic acid values [mean ± standard deviation (SD)] were peak concentration (C_{max}) = 371 ± 191 μM; AUC (0–6 h) = 929 ± 643 μM × h; and half-life ($t_{1/2}$) = 1.2 ± 0.8 h. The results for dihydroperillic acid were C_{max} = 27 ± 20 μM; AUC (0–6 h) = 96 ± 78 μM × h; and $t_{1/2}$ = 5 ± 3 h. These results are similar to prior phase I experience with POH [5, 41].

Plasma TGF-β1

Plasma TGF-β1 levels were determined at baseline and then weekly for 4–8 weeks in eight of nine patients enrolled at the University of Wisconsin, Madison. Values were as follows [mean ± SD, number (n)]: baseline 5.5 ± 3.4 ng/ml, 8;

Table 4 Best patient outcome ($N = 14$) with a median 13.4 months of follow up

Outcome	Estimate
Best objective response	
Evaluable	13
CR	0
PR	0
SD	2
PD	11
Time to progression	
Progressions	14
Median[a] (95% CI)	35 days (29–123 days)
% Progression-free	
1 month	53.9%
2 months	15.4%
6 months	7.7%
Survival	
Deaths	14
Median[a] (95% CI)	389 days (202–776 days)
% Alive	
6 months	69.2%
12 months	61.5%
18 months	46.2%
24 months	15.4%

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CI* confidence interval

[a] Kaplan–Meier method

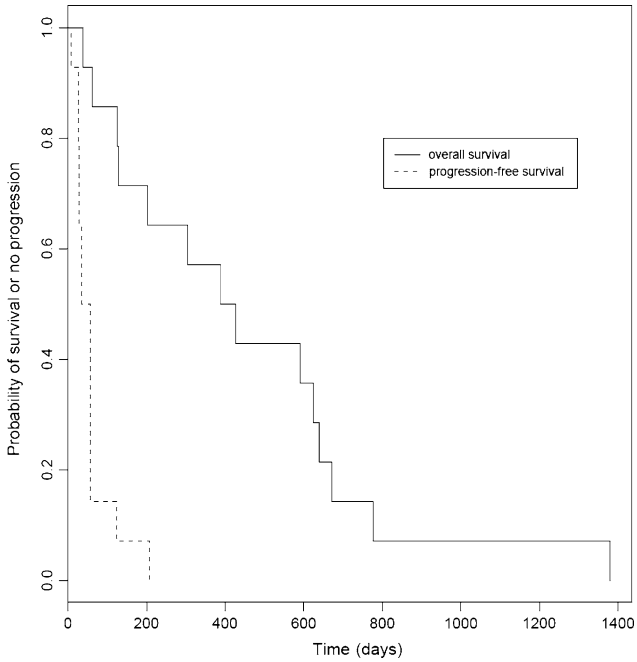

Fig. 1 Kaplan–Meier plot demonstrating a median time-to-progression of 35 days (95% confidence interval (CI): 29–123 days) and a median overall survival of 389 days (95% CI: 202–776 days) in 14 women with advanced, treatment-refractory breast cancer administered perillyl alcohol four times daily at 1,200–1,500 mg m^{-2} $dose^{-1}$ on a 28 day cycle

week 1 5.7 ± 3.7; 5; week 2 4.4 ± 1.8, 4; week 3 9.6 ± 11, 4; week 4 11.1 ± 10, 7; and week 8 3.2 ± 1.1, 3. The ability to correlate TGF-β1 with outcome was diminished by the lack of observed clinical benefit and to the large inter- and intra-patient variability.

Discussion

This study was designed to accrue 40 patients to evaluate the clinical efficacy of the naturally occurring lipid POH in females with treatment-refractory metastatic breast cancer. Because of a lack of response and concerns regarding intolerability, as well as the development of a new formulation of POH, the investigators and the study sponsor (NCI/CTEP) decided to discontinue enrollment short of the accrual goal.

