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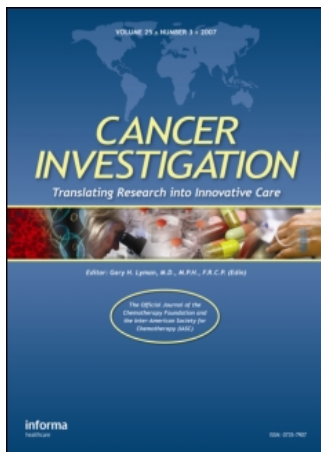
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### A Pilot Phase II Trial of Valspodar Modulation of Multidrug Resistance to Paclitaxel in the Treatment of Metastatic Carcinoma of the Breast (E1195): A Trial of the Eastern Cooperative Oncology Group

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ORIGINAL ARTICLE

# A Pilot Phase II Trial of Valspodar Modulation of Multidrug Resistance to Paclitaxel in the Treatment of Metastatic Carcinoma of the Breast (E1195): A Trial of the Eastern Cooperative Oncology Group

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## ABSTRACT

**Background:** To assess the activity and toxicity of valspodar (PSC-833) in combination with paclitaxel in women with anthracycline refractory, metastatic breast cancer. **Patients and Methods:** Limited, multi-institutional, Phase II trial of valspodar at 5 mg/kg/dose orally every 6 hours for 12 doses in combination with paclitaxel 70 mg/m<sup>2</sup> administered intravenously as a 3-hour infusion beginning 4 hours after the fifth dose of valspodar, every 3 weeks. Eligible patients had bi-dimensionally measurable metastatic carcinoma of the breast, prior anthracycline therapy or a medical contraindication to anthracycline therapy, no more than one prior chemotherapy for recurrent or metastatic breast cancer, and adequate organ function. Treatment was continued until disease progression or unacceptable toxicity. **Results:** Thirty-four patients are evaluable for response and 37 for toxicity. Two (6 percent) patients achieved a complete response and 5 (15 percent) a partial response for an objective response rate of 21 percent (95 percent confidence interval of 9 to 38 percent). Median duration of response was 9.7 months (95 percent confidence interval 8.0–17.2 months), median time to progression was 3.3 months (95 percent confidence interval 2.0–4.2 months), and median survival was 12 months (95 percent confidence interval 8.1–17.3 months). The toxicity experienced was acceptable. **Conclusions:** Combination valspodar plus paclitaxel is an active regimen and has acceptable toxicity. The combination is not clearly more active than single agent paclitaxel.

This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, M.D., Chair) and supported in part by Public Health Service Grants CA23318, CA66636, CA21115, CA27525, CA21076, CA16116 and from the National Cancer Institute, National Institutes of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Keywords: Breast neoplasms, Multidrug resistance, Paclitaxel, Valdospar.

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## INTRODUCTION

Cytotoxic drug resistance may be present *de novo* or arise by somatic mutations during tumor growth and is an important cause of cancer chemotherapy failure. Most cellular models of drug resistance against the anthracyclines, vinca alkaloids, or epipodophyllotoxins display multidrug resistance (MDR) at the molecular and cellular level (1–4). The MDR phenotype is related to the expression of the *MDR 1* gene coding for P-glycoprotein. P-glycoprotein acts as an efflux pump with very broad specificity and actively transports antineoplastic drugs out of cells, thereby reducing the intracellular drug concentrations.

Expression of *MDR 1* is strongly implicated in both intrinsic and acquired drug resistance in human cancers (1). It is likely that P-glycoprotein in normal tissues has an important role in the detoxification of certain anticancer agents and in drug distribution as a component of the blood-brain and blood-testicular barriers.

Several noncytotoxic drugs, such as verapamil, phenothiazines, and cyclosporins have been shown to modulate MDR, at least in part by competitive inhibition of P-glycoprotein function (3, 4). Valspodar is an analog of cyclosporin D, and is highly effective at modulating MDR *in vitro* (5–7). Valspodar is superior in MDR modulation compared to amiodarone, verapamil, procaine, quinidine, quinacrine, lidocaine, and cyclosporin A. Valspodar produces a dose-dependent therapeutic effect in mice inoculated with multidrug resistant tumors and treated with otherwise ineffective cytostatic chemotherapeutic drug doses (5–7).

Phase I trials of single agent valspodar identify a rapidly reversible ataxia as the dose limiting toxicity. Other toxicities include hyperbilirubinemia, nausea, and fatigue. In Phase I trials of combination paclitaxel and valspodar, the pharmacokinetics of paclitaxel were prolonged, with a recommended Phase II dose of paclitaxel of 70 mg/m<sup>2</sup> by 3-hour continuous infusion given every 3 weeks (8, 9).

