Published in final edited form as:

Clin Breast Cancer. 2008 December ; 8(6): 511–515. doi:10.3816/CBC.2008.n.062.

A Phase II Study of Imatinib Mesylate and Capecitabine in Metastatic Breast Cancer: Southwest Oncology Group Study 0338

Helen K. Chew, MD¹, William E. Barlow, PhD², Kathy Albain, MD³, Danika Lew, PhD², Allen Gown, MD⁴, Daniel F. Hayes, MD⁵, Julie Gralow, MD⁶, Gabriel N. Hortobagyi, MD⁷, and Robert Livingston, MD⁸

¹Department of Internal Medicine, Division of Hematology/Oncology, University of California Davis, Sacramento, CA

²Southwest Oncology Group Statistical Center, Seattle, WA

³Loyola University Medical Center, Maywood, IL

⁴PhenoPath Laboratories, Seattle, WA

⁵University of Michigan, Ann Arbor, MI

⁶University of Washington, Seattle, WA

⁷University of Texas M. D. Anderson Cancer Center, Houston, TX

⁸Arizona Cancer Center, Tucson, AZ

Abstract

Purpose—Imatinib mesylate is a potent inhibitor of the Bcr-Abl, c-kit, and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. Based on variable expression of c-kit and PDGFR in breast cancer, and on in vitro data supporting synergy between imatinib and capecitabine, the Southwest Oncology Group conducted a phase II trial of the combination in metastatic breast cancer.

Patients and Methods—Eligible patients had progressive, measurable metastatic breast cancer and received up to two prior chemotherapy regimens for metastatic disease. Prior 5-fluorouracil or capecitabine for metastatic disease was not allowed. Patients were accrued on a 2-stage design and received imatinib mesylate 400 mg by mouth daily and capecitabine at 1000 mg/m² by mouth twice daily for 14 days of a 21-day cycle. The primary endpoint was the confirmed response rate (RR). Tumors were evaluated for c-kit, PDGFR β , and hormone receptor expression.

Results—Nineteen fully evaluable patients were enrolled with a confirmed RR of 11% (95% CI 1–33%). Eleven percent had unconfirmed partial responses and 42% had stable disease. The trial did not accrue to the second stage. The estimated 6-month progression-free survival was 16% (95% CI 0–32%) and the median overall survival was 14 months (95% CI 7–15). The combination was well tolerated. Of 8 available tumor samples, 2 stained for c-kit and all had stromal staining for PDGFR β .

Address correspondence to: Helen K. Chew, M.D., Division of Hematology/Oncology, 4501 X Street, Suite 3016, Sacramento, CA 95817, Tel: (916) 734-3771, FAX: (916) 734-7946, helen.chew@ucdmc.ucdavis.edu.

Address reprint requests to: Southwest Oncology Group Operations Office, 14980 Omicron Drive, San Antonio, TX 78245

Presented in abstract format at the 42nd Annual Meeting of the American Society of Clinical Oncology, Atlanta, GA, June 2–6, 2006 (abstract 10529). This article is an update and the first complete reporting of SWOG study 0338.

Conclusion—In unselected patients, the combination of imatinib mesylate and capecitabine was well tolerated but did not result in improved response rates compared to that reported with capecitabine alone.

Keywords

breast cancer; imatinib mesylate; capecitabine

INTRODUCTION

Recent improvements in outcomes in metastatic breast cancer have been reported with the combination of cytotoxic chemotherapy and novel agents. These agents, which include monoclonal antibodies and tyrosine kinase inhibitors, target clinically relevant molecular pathways in breast cancer [1–3]. Imatinib mesylate has potential activity in breast cancer. It is a selective and potent tyrosine kinase inhibitor of Bcr-Abl, c-kit, and platelet-derived growth factor receptor (PDGFR). Its specificity in inhibiting Bcr-Abl and c-kit led to unprecedented responses in chronic myelogenous leukemia and gastrointestinal stromal tumors, respectively [4, 5]. While c-kit and PDGFR are variably expressed in breast cancer, in vitro studies suggested a decrease in tumor cell growth with inhibition of these tyrosine kinases [6–8] and specific growth inhibition of breast cancer cell lines by imatinib mesylate [9]. Furthermore, in vitro studies supported improvement in drug delivery through PDGFR inhibition and subsequent decrease in tumor interstitial pressure [10]. Enhanced drug uptake through PDGFR inhibition represented a novel target with potential benefit in breast cancer.

