A Pilot Study of Adjuvant Doxorubicin and Cyclophosphamide Followed by Paclitaxel and Sorafenib in Women With Node-Positive or High-Risk Early-Stage Breast Cancer

David R. Spigel, MD, John D. Hainsworth, MD, Howard A. Burris, III, MD, David C. Molthrop, MD, Nancy Peacock, MD, Michael Kommor, MD, Elizabeth R. Vazquez, BA, CCRP, F. Anthony Greco, MD, and Denise A. Yardley, MD

Dr. Spigel is Director of Lung Cancer Research, Dr. Hainsworth is Chief Scientific Officer, and Dr. Burris is Chief Medical Officer and Director of Drug Development at Sarah Cannon Research Institute in Nashville, Tennessee. Dr. Molthrop is a physician in Medical Oncology at Florida Hospital Cancer Institute in Orlando, Florida. Dr. Peacock is a physician in Medical Oncology at Tennessee Oncology, PLLC in Nashville, Tennessee. Dr. Kommor is a physician in Medical Oncology at Consultants in Blood Disorders and Cancer in Louisville, Kentucky. Ms. Vazquez is a Manager in Clinical Research Operations, Dr. Greco is Director of the Sarah Cannon Cancer Center, and Dr. Yardley is Senior Investigator in Breast Cancer Research at the Sarah Cannon Research Institute in Nashville, Tennessee.

Address correspondence to:
David R. Spigel, MD
Sarah Cannon Research Institute
250 25th Avenue North, Suite 110
Nashville, TN 37203
Phone: (615) 329-7272
Fax: (615) 340-1535
E-mail: dspigel@tnonc.com

Keywords
Adjuvant therapy, doxorubicin, cyclophosphamide, paclitaxel, sorafenib, phase II, breast cancer

Abstract: Purpose: To examine the safety of sorafenib combined with standard adjuvant treatment in patients with node-positive or otherwise high-risk breast cancer. Patients and Methods: Eligibility: mastectomy/breast-conserving surgery; axillary node assessment for stage I/II/IIIA/IIIC (T1–3, N3a only) breast cancer; node-positive/high-risk node-negative (tumor size >2 cm; hormone-receptor negative; grade 2/3; or age <35 years); Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–1; and adequate organ function. Treatment: doxorubicin (60 mg/m^2 intravenous) and cyclophosphamide (600 mg/m^2 intravenous; AC) on day 1, every 3 weeks (x 4 cycles), followed by paclitaxel 175 mg/m^2 intravenous on day 1, (every 3 weeks x 4 cycles) or 80 mg/m^2 intravenous (every week/x 12 cycles), combined with sorafenib (400 mg oral twice a week; TS) for 12 months or less. Results: Forty-five patients were enrolled from 5/07–1/08. Baseline characteristics included: median age of 54 years (range, 35–74 years); 93% of patients with ECOG-PS 0; 84% node-positive; 33% hormone-receptor negative. All patients completed AC treatment and were eligible to receive TS; of these, 8 (13%) patients came off study due to physician/patient decision; 21 (47%) patients came off study due to toxicity; 2 (4%) patients completed TS but did not proceed with maintenance sorafenib; and 14 (31%) patients completed TS and entered the maintenance phase of sorafenib treatment. Sorafenib was taken for 6.1 weeks during the paclitaxel phase and 15 weeks during maintenance. Severe toxicities during sorafenib therapy were limited, including neutropenia, anorexia, arthralgia, diarrhea, and dyspnea. After a median follow-up of 21.0 months (range, 18.9–25.9), all patients were alive and without recurrence. Conclusion: Sorafenib was generally associated with limited severe toxicity when combined with paclitaxel following AC. However, many patients discontinued sorafenib early due to grade 1/2 toxicity, physician/patient decision, and treatment compliance. Additional studies of sorafenib in breast cancer in the neoadjuvant and triple-negative settings are warranted.

Introduction

Adjuvant systemic treatment improves survival in breast cancer.[1] The role of adjuvant therapy is to kill occult disease and prevent recurrence. Multiple chemotherapy regimens are considered standard in the adjuvant setting, with selection guided by clinicopathologic factors and physician/patient preference. Despite the varied options and advances in systemic treatment, adjuvant therapy does not benefit all patients.