Studies have demonstrated substantial anti tumor efficacy of single agent paclitaxel in the treatment of metastatic breast cancer (10–18). This study was designed to assess the antitumor activity and toxicity of paclitaxel in combination with valspodar in the treatment of women with anthracycline refractory, metastatic breast cancer.

## PATIENTS AND METHODS

### *Patient selection*

Patients were enrolled from 7 institutions participating in the Eastern Cooperative Oncology Group between June 1997 and February 2001. Eligible patients were female, had histologically confirmed adenocarcinoma of the breast with at least one site of bi-dimensionally measurable recurrent or metastatic disease, had prior anthracycline therapy or a medical contraindication to anthracycline therapy, had no more than one prior chemotherapy for recurrent or metastatic breast cancer (prior adjuvant chemotherapy within 6 months of diagnosis of metastatic disease was considered therapy for metastatic disease) and no prior

taxane therapy. They had to have ECOG performance status of 0 to 2, adequate bone marrow, liver, and renal function, no central nervous system metastasis, and received no concurrent treatment with agents known to increase or decrease the concentrations of cyclosporin A. All patients were required to provide signed, informed consent.

### *Treatment*

This was a single-arm trial with all patients receiving the same initial doses of therapy. Valspodar was supplied as a microemulsion drink solution and was administered at 5 mg/kg/dose orally every six hours for 12 doses taken at least 1 hour before or 2 hours after meals. Patients were encouraged to mix the valspodar in a chilled, nonalcoholic beverage other than grapefruit juice. Following premedication with dexamethasone, diphenhydramine, and an H<sub>2</sub> receptor antagonist, paclitaxel 70 mg/m<sup>2</sup> was administered intravenously as a 3-hour infusion beginning 4 hours after the fifth dose of valspodar. Treatment was continued every 3 weeks until disease progression or unacceptable toxicity.

### *Dose modification*

Valspodar may cause rapidly reversible cerebellar toxicity (ataxia, dysmetria) and paresthesias. A cerebellar dysfunction scale was utilized: Grade 1—Slight subjective incoordination without difficulty walking; Grade 2—Definite subjective incoordination on walking but able to walk without assistance; Grade 3—Unable to walk without assistance from another person or walker; Grade 4—Unable to walk because of incoordination, even with assistance. For Grade 3 or 4 neurotoxicity, valspodar was withheld until the neurotoxicity resolved and was then reinitiated at a reduced dose of 3.75 mg/kg/dose. If Grade 3 or 4 neurotoxicity recurred at the reduced dose level, the patient was removed from study. Paclitaxel was delayed for up to 3 weeks if the absolute neutrophil count was <1,500/mm<sup>3</sup> and/or platelet count was <100,000/mm<sup>3</sup> on the day of treatment. Paclitaxel was permanently reduced by 25 percent if the patient experienced an episode of febrile neutropenia, and absolute neutrophil count of less than 500/m<sup>3</sup> for 5 days or longer, bleeding with platelet count ≤40,000/mm<sup>3</sup>, platelet count ≤20,000/mm<sup>3</sup> with or without bleeding, Grade 3 or 4 mucositis or diarrhea, or Grade 3 neurosensory or neuromotor toxicity felt secondary to paclitaxel. Patients with Grade 4 neurosensory or neuromotor toxicity to paclitaxel were removed from study.

### *Measurement of response*

Complete response (CR) required the disappearance of all clinically detectable malignant disease for at least 4 weeks, including resolution of radiographic evidence of bony metastasis. Partial response (PR) required a greater than or equal to 50 percent decrease in the sum of the products of the 2 largest perpendicular measurements for at least 4 weeks without increase in size of any area of known malignant disease of greater than 25 percent or appearance of any new areas of malignant disease. For nonmeasurable and evaluable sites of disease, definite

improvement in excess of 50 percent as determined by 2 independent investigators was required. Stable disease (SD) required no significant change in measurable or evaluable disease for at least 4 weeks (12 weeks for bony sites). Progression of disease (PD) was the significant increase in size of lesions present at the start of therapy or after a response, or appearance of new metastatic lesions known not to be present at the start of therapy or stable objective disease associated with a deterioration in ECOG performance status of greater than or equal to one level and related to malignancy. Overall response rate was defined as the rate of CR plus PR.