Capecitabine is an active oral agent in metastatic breast cancer, both as monotherapy and in combination with docetaxel [11, 12]. Capecitabine is an oral 5-fluorouracil (5-FU) pro-drug, which is activated by thymidine phosphorylase, an enzyme expressed in greater concentrations in tumor tissue compared to nonmalignant cells. An animal model of colorectal cancer demonstrated a decrease in tumor volume with the addition of imatinib mesylate to 5-FU compared to either agent alone [13].

The potential benefit of imatinib mesylate inhibition of both c-kit and PDGFR tyrosine kinases in breast cancer and the hypothesized synergy with capecitabine provided the rationale for the Southwest Oncology Group study S0038. This phase II study also explored the expression of c-kit and PDGFR in tumor tissue to correlate their relationship to hormone receptor status and clinical outcomes.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients were 18 years of age or older and had histologically confirmed measurable metastatic breast cancer. Patients must have progressed on at least one but no more than two prior regimens for metastatic disease. Prior capecitabine or 5-fluorouracil for metastatic disease was not allowed. Patients with tumors that overexpressed HER-2/neu should have received trastuzumab in the adjuvant or metastatic setting, unless there was a contraindication. Patients could have received any number of prior endocrine therapies. All patients had to have a Zubrod performance status 0–2 and adequate hematologic, renal and hepatic function indicated by an absolute neutrophil count (ANC) > 1500/ μ l, platelets > 100,000, creatinine clearance > 60 ml/min, bilirubin within normal institutional limits and SGOT and SGPT < 2.5 times the normal institutional limit. Patients were excluded if they had brain or CNS metastases, were pregnant, were HIV-positive, or had another invasive cancer within 5 years or any prior cancer not in remission.

All patients were informed of the investigational nature of the study and gave written informed consent in accordance with institutional and federal guidelines.

Study Design and Treatment

This phase II study was a two-stage design, and required patients with measurable disease in the first stage. If response criteria were met to proceed to the second stage, patients with both measurable and non-measurable disease were eligible. The two-stage design was based on the Green and Dalhberg modification of the Simon design [14, 15]. The overall accrual goal was 45 patients, with 25 accrued in the first stage and 20 in the second stage. If 5 or more confirmed responses were observed in the first stage, then the trial would continue to the second stage. As designed, the trial had 91% power ($\alpha=0.05$) to detect a 40% confirmed response rate compared to a historical expected rate of 20%.

Protocol treatment consisted of imatinib mesylate 400 mg by mouth daily and capecitabine at 1000 mg/m² by mouth twice daily on days 1–14 of a 21-day cycle. If imatinib mesylate 400 mg was well tolerated, the dose was increased to 600 mg daily in subsequent cycles. Treatment day parameters included an ANC 1500/ μ l and platelets 100,000. Dose reductions of both agents were required for grade 4 hematologic toxicities and grade 3 non-hematologic toxicities. Patients were removed from protocol for any grade 4 non-hematologic toxicities. The use of G-CSF was not permitted on study. Recombinant erythropoietin was permitted at the discretion of the treating physician.

End Points and Definitions

The objectives of this phase II study were to evaluate the confirmed response rate, to estimate the 6-month progression-free survival (PFS), and to evaluate the toxicity of this drug combination and schedule. Response rates (complete and partial response) were confirmed at least 4 weeks apart. PFS was defined as the time from registration to the date of the first observation of progressive disease or death due to any cause. Patients were evaluated for treatment-related toxicity at a minimum of every 21 days per the National Cancer Institute Common Toxicity Criteria version 3.0. The worst grade of toxicity per patient was recorded.

Correlative Studies

Immunohistochemical studies were performed using deparaffinized tissue sections from the submitted paraffin blocks. Four micron cut sections were deparaffinized in xylene and rehydrated with graded alcohols.

Epitope retrieval was performed on the deparaffinized tissue sections prior to application of primary antibodies. Table 1 contains details of the primary antibodies, to ER, PR, c-kit and PDGFR-beta, and their respective epitope retrieval methods. Slides were incubated at room temperature using a Dako autostainer. Primary antibody incubation was 40 minutes followed by Envision+ labeled polymer for 30 minutes and DAB+ substrate for 5 minutes (Dako, Carpinteria, CA). Sections were counterstained with hematoxylin. Results of all antibodies were scored in a semiquantitative fashion (0, 1+, 2+, 3+) based on the percentage of positive cells.