Targeting angiogenesis has proven to be an effective treatment strategy in metastatic breast cancer. Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF), an important target of endothelial proliferation and vascular permeability.[2] In a randomized phase III trial, bevacizumab and paclitaxel improved the objective response rate and progression-free survival (PFS) compared to paclitaxel alone in women newly diagnosed with advanced breast cancer (median PFS, 11.8 vs 5.9 months; hazard ratio for progression, 0.60; $P<.001$).[3]

Sorafenib (Nexavar, Bayer) is an oral small molecule inhibitor of angiogenesis and other tumor growth signaling. Sorafenib inhibits multiple intracellular (CRAF, BRAF, and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, PDGFR-ß), including the receptors to VEGF (VEGFR-1, VEGFR-2, VEGFR-3). Sorafenib is approved by the US Food and Drug Administration (FDA) for the treatment of advanced renal cell and hepatocellular carcinomas as a single agent based on respective progression-free and overall survival advantages over supportive care alone.[4-6]

Sorafenib has been studied as a single agent and in combination regimens in several solid tumors including breast cancer.[7-17] Herein, we report the results of a pilot, phase II, multicenter trial of sorafenib in combination with standard adjuvant breast cancer treatment.

Patients and Methods

This trial was initiated in May 2007. Participating centers included the Sarah Cannon Research Institute and select sites from the Sarah Cannon Oncology Research Consortium, a national community-based research network.

Patients

Patients with histologically confirmed breast cancer were enrolled. Patients must have had definitive surgery, defined as either mastectomy or breast conserving surgery, each with axillary node assessment. All margins must have been free of invasive disease and/or ductal carcinoma in situ (DCIS). The finding of lobular carcinoma in situ was not scored as a positive margin. The interval between surgery and initiation of study treatment must have been equal to or less than 84 days. Eligible stages of disease included stage I, II, IIIA, and IIIC (T1–3, N3a only). Patients must have been either node-positive or high-risk node-negative. Node positivity was defined as having invasive adenocarcinoma in at least 1 axillary node (pN1) or intramammary node. At least 6 axillary or intramammary nodes must have been histologically examined. Malignant involvement must have been detectable by routine pathologic examination with hematoxylin and eosin staining. Patients with immunohistologic staining as the only evidence of nodal involvement were considered node-negative. High-risk node-negative disease was defined as invasive adenocarcinoma not involved in a node determined by sentinel node biopsy and at least one of the following: tumor size greater than 2 cm; estrogen receptor negative; progesterone receptor negative; histologic and/or nuclear grade 2/3; or age less than 35 years. Patients receiving anticoagulation treatment with an agent such as warfarin or heparin were eligible. Other eligibility criteria included: age 18 years or older; no prior chemotherapy, primary radiation, or biologic treatment; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 (ranging from normal to ambulatory, but restricted in strenuous activity); cardiac function equal to or above the lower limit of institutional normal confirmed by left ventricular ejection fraction (LVEF) on echocardiography or multigated acquisition scan and electrocardiogram; and adequate organ function (defined as absolute neutrophil count [ANC] $\geq 1.5 \times 10^9$/L; hemoglobin [Hgb] $\geq$ 10 g/dL; platelet count $\geq 100 \times 10^9$/L; serum aspartate aminotransferase and alanine transaminase $< 2.5 \times$ the upper limit of normal; and serum creatinine ≤ 2 mg/dL).

Exclusion criteria included: HER2-positive breast cancer as determined by fluorescence in situ hybridization or immunohistochemistry 3+; bilateral invasive disease; any T4 or known M1 breast cancer; pre-existing motor or sensory neurotoxicity of a severity of 2 or greater by the common terminology criteria for adverse events (CTCAE version 3) of the National Cancer Institute (NCI); major surgery within 4 weeks of treatment; major bleeding or hemoptysis; pregnancy or lactation; clinically significant cardiovascular disease; medically uncontrolled hypertension; and prior malignancy within 5 years, except nonmelanoma skin cancer and cervical carcinoma in situ. All patients provided written informed consent prior to enrollment.