Response was determined by both organ site and by total patient response. Onset of response was the time between initiation of therapy and the first onset of PR or CR. Duration of response was time from onset of response until objective evidence of progression.

### Statistical design

Early results from E1193, a study that included a treatment arm in which patients with metastatic breast cancer who had no prior anthracycline therapy crossed to paclitaxel after disease progression while on treatment with doxorubicin (12, 18) showed that 20 percent of the patients who crossed over to paclitaxel experienced an objective response. Given the "mix" of patients for E1195, a 30 percent response rate was targeted. A two-stage Phase II design was used where if at least 2 patients responded out of an initial 15, 17 additional patients would be entered. The regimen would be considered promising if at least 6 patients of 32 responded. The probability of concluding that the drug was effective was 0.93 if the true response rate was 30 percent and 0.09 if the true rate was 10 percent. Allowing for 10 percent of the patients to be ineligible, a total of 36 patients could have been entered.

Confidence intervals for response rates were estimated using methods for exact binomial confidence intervals (19). The Kaplan-Meier method was used to estimate duration of response, progression, and survival distributions (20) and confidence intervals for median survival and progression estimates were calculated using Greenwood's formula (20). Analyses of outcome (response, progression, survival) excluded ineligible patients and toxicity summaries included ineligible patients.

## RESULTS

A total of 37 patients were enrolled. Three patients were ineligible (one had received more than one prior chemotherapy for metastatic disease, 1 enrolled less than 3 weeks from discontinuation of prior hormonal therapy, one had no bi-dimensionally measurable disease) and were excluded from analyses of response, progression, and survival. All 37 patients were assessed for toxicity. Characteristics of eligible patients are found in Table 1. Eighty-two percent of the patients had visceral involvement, 38 percent nodal involvement, 29 percent skin involvement, 12 percent disease in the breast, and 35 percent had bone involvement.

**Table 1.** Patient characteristics

Characteristic	N of patients (%)
Race	
White, non-Hispanic	29 (85)
Hispanic	1 (3)
Black	2 (6)
Unknown	2 (6)
Age, median (range)	52 years (25-77 years)
Performance status	
ECOG 0	22 (65)
ECOG 1	8 (23)
ECOG 2	4 (12)
Prior doxorubicin	31 (91)
Sites of disease	
Breast	4 (12)
Nodes	13 (38)
Skin	10 (29)
Visceral	28 (82)
Bone	12 (35)

### Response analysis

The median number of cycles of treatment was 4 (range 1–24 cycles). Twenty-six patients went off treatment secondary to progressive disease, 4 secondary to toxicity, 2 secondary to withdrawal by patient, 1 following death without progression, and 1 secondary to nonprotocol treatment. One patient refused further treatment on Day 3 of protocol treatment and expired 1 month later, and is considered unevaluable for response.

Two (6 percent) patients achieved a complete response and 5 (15 percent) a partial response for an overall rate of response of 21 percent (95 percent confidence interval of 9 percent to 38 percent) (Table 2). Twelve (35 percent) patients experienced stable disease. Median duration of response was 9.7 months (95 percent confidence interval 8.0–17.2 months).

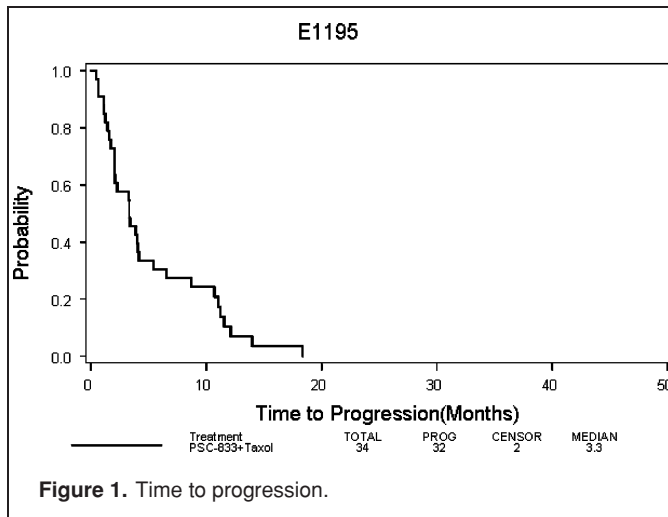
Median time to progression was 3.3 months (95 percent confidence interval 2.0–4.2 months) (see Figure 1). Median survival was 12 months (95 percent confidence interval 8.1–17.3 months) (see Figure 2), with 5 patients remaining alive at 27.8–60.3 months at the time of analysis.