Statistical Analysis

The primary outcome was confirmed response rate. If the trial continued to the second stage, the method of Jung and Kim would be used to calculate an unbiased estimate of the response rate and associated confidence interval [16]. Since the trial stopped after the first stage, standard binomial methods were used for response and toxicity rates and Kaplan-Meier survival estimation was used for progression-free survival.

RESULTS

Patients

A total of 27 female patients was accrued from 16 institutions between June 2004 and April 2005. Six patients were ineligible for the following reasons: 2 patients did not have measurable disease, 1 did not have histologically confirmed disease, 1 did not have prior chemotherapy, 1 had laboratory values out of range and 1 did not have disease assessment within the specified time prior to registration. Of the 21 eligible patients, 2 never started treatment and were not assessable for toxicity or response. The characteristics of the 19 fully evaluable patients are shown in Table 2. Median age was 59.5 years (range 36.1–78.3), 74% were Caucasian and 11% were Black. Fifty-three percent of patients had a Zubrod Performance Status of 0. Most patients (84%) had received only 1 prior chemotherapy regimen for metastatic disease, and 68% had hormone-receptor positive breast cancer. Patients received a median of 2 cycles of imatinib mesylate and capecitabine.

Efficacy

Accrual was temporarily suspended after the first 27 patients were enrolled. Determination of eligibility reduced the number evaluable for response to 19. To continue to the second stage, 4 confirmed responses were required. At the time the trial was suspended, only two confirmed responses had been observed and one more unconfirmed response had been noted. After nine months of temporary suspension, the trial was closed since no additional confirmed responses were observed.

Table 3 summarizes the outcomes of the patients treated with this combination. The confirmed overall response rate was 11% (95% CI 1–33%). There were 2 unconfirmed partial responses (11%) and 42% of the patients had stable disease. The estimated 6-month progression-free survival (PFS) was 16% (95% CI 0–32%) as shown in Figure 1 and the median overall survival (OS) was 14 months (95% CI 7–15) as shown in Figure 2.

Toxicity

All 19 patients treated on protocol were assessable for toxicity. No Grade 4 toxicities or treatment-related deaths were reported with this combination. Table 4 summarizes the Grade 2 and 3 attributable toxicities. Only 7 patients (37%) reported Grade 3 toxicities. The most common Grade 3 toxicities were fatigue, diarrhea, and hand-foot syndrome, each reported in 10%. Grade 2 toxicities included fatigue (37%), nausea (26%), anemia, and extremity edema (each 16%).

c-kit and PDGFR staining

Tumor samples from 8 patients were available for correlative studies and the results are shown in Table 5. Of the samples tested, 6 of 8 were hormone receptor positive by immunohistochemistry, 2 of 8 stained for c-kit, and all samples stained positive for PDGFR β in stromal cells around the tumors. None of the tumors expressed PDGFR β . Among the 8 patients with available tumor samples, 1 patient with a hormone receptor positive breast cancer had a partial response. This tumor did not stain for c-kit or PDGFR β .

DISCUSSION

This phase II trial is the first to report on the combination of imatinib mesylate and capecitabine. The primary endpoint of confirmed response rate was 11% in patients with metastatic breast cancer and precluded accrual to the second-stage of this trial. This response was no better than the 20% response rate of single agent capecitabine in previously treated breast cancer patients [11]. A phase II trial of single agent imatinib mesylate in heavily-

pretreated metastatic breast cancer resulted in no responses in 16 patients and a median duration of therapy of 28 days [17]. Similar disappointing results were reported in a separate phase II trial with no objective responses in 12 patients with metastatic breast cancer [18]. Single agent activity among tyrosine kinase inhibitors has been modest in the majority of solid tumors, and it was anticipated that the combination of imatinib mesylate and capecitabine, based on preclinical studies suggesting synergy, would lead to encouraging results. However, this study does not support the use of the combination regimen over single agent capecitabine alone.