Pretreatment Evaluation

Prior to treatment, patients were evaluated by history, physical exam, and laboratory testing. A complete staging work-up was required on all patients within 5 weeks of initiation of study treatment, with the exception of baseline mammography, which must have been done within

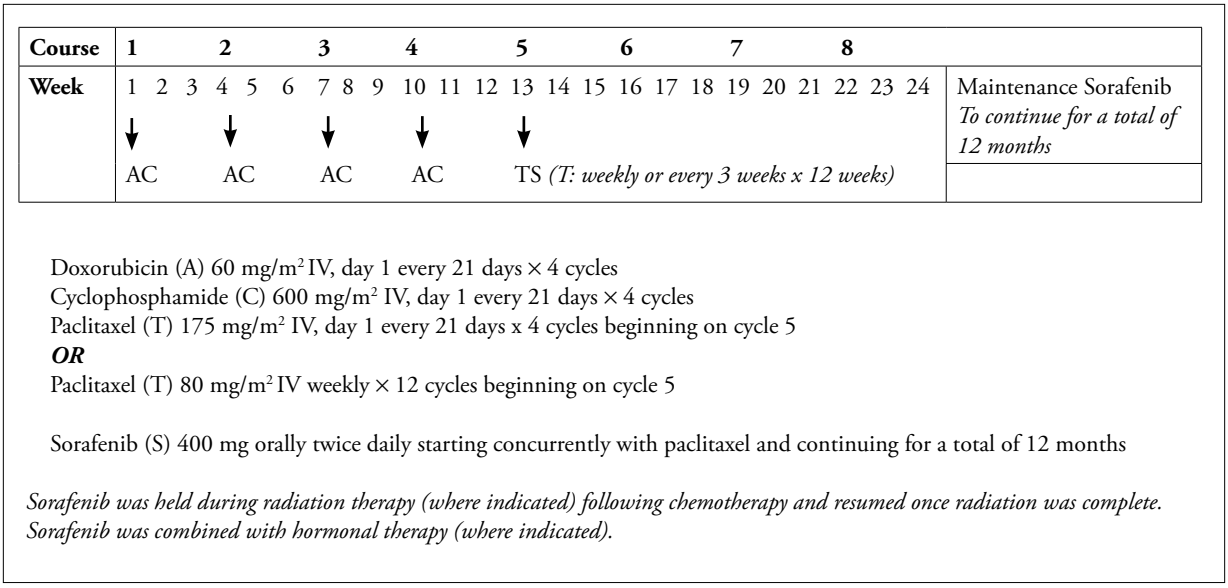

Figure 1. Trial schema.

120 days of treatment initiation. All patients must have had mammography and/or ultrasound, computed tomography (CT) scans of the chest and abdomen/pelvis, and either bone scan or positron emission tomography.

Treatment Plan

All patients received doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC), both administered intravenously on day 1, every 3 weeks, for 4 cycles, followed by paclitaxel 175 mg/m^2 intravenously on day 1, every 3 weeks, for 4 cycles or 80 mg/m^2 weekly for 12 cycles (physician discretion), combined with sorafenib 400 mg orally twice daily (Figure 1). Sorafenib was held during radiation therapy, where indicated, and resumed once completed. Sorafenib was continued for a total of 12 months and in combination with adjuvant hormonal therapy where indicated.

All patients were evaluated by history, physical exam, and laboratory parameters every 3 weeks during chemotherapy (and every 4 weeks while on sorafenib following chemotherapy). Blood pressure was measured weekly for the first 6 weeks on sorafenib. Left ventricular assessments occurred after AC, paclitaxel, and every 3 months during maintenance sorafenib. Breast exams were performed every 3 months. Follow-up mammography and other imaging was at the discretion of the treating physician. All patients were followed for survival.

Chemotherapy dose modifications were based on ANC, Hgb, and platelet counts on day 1 of each cycle; doses were not increased once modified. No adjustments were required if the ANC was greater than or equal to 1.5×10^9/L, Hgb was greater than or equal to 10 g/dL, and platelet count was greater than or equal to 100×10^9/L. If the ANC was less than 1.5×10^9/L, Hgb was less than 10 g/dL, or platelets were less than 100×10^9/L, chemotherapy was held until counts recovered to baseline parameters. If recovery was from thrombocytopenia or anemia, doses were resumed with planned dose reductions. If the counts did not recover within 2 weeks, the patient came off study. Prophylactic antibiotics and planned dose reductions were used for episodes of neutropenia and fever. Chemotherapy was also reduced for grade 3/4 nonhematologic toxicity.

Sorafenib was held and adjusted for rash and hand-foot skin reaction, grade 2 or higher hypertension, and other grade 3 or 4 hematologic and nonhematologic toxicities. Sorafenib was stopped permanently for repeated episodes of grade 2 or higher rash or hand-foot skin reaction (and at physician and patient discretion), grade 4 hypertension, any grade 4 toxicity (physician and patient discretion), or any sorafenib treatment delay of more than 21 days.

Where indicated, adjustments in radiation and/or hormonal therapy were at the discretion of the treating physician, and were to follow standard institutional practice.