### Toxicity

The toxicity experience is outlined in Table 3. Thirteen (35 percent) patients experienced Grade 3-4 leukopenia and 23 (62 percent) experienced Grade 3-4 neutropenia. Fever and neutropenia was observed in 1 (3 percent) patient, and 1

**Table 2.** Rates of Response

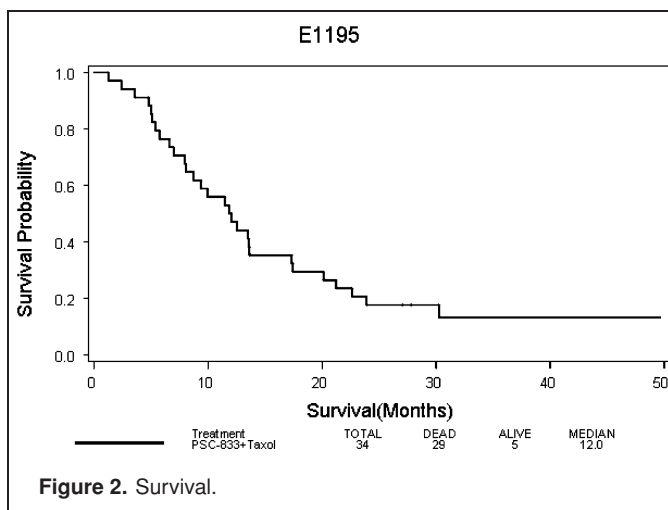
Response	N of patients n = 34
Complete response	2 (6%)
Partial response	5 (15%)
Stable disease	12 (35%)
Progressive disease	14 (41%)
Unevaluable	1 (3%)



(3 percent) patient died secondary to infection. Fourteen (38 percent) patients experienced reversible ataxia felt secondary to PSC-833. Other neurological toxicities were frequent, usually low grade, and consistent with the known single agent toxicity of paclitaxel. Nausea and vomiting, usually low grade, was observed in 16 patients (43 percent) and hepatic toxicity (usually transient hyperbilirubinemia) in 13 (35 percent). Other toxicities were those expected in patients treated with paclitaxel as a single agent.

## DISCUSSION

This Phase II trial documents that the combination of valsopodar and paclitaxel may be given safely if the total dose of the paclitaxel is limited to 70 mg/m<sup>2</sup> on an every 3-week basis. The rate of objective response of 21 percent (95 percent confidence interval of 9 percent to 38 percent) in the treatment of anthracycline resistant metastatic breast cancer is similar to the 22 percent rate of objective response observed with single agent paclitaxel following failure of doxorubicin in E1193 (18). Thus, it appears unlikely that the use of valsopodar to inhibit P-glycoprotein as a



**Table 3.** Patients with toxicities, Common Toxicity Criteria 1. (N = 37)

Toxicity	Grade 1,2	Grade 3	Grade 4	Grade 5
Leukopenia	14	9	4	
Granulocytopenia	1	8	15	
Thrombopenia	12		1	
Anemia	26			
Hemorrhage	1			
Fever (no infection)	13			
Infection	10	2		1
Fever with neutropenia		1		
Neuro-sensory	23	3		
Neuro-motor	13	4		
Neuro-psych	9		1	
Neuro-clinical	14			
Ataxia	12	2		
Nausea/vomiting	15	1		
Diarrhea	9	1		
Stomatitis	13	1		
Liver	11	1	1	
Alopecia	22			
Elevated glucose	8	5	1	
Arthralgias	6	1		
Myalgias	5	2		
Fatigue	18	1		
Pain	15	1		

mechanism of resistance results in a meaningful increase in anti-tumor efficacy in women with anthracycline resistant metastatic breast cancer.

Paclitaxel exerts its cytotoxicity by binding to  $\beta$ -tubulin thereby stabilizing microtubules and disrupting mitosis along with other functions dependent upon microtubules. Multiple mechanisms of intrinsic and acquired resistance to paclitaxel have been identified including *MDR1/P*-glycoprotein expression, variation in the isotype expression of  $\beta$ -tubulin, mutations in  $\beta$ -tubulin, and potentially via a number of other alterations in apoptosis regulatory genes (21, 22). The relative contribution to intrinsic and acquired paclitaxel resistance is not known.