The combination was well tolerated, with no grade 4 toxicities, including hematologic toxicities in the absence of growth factors. Anticipated grade 3 toxicities, including diarrhea and hand foot syndrome, occurred in 10% of this patient population. This finding is likely due to the clinically useful doses of capecitabine and imatinib mesylate chosen for the combination, compared to the full dose of capecitabine in combination trials and the high dose of imatinib mesylate in the single agent phase II study [12, 17].

Possible explanations for the low response rate in this unselected breast cancer population are the variable reports of c-kit staining in breast cancer and the undefined role of c-kit in breast tumorigenesis or as a therapeutic target for imatinib. Reports of c-kit staining range from 2.6% to 82% [19–26]. These widely disparate results reflect differing methodologies and interpretations of positive immunohistochemistry staining. Several studies agreed that normal breast epithelium uniformly stained positive for c-kit [19, 20, 22], and the lower percentage of c-kit staining in adjacent tumor implied that loss of c-kit expression might be involved in malignant transformation. Furthermore, the importance of c-kit activating mutations in breast carcinoma is unknown. In a series of over 1600 breast cancers in a tissue microarray, no activating mutations were detected in 10 of 43 c-kit positive tumors [19].

There are few published studies investigating expression of PDGFR β by immunohistochemistry in breast cancer, with conflicting and somewhat confusing findings. In one earlier study, PDGFR β expression was found in a subset of breast cancer specimens [27] along with the tumor stromal cells, but in another study, only stromal cell positivity was noted [28]. Differences may relate to the disparate nature of tissue fixation in these two studies; the immunostaining pattern seen in the present study resembles that of Bhardwaj and colleagues, with immunostaining only of the stromal cell population. While this does suggest the potential of paracrine stimulation of adjacent stromal tissue by the breast cancer epithelial cells, PDGFR β immunostaining staining in our study did not correlate with tumor response to imatinib mesylate and capecitabine.

As only 8 tumor samples were available of the 19 patients reported, the results of c-kit and PDGFR β staining must be interpreted with caution. Only 2 of 8 samples stained positive for c-kit, and the small sample size prevents any meaningful correlation with hormone receptor status. All 8 samples stained for PDGFR β in the stroma, with no staining of the epithelial breast cancer cells.

The clinical importance of c-kit and PDGFR β in the biology of breast cancer remains undefined. The combination of imatinib mesylate and capecitabine, while well tolerated, should not be used in metastatic breast cancer. Further studies that delineate the role of c-kit and PDGFR β in breast cancer tumor growth are needed.

Acknowledgments

Supported in part by the following PHS Cooperative Agreement grants from the National Cancer Institute: CA32102, CA38926, CA46441, CA04919, CA35281, CA86780, CA45560, CA20319, CA63850, CA45807, CA67575, CA45808, CA42777, CA63844