Tolerance to this regimen was poor in that only three of 14 patients met tolerability requirements after cycle 1 to allow dose escalation to 1,500 mg/m^2. Toxicities were similar to that of our prior experience with POH [41, 42]; i.e., principally, mild to moderate gastrointestinal toxicities and fatigue. Patient intolerance of this regimen may be secondary to any of several factors. First, the subjectivity in experiencing and reporting gastrointestinal side effects may be at play. Second, intensity of a regimen with multiple daily dosing continuously throughout a 28-day cycle may contribute to poor compliance and attrition; however, a seemingly less intense regimen from a phase I study of POH on a 14-day-on, 14-day-off schedule showed no clear advantage with regard to tolerability and toxicity [5]. Third, selection of heavily pre-treated patients in this study who may have a lower threshold to reject new or recurrent toxicity may contribute. Fourth, variables related to the formulation and administration schedule may be important. The higher maximum tolerated dose (8,400 mg/m^2 per day) recommended in a different phase I study of POH [3] is, at least in part, explainable with these suppositions.

There were no objective responses, with only two of 13 evaluable patients demonstrating disease stability beyond two cycles of protocol therapy. Given the promising in vitro [7, 46, 55] and in vivo [55] data in breast cancer models with POH, why did this occur? We propose several possibilities, acting alone or together. First, perhaps this regimen does not have a reasonable therapeutic ratio to be effective against these patients' breast cancers. Second, a drug such as POH, with a presumed static tumor effect, may require substantial time to show a response and therefore

may not perform well in a clinical situation requiring a rapid response; in support of this, many patients had subjective or objective signs of progression after one cycle of POH. Third, despite interesting preclinical results, in vitro and animal breast cancer models may not be predictive of the efficacy of POH as treatment of human breast cancer. Indeed, encouraging preclinical data with POH in solid tumors [6, 10, 14, 25, 36, 39, 48, 49, 53, 54] have not translated into promising efficacy in the phase II setting in prostate [30], colorectal [32] and ovarian cancers [4]. Fourth, it is plausible that POH may be capable of preventing breast cancer initiation, but have no clinically detectable effect in humans on the part of the carcinogenesis spectrum examined in this study; namely, progression. There have been no randomized clinical trials focusing on the chemo-preventative potential of POH in human cancer. However, several interesting studies have explored this possibility [13, 50, 52]. Fifth, it is possible, given the number of patients evaluated on this study, that a larger patient sample is necessary to detect clinical activity of POH in this cancer subgroup. However, cancer patients and their clinicians would not favorably view a drug with the side effect profile of this regimen requiring at least 15 patients to be treated before receiving a clear benefit. Lastly, perhaps the discovery of the clinical efficacy of POH awaits its use in combination with other agents. Data suggest in vitro synergy between POH and pentoxiphylline in a human myelomonocytic leukemia cell line [21] as well as potential as a radiosensitizer in head and neck squamous cell cancer [45], malignant glioma [38], and prostate cancer [37]. Synergic regimens may allow the clinical use of a lower, more tolerable dose of POH.

Future plans with POH are uncertain, but likely do not include the formulation used in this study. Resolution regarding the mechanisms of action of POH and the reasons for the variability in patient tolerance may enhance its promise as an anti-cancer drug. Our clinical study, like others [4, 30, 32], does not support a therapeutic potential for POH in solid tumors, yet interest remains in POH and monoterpenes as preventative agents and in the treatment of other malignancies. For instance, an interesting prospective use of POH suggested by in vitro data includes the treatment of hematologic cancers, such as lymphoma [8] and leukemia [15–17, 44].

Acknowledgments We thank our patients and their families for their contribution to the advancement of clinical breast cancer research. We thank Marcia Pomplun and Amy Dresen of the University of Wisconsin Carbone Cancer Center 3P Laboratory for their technical assistance with the perillyl alcohol and TGF-β1 assays. We are grateful to Bo Huang for his statistical assistance as well as to Amyé Tevaarwerk for proofreading the manuscript. This study was supported by National Institutes of Health grants R21 CA 72500 and P30 CA 14520 as well as NCRR grant MOI RR03186.

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