Toxicity assessments were made according to the NCI CTCAE. Cytokines were not administered with the first course of treatment; however, prophylactic granulocyte colony-stimulating factor for patients experiencing

febrile neutropenia was permitted at the discretion of the treating physician. Routine antiemetics were used as premedication.

This trial was approved by the institutional review boards of all participating institutions. The Sarah Cannon Research Institute designed and coordinated the trial and was responsible for all aspects of data collection and analysis. Sorafenib (formerly BAY 43-9006; Cancer Chemotherapy National Service Center code 724772) was provided by Bayer/Onyx. Commercially available forms of chemotherapy and, where indicated, hormonal therapies were used.

Statistical Considerations

The primary objective of this pilot, multicenter, phase II study was to assess the safety and tolerability of AC followed by paclitaxel in combination with sorafenib in patients with early-stage node-positive or otherwise high-risk breast cancer. The secondary objectives were to assess the activity in the form of recurrence-free interval, distant recurrence-free interval, and overall survival.

It was hypothesized that sorafenib would be well tolerated in combination with paclitaxel following AC, and, additionally, would prove safe in combination with radiotherapy (for those patients who were candidates for radiation) and in combination with hormonal therapy (for those patients who were candidates for tamoxifen or an aromatase inhibitor). The sample size for this pilot study was 40 patients. It was estimated that a sample size of 40 patients would be sufficient to assess safety and tolerability while also accounting for potential patients who come off study early due to patient/physician choice, toxicity, or comorbidity.

Recurrence-free survival was defined as the interval between the start date of treatment and the date of disease recurrence (regional or distant). Overall survival was measured from the date of study entry until the date of death. If there was intolerable toxicity or discontinuation of treatment secondary to toxicity, the patient was considered assessable, but was classified as a treatment failure. If other cancer therapy was initiated before progressive disease occurred, the patient was censored on the date on which the other therapy began. If a patient was lost to follow-up, the patient was censored on the date of last contact. Survival curves were constructed using the Kaplan-Meier method.[18] Toxicity was evaluated in all patients who received at least 1 dose of therapy.

Results

Patient Characteristics

Forty-five patients were enrolled from May 2007 to January 2008, 62% from Tennessee and 38% from Michigan, Kentucky, and Florida. Baseline characteristics for all patients are described in Table 1. The median age was 54 years (range, 35–71 years). Forty-one (91%) patients were white and 4 patients were African-American. ECOG PS was 0 in 42 patients (93%) and 1 in 3 (7%) patients. Twenty-nine (64%) patients had hormone receptor–positive tumors. Thirty-eight (84%) patients had node-positive tumors. There were 2 (4%), 23 (51%), and 20 (45%) stage I, II, and III tumors, respectively.

Trial Summary

The flow of patients in this trial is summarized in the CONSORT diagram (Figure 2). At a median follow-up of 21.0 months (range, 18.9–25.9 months), all patients were alive and without evidence of recurrence. All patients received AC treatment and were eligible to receive paclitaxel and sorafenib (TS). Thirty-seven (82%) patients completed all planned AC treatment without dose reductions or delays. Among all 45 patients eligible for TS treatment, 8 (13%) patients came off study due to physician/patient decision, 21 (47%) patients came off study due to toxicity, 2 (4%) patients completed TS but did not proceed with maintenance sorafenib, and

Table 1. Baseline Characteristics

Characteristic	Patients No. (%)
Age	
Median	54 years
Range	35–74 years
Race	
White	41 (91%)
African-American	4 (9%)
ECOG Performance Status	
0	42 (93%)
1	3 (7%)
Hormone Receptor Status	
ER+/PR+	24 (53%)
ER+/PR-	5 (11%)
ER-/PR+	1 (2%)
ER-/PR-	15 (33%)
Nodal Status	
Positive	38 (84%)
Negative	7 (16%)
Stage	
I	2 (4%)
II	23 (51%)
III	20 (45%)

ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; PR=progesterone receptor.