REFERENCES

1. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001; 344(11):783–792. [PubMed: 11248153]
2. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007; 357(26):2666–2676. [PubMed: 18160686]
3. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, Jagiello-Gruszfeld A, Crown J, Chan A, Kaufman B, Skarlos D, Campone M, Davidson N, Berger M, Oliva C, Rubin SD, Stein S, Cameron D. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006; 355(26):2733–2743. [PubMed: 17192538]
4. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, Capdeville R, Talpaz M. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med*. 2001; 344(14):1038–1042. [PubMed: 11287973]
5. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002; 347(7):472–480. [PubMed: 12181401]
6. DiPaola RS, Kuczyński WI, Onodera K, Ratajczak MZ, Hijiya N, Moore J, Gewirtz AM. Evidence for a functional kit receptor in melanoma, breast, and lung carcinoma cells. *Cancer Gene Ther*. 1997; 4(3):176–182. [PubMed: 9171936]
7. Hines SJ, Litz JS, Krystal GW. Coexpression of c-kit and stem cell factor in breast cancer results in enhanced sensitivity to members of the EGF family of growth factors. *Breast Cancer Res Treat*. 1999; 58(1):1–10. [PubMed: 10634512]
8. Bagheri-Yarmand R, Kourbali Y, Morere JF, Jozefonvicz J, Crepin M. Inhibition of MCF-7ras tumor growth by carboxymethyl benzylamide dextran: blockage of the paracrine effect and receptor binding of transforming growth factor beta1 and platelet-derived growth factor-BB. *Cell Growth Differ*. 1998; 9(6):497–504. [PubMed: 9663468]
9. Roussidis AE, Mitropoulou TN, Theocharis AD, Kiamouris C, Papadopoulos S, Kletsas D, Karamanos NK. STI571 as a potent inhibitor of growth and invasiveness of human epithelial breast cancer cells. *Anticancer Res*. 2004; 24(3a):1445–1447. [PubMed: 15274308]
10. Pietras K, Ostman A, Sjoquist M, Buchdunger E, Reed RK, Heldin CH, Rubin K. Inhibition of platelet-derived growth factor receptors reduces interstitial hypertension and increases transcapillary transport in tumors. *Cancer Res*. 2001; 61(7):2929–2934. [PubMed: 11306470]
11. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, Osterwalder B, Burger HU, Brown CS, Griffin T. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol*. 1999; 17(2):485–493. [PubMed: 10080589]
12. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, Leonard R. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. 2002; 20(12):2812–2823. [PubMed: 12065558]
13. Pietras K, Rubin K, Sjoblom T, Buchdunger E, Sjoquist M, Heldin CH, Ostman A. Inhibition of PDGF Receptor Signaling in Tumor Stroma Enhances Antitumor Effect of Chemotherapy. *Cancer Res*. 2002; 62(19):5476–5484. [PubMed: 12359756]
14. Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. *Stat Med*. 1992; 11(7):853–862. [PubMed: 1604065]
15. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989; 10(1):1–10. [PubMed: 2702835]
16. Jung SH, Kim KM. On the estimation of the binomial probability in multistage clinical trials. *Stat Med*. 2004; 23(6):881–896. [PubMed: 15027078]

17. Modi S, Seidman AD, Dickler M, Moasser M, D'Andrea G, Moynahan ME, Menell J, Panageas KS, Tan LK, Norton L, Hudis CA. A phase II trial of imatinib mesylate monotherapy in patients with metastatic breast cancer. *Breast Cancer Res Treat.* 2005; 90(2):157–163. [PubMed: 15803362]
18. Chedid S, Booser D, Krishnamurthy S, Reuben JM, Saklaruk J, Green M, Arun B, Valero V, Royce M, Sison M, Frye D, Hortobagyi GN, Murgo A, Cristofanilli M. Phase II study of imatinib mesylate for patients with metastatic breast cancer with tumors that overexpress PDGFRbeta and/or c-kit. *Proc Am Assoc for Cancer Research.* 2004; 45 (abstract 2219).
19. Simon R, Panussis S, Maurer R, Spichtin H, Glatz K, Tapia C, Mirlacher M, Ruffle A, Torhorst J, Sauter G. KIT (CD117)-positive breast cancers are infrequent and lack KIT gene mutations. *Clin Cancer Res.* 2004; 10(1 Pt 1):178–183. [PubMed: 14734467]
20. Ulivi P, Zoli W, Medri L, Amadori D, Saragoni L, Barbanti F, Calistri D, Silvestrini R. c-kit and SCF expression in normal and tumor breast tissue. *Breast Cancer Res Treat.* 2004; 83(1):33–42. [PubMed: 14997053]
21. Natali PG, Nicotra MR, Sures I, Mottolese M, Botti C, Ullrich A. Breast cancer is associated with loss of the c-kit oncogene product. *Int J Cancer.* 1992; 52(5):713–717. [PubMed: 1385336]
22. Yared MA, Middleton LP, Meric F, Cristofanilli M, Sahin AA. Expression of c-kit proto-oncogene product in breast tissue. *Breast J.* 2004; 10(4):323–327. [PubMed: 15239791]
23. Tsuda H, Morita D, Kimura M, Shinto E, Ohtsuka Y, Matsubara O, Inazawa J, Tamaki K, Mochizuki H, Tamai S, Hiraide H. Correlation of KIT and EGFR overexpression with invasive ductal breast carcinoma of the solid-tubular subtype, nuclear grade 3, and mesenchymal or myoepithelial differentiation. *Cancer Sci.* 2005; 96(1):48–53. [PubMed: 15649255]
24. Diallo R, Ting E, Gluz O, Herr A, Schutt G, Geddert H, Mohrmann S, Gabbert HE, Nitz U, Poremba C. C-kit expression in high-risk breast cancer subgroup treated with high-dose or conventional dose-dense chemotherapy. *Verh Dtsch Ges Pathol.* 2006; 90:177–185. [PubMed: 17867595]
25. Tsutsui S, Yasuda K, Suzuki K, Takeuchi H, Nishizaki T, Higashi H, Era S. A loss of c-kit expression is associated with an advanced stage and poor prognosis in breast cancer. *Br J Cancer.* 2006; 94(12):1874–1878. [PubMed: 16721362]
26. Palmu S, Soderstrom KO, Quazi K, Isola J, Salminen E. Expression of C-KIT and HER-2 tyrosine kinase receptors in poor-prognosis breast cancer. *Anticancer Res.* 2002; 22(1A):411–414. [PubMed: 12017324]
27. Coltrera MD, Wang J, Porter PL, Gown AM. Expression of platelet-derived growth factor B-chain and the platelet-derived growth factor receptor beta subunit in human breast tissue and breast carcinoma. *Cancer Res.* 1995; 55(12):2703–2708. [PubMed: 7780988]
28. Bhardwaj B, Klassen J, Cossette N, Sterns E, Tuck A, Deeley R, Sengupta S, Elliott B. Localization of platelet-derived growth factor beta receptor expression in the periepithelial stroma of human breast carcinoma. *Clin Cancer Res.* 1996; 2(4):773–782. [PubMed: 9816230]