Many studies have reported a variable incidence of *MDR1/P*-glycoprotein expression in breast cancers (23, 24). This incidence appears to increase after treatment with MDR related agents such as anthracyclines and taxanes. Approximately 30–40 percent of breast cancers express P-gp prior to therapy, and this increases to 40–50 percent in patients who have been treated with MDR-related chemotherapies (23). Serial sampling of patients' tumors before and after neoadjuvant chemotherapy which included MDR-related drugs demonstrated that 43 percent of breast cancer were positive for P-glycoprotein by immunohistochemistry before therapy and 64 percent were positive after therapy (24). Thus, 37 percent of cases in the seven reviewed studies changed from negative to positive for P-glycoprotein expression after the neoadjuvant therapy (23). Expression of *MDR1/P*-glycoprotein was associated with a three-fold increase in the likelihood of failure of response to chemotherapy in a meta-analysis of 31 studies in breast cancer patients (23).

In patients with metastatic breast cancer previously treated with an anthracycline, the response rate of 21 percent this study of valsopodar in combination with paclitaxel (70 mg/m<sup>2</sup> as a

3-hour infusion) is similar to that observed in a similar population of patients treated with single agent paclitaxel (175 mg/m<sup>2</sup> as a 3-hour infusion) (18). Pharmacokinetic studies document that valspodar treatment is associated with prolongation of paclitaxel pharmacokinetics when compared with paclitaxel alone (8, 9). This likely explains the similar response rates with differing doses of paclitaxel. A Phase II study in patients with refractory epithelial ovarian carcinoma of valspodar and paclitaxel at the same dose and schedule of valspodar and paclitaxel used in the current study also demonstrated only limited activity (25).

The toxicity experience observed in this trial is as predicted from the single agent experience and from the Phase I trials. Specifically, rapidly reversible ataxia secondary to valspodar was observed, and suggests that dose escalation of valspodar is unlikely to be tolerated. Rapidly reversible hyperbilirubinemia was also observed. The neurological toxicity of paclitaxel did not appear to be increased by combination with valspodar.

The reason for the failure of valspodar to increase the objective rate of response is not known, but may relate to the multiplicity of mechanisms of drug resistance that may occur or to the reduction in the dose of paclitaxel required to safely administer the combination of paclitaxel and valspodar. Based upon the results of this study, we believe that further study of valspodar as a method of reversing single-agent paclitaxel drug resistance is not warranted in a non selected population of breast cancer patients. However, this approach may be viewed as a targeted therapy, and it may be possible to identify clinical benefit via studies in patients whose tumors are shown to express P-glycoprotein.