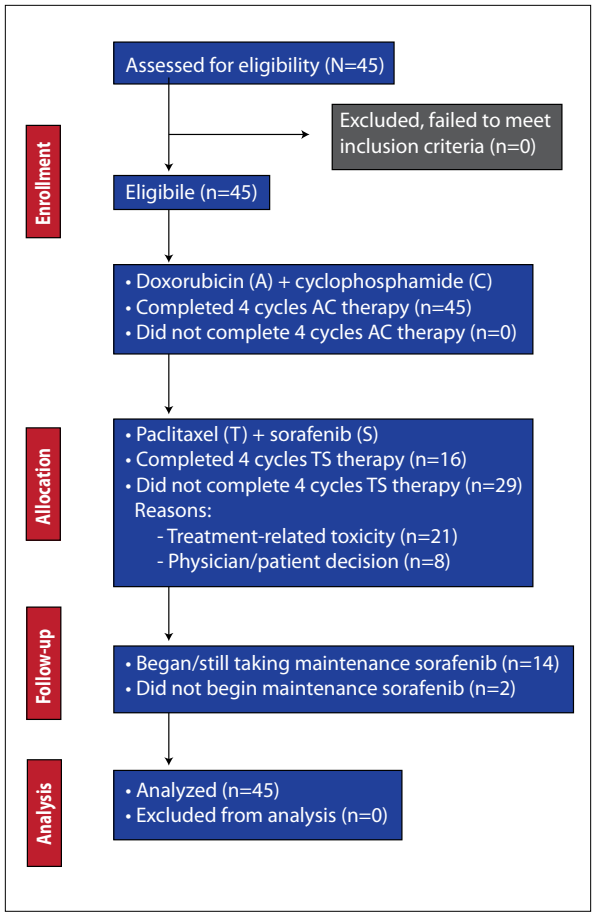

Figure 2. CONSORT flow chart for patients treated with doxorubicin plus cyclophosphamide followed by paclitaxel plus sorafenib.

14 (31%) patients completed TS and entered the maintenance phase of sorafenib treatment. Sixty-five percent of patients did not complete all planned TS therapy due to toxicity (47%) or physician/patient decision (18%). Four (9%) patients completed concurrent TS planned therapy without dose reductions or delays. Nineteen and 6 patients had paclitaxel held and/or reduced, respectively. Thirty-three and 8 patients had sorafenib held and/or reduced, respectively.

The use of every-3-week and weekly paclitaxel was well balanced. Sorafenib was taken for 6.1 weeks on average during the paclitaxel phase and for 15 weeks during the maintenance phase.

Treatment-related Toxicity

Treatment-related toxicity for each phase of treatment is summarized in Tables 2–4. In general, the AC phase of treatment (weeks 1–12) was well tolerated, with expected grade 3/4 cytopenia (neutropenia, 40%). Febrile neutropenia was limited to 1 (2%) patient. Severe toxicity was also generally limited during the concurrent TS phase of treatment (weeks 13–24), with minimal severe hematologic or nonhematologic toxicity. Select serious (grade 1/2/3) toxicities included rash (33%/20%/16%), hand-foot skin reaction (4%/11%/11%), sensory neuropathy (20%/33%/7%), myalgia (11%/18%/11%), and fatigue (40%/24%/4%).

Table 2. Grade 3/4 Toxicity During Doxorubicin Plus Cyclophosphamide Phase (Weeks 1–12) in More Than 1 (2%) Patient (N=45)

Toxicity	Grade 3	Grade 4
Neutropenia	2 (4%)	16 (36%)
Leukopenia	7 (16%)	5 (11%)
Arthralgia	2 (4%)	0
Fatigue	3 (7%)	0
Pain	5 (11%)	0

There were no deaths on treatment. There were 3 treatment-related serious adverse events during the TS phase of therapy. One patient had grade 3 congestive heart failure. This patient was noted to have a severe decline in left ventricular ejection fraction after AC and TS. This patient may have had a baseline low/normal ejection fraction and dilated left ventricle. Of note, this patient also received left-sided radiation. A second patient developed pancreatitis (grade 2) with elevated enzymes and confirmation on CT imaging, requiring hospitalization. A third patient developed grade 2 pneumonia leading to hospitalization, deemed possibly related to paclitaxel therapy.

Discussion

Adjuvant therapy improves survival in breast cancer, but does not benefit all patients. As newer therapies advance treatment in the metastatic setting and in other solid tumors, it is possible that these novel agents will work better in earlier treatment settings where there is a smaller tumor burden. Antiangiogenic therapies have recently emerged as promising agents in multiple advanced treatment settings in colorectal, non-small cell lung, kidney, hepatocellular, glioma, and breast cancers.[3,5,6,19-21] Many ongoing studies are currently evaluating these therapies in earlier breast cancer treatment, including the neoadjuvant setting.