Figure 1.
Kaplan-Meier estimation of progression-free survival.

Figure 2.
Kaplan-Meier estimation of overall survival

Table 1

Immunohistochemistry

<i>Primary Antibody to:</i>	<i>Clone Designation</i>	<i>Vendor</i>	<i>Working Dilution</i>	<i>Epitope Retrieval method</i>
ER	Clone ID5	DAKO M7047	1:200	Citrate buffer pH6.0
PR	Clone PR636	DAKO M3569	1:500	Citrate buffer pH6.0
c-kit	Rabbit polyclonal	DAKO A4502	1:400	EDTA buffer pH8.0
PDGFR-beta	Rabbit mab, Clone Y92	Epitomics 1469-1	1:500	Tris/EDTA buffer pH9.0

Table 2

Patient Characteristics

Characteristic	N=19
Age, years	
Median	59.5
Range	36.1–78.3
Zubrod Performance Status	
0	10 (53%)
1	8 (42%)
2	1 (5%)
Race/Ethnicity	
White	14 (74%)
Black	2 (11%)
Pacific Islander	2 (11%)
Native American	1 (5%)
Prior Chemotherapy for Metastatic Disease	
1 regimen	16 (84%)
2 regimens	3 (16%)
Tumor ER and/or PgR positive	13 (68%)

Table 3

Patient Response

Response	Number N=19	%
Overall response	2	11 (95% CI 1–33)
Complete Response	1	5
Partial Response	1	5
Unconfirmed Partial Response	2	11
Stable Disease	8	42
Progressive Disease	5	26
Assessment Inadequate	2	11

Table 4

Major Attributable Grade 2 and 3 Toxicities (N=19)

Adverse Event	Toxicity Grade (worse per patient)	
	Grade 2 N (%)	Grade 3 N (%)
Neutrophils	2 (10)	1 (5)
Hemoglobin	3 (16)	0
Fatigue	7 (37)	2 (10)
Diarrhea	1 (5)	2 (10)
GI pain	1 (5)	1 (5)
Nausea	5 (26)	0
Hand-foot syndrome	2 (10)	2 (10)
Edema, limb	3 (16)	0
Sensory Neuropathy	0	1 (5)
Motor Neuropathy	0	1 (5)
Rash	0	1 (5)
Mucositis	0	1(5)

\$watermark-text

\$watermark-text

\$watermark-text

Table 5

Correlative Studies

Sample	ER	PgR	c-kit	PDGFR β *	ORR
1	3+	3+	Negative	Positive	Not assessable
2	3+	2+	Negative	Positive	Partial response
3	2+	Negative	Negative	Positive	Stable disease
4	3+	Negative	Positive	Positive	Not assessable
5	Negative	Negative	Negative	Positive	Stable disease
6	3+	2+	Negative	Positive	Not assessable
7	3+	2+	Negative	Positive	Stable disease
8	Negative	Negative	Positive	Positive	Stable disease

* Stromal staining