## REFERENCES

- Goldstein, L.J.; Galski, H.; Fojo, A.; Willingham, M.; Lai, S. L.; Gazdar, A.; et al. Expression of a multidrug resistance gene in human cancers. *J. Natl. Cancer Inst.* **1989**, *81*, 116–124.
- Goldstein, L.J.; Pastan, I.; Gottesman, M.M.; Multidrug resistance in human cancer. *Crit Rev Oncol Hematol.* **1992**, *12*, 243–253.
- Sikic, B. Modulation of multidrug resistance: at the threshold. *J Clin Oncol.* **1993**, *11*, 1629–1635.
- Sikic, B.I.; Fisher, G.A.; Lum, B.L.; Halsey, J.; Beketic-Oreskovic, L.; Chen, G. Modulation and prevention of multidrug resistance by inhibitors of P-glycoprotein. *Cancer Chemother Pharmacol.* **1997**, *40 (Suppl)*, S13–S19.
- Jachez, B.; Nordmann, R.; Loor, F. Restoration of taxol sensitivity of multidrug-resistant cells by the cyclosporine SDZ PSC 833 and the cyclopeptide SDZ 280-446. *Journal of the National Cancer Institute.* **1993**, *85*, 478–446.
- Boesch, D.; Gaveriaux, C.; Jachez, B.; Pourtier-Manzanedo, A.; Bollinger, P.; Loor, F. In vivo circumvention of P-glycoprotein-mediated multidrug resistance of tumor cells with SDZ PSC 833. *Cancer Res.* **1991**, *51*, 4226–4233.
- Twentymann, P.R.; Bleehen, N.M. Resistance modification by PSC-833, a novel non-immunosuppressive cyclosporin [corrected][published erratum appears in *European Journal of Cancer* 1992;28:616]. *European Journal of Cancer.* **1992**, *27*, 1639–1642.
- Fracasso, P.M.; Fisher, G.A.; Wiehl, J.G.; Collins, H.; Hausdorff, J.; Williams, K.M.; Halsey, J.; Pearce, T.E.; Sikic, B.I. Phase I trial of paclitaxel (Taxol) and SDZ PSC 833 in patients with solid tumors. *Proc Am Soc Clin Oncol.* **1995**, *14*.
- Collins, H.L.; Fisher, G.A.; Hausdorff, J.; Lum, B.L.; Pearce, T.; Halsey, J.; Sikic, B.I. Phase I trial of paclitaxel in combination with SDZ PSC 833, a multidrug resistance modulator. *Proc Am Soc Clin Oncol.* **1995**, *14*.
- Schiller, J.H.; Storer, B.; Tutsch, K.; Arzooonian, R.; Alberti, D.; Feierabend, C.; Spriggs, D. Phase I trial of 3-hour infusion of paclitaxel with or without granulocyte colony-stimulating factor in patients with advanced cancer. *J Clin Oncol.* **1994**, *12*, 241–248.
- Seidman, A.; Tiersten, A.; Hudis, C.; Gollub, M.; Barrett, S.; Yao, T.; Lepore, J.; Gilewski, T.; Currie, V.; Crown, J. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol.* **1995**, *13*, 2575–2581.
- Sledge Jr, G.W.; Neuberg, D.; Ingle, J.; Martino, S. and Wood, W. Phase III trial of doxorubicin (A) vs. paclitaxel (T) vs. doxorubicin + paclitaxel (A + T) as first-line therapy for metastatic breast cancer (MBC): an intergroup trial. *Proc Am Soc Clin Oncol.* **1997**, *16*, 1a.
- Holmes, F.A.; Valero, V.; Buzdar, A.U.; Booser, D.J.; Winn, R.; Tolcher, A.; et al. Final results: randomized phase III trial of paclitaxel by 3-hr versus 96-hr infusion in patients (pt) with met breast cancer (mbc). The long & short of it. *Proc Am Soc Clin Oncol.* **1998**, *17*, 110a.
- Smith, R.E.; Brown, A.M.; Mamounas, E.P.; Anderson, S.J.; Lembersky, B.C.; Atkins, J.H.; et al. Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast Cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B- 26. *J Clin Oncol.* **1999**, *17*, 3403–3411.
- Perez, E.A.; Vogel, C.L.; Irwin, D.H.; Kirshner, J.J.; Patel, R. Multi-center phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol.* **2001**, *19*, 4216–4223.
- Reichman, B.S.; Seidman, A.D.; Crown, J.P.; Heelan, R.; Hakes, T.B.; Lebowitz, D.E.; Gilewski, T.A.; Surbone, A.; Currie, V.; Hudis, C.A.; et al. Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol.* **1993**, *11*, 1943–1951.
- Holmes, F.A.; Valero, V.; Walters, R.S.; Theriault, R.L.; Booser, D.J.; Giuseppe, F.; Buzdar, A.U.; Frye, D.; Gibbs, H.R.; Hoortobagyi, G.N. The M.D. Anderson Cancer Center experience with taxol in metastatic breast cancer. *Monogr Natl Cancer Inst.* **1993**, *15*, 161–169.
- Sledge, G.W.; Neuberg, D.; Bernardo, P.; Ingle, J.N.; Martino, S.; Rowinsky, E.K.; Wood, W.C. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol.* **2003**, *21*, 588–592.
- Cox, D.R.; Snell, E.J. *Analysis of Binary Data*, Second Edition. London, **1989**, 26–105.
- Kaplan, E.L.; Meier, P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association.* **1958**, *53*, 457–481.
- Sangrajrang, S.; Fellous, A. Taxol resistance. *Chemotherapy.* **2000**, *46*, 327–334.
- Yusuf, R.Z.; Duan, Z.; Lamendola, D.E.; Penson, R.T.; Seiden, M.V. Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation. *Curr Cancer Drug Targets.* **2003**, *3*, 1–19.
- Trock, B.J.; Leonessa, F., and Clarke, R. Multidrug resistance in breast cancer: a meta-analysis of MDR1/gp170 expression and its possible functional significance. *J Natl Cancer Inst.* **1997**, *89*, 917–931.
- Leonessa, F., and Clarke, R. ATP binding cassette transporters and drug resistance in breast cancer. *Endocr Relat Cancer.* **2003**, *10*, 43–73.
- Fracasso, P.M.; Brady, M.F.; Moore, D.H.; Walker, J.L.; Rose, P.G.; Letvak, L.; Grogan, T.M.; McGuire, W.P. Phase II study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma: a gynecologic oncology group study. *J Clin Oncol.* **2001**, *19*, 2975–2982.