Sorafenib is an oral small-molecule kinase inhibitor that targets angiogenesis at the level of the VEGF receptors, but also inhibits other key signaling pathways including the RAS/RAF/MAP kinase and PI3 kinase/

Table 3. Grade 3/4 Toxicity During Paclitaxel Plus Sorafenib Phase (Weeks 13–24) in More Than 1 (2%) Patient (N=45)

Toxicity	Grade 3	Grade 4
Neutropenia	4 (9%)	0
Leukopenia	3 (7%)	0
Anorexia	2 (4%)	0
Arthralgia	3 (7%)	0
Diarrhea	4 (9%)	0
Dyspnea	3 (7%)	0
Edema	2 (4%)	0
Infection	2 (4%)	0
Left ventricle dysfunction*	2 (7%)	0

*Unrelated cases.

MTOR pathways, which play important roles in breast cancer progression.[10,17] Recently, sorafenib was evaluated as a single agent in patients with previously treated breast cancer in a phase II study by Moreno-Aspitia and colleagues.[7] Although well tolerated, sorafenib did not demonstrate any activity in this cohort. It is possible that sorafenib may have a greater role in an earlier treatment setting, and, like bevacizumab, when used in combination with chemotherapy.

Our pilot trial was designed to assess the safety and tolerability of incorporating sorafenib into a standard adjuvant breast cancer regimen. Because of the potential drug-drug interactions with sorafenib and doxorubicin, sorafenib was not initiated until the paclitaxel phase of the trial, based on studies showing this combination to be safe and generally well tolerated.[15]

This study was limited by its design and small sample size. Patient selection bias could have influenced which patients entered this trial and which taxane schedule was used. Additionally, the majority of patients came off study during the initial sorafenib phase of treatment. This withdrawal rate did not appear to be related to severe toxicity, which aside from rash and hand-foot skin reaction, was not increased with sorafenib. Multiple factors could potentially explain this high withdrawal rate, including grade 1 and 2 toxicity, physician and/or patient decision, and difficulty with treatment compliance. Importantly, this dropout led to a high rate of patients not receiving all planned paclitaxel. It is possible that this withdrawal rate would have been lower in a nonathracycline regimen when started with the first cycle of chemotherapy, or in a sequential fashion following paclitaxel. Another limitation of this trial were the potential confounding effects of adjuvant hormonal therapy. It is possible that negative drug-drug interactions could have contributed to toxicity and dose modifications.

At a median follow-up of 21 months, all patients were alive and without recurrence. This finding is not surprising given the early median follow-up in a small adjuvant trial. It seems unlikely that such brief and limited exposure to a biologic agent could impact longer survival outcomes in this group; however, longer follow-up is needed.

Additional study of sorafenib is warranted in early breast cancer. However, concurrent use with paclitaxel does not appear to be feasible. These early safety data support evaluating sorafenib as part of a more limited preoperative regimen. Sorafenib may also be an ideal oral therapy for patients with triple negative disease where compliance with oral therapy is not complicated by another daily hormonal pill. Any of these strategies should also incorporate correlative molecular studies. Identifying predictive markers will help us ultimately select those patients who can most benefit from targeted therapies like sorafenib.

Table 4. Select Grade 1–4 Toxicity During Paclitaxel Plus Sorafenib Phase (Weeks 13–24)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Rash	15 (33%)	9 (20%)	7 (16%)	0
Hand/Foot Skin Reaction	2 (4%)	5 (11%)	5 (11%)	0
Sensory Neuropathy	9 (20%)	15 (33%)	3 (7%)	0
Myalgia	5 (11%)	8 (18%)	5 (11%)	0
Fatigue	18 (40%)	11 (24%)	2 (4%)	0

Acknowledgment

Supported in part by grants from Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ, and Onyx Pharmaceuticals, Inc., Emeryville, CA.

Dr. Spigel has been an unpaid consultant to, and received research funding from, Bayer Onyx. All other coauthors state that they have no conflicts of interest.

Registered with ClinicalTrials.gov October 15, 2007; ID# NCT00544167 (SCRI BRE 112).

References

1. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med.* 2005;353:1784-1792.
2. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev*. 1997;18:4-25.
3. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357:2666-2676.
4. Bukowski RM, Eisen T, Szczylik C, et al. Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: survival and biomarker analysis. *J Clin Oncol.* 2007;25:Abstract 5023.
5. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356:125-134.
6. Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib improves survival in advanced hepatocellular carcinoma (HCC): results of a phase III randomized placebo-controlled trial (SHARP trial). *J Clin Oncol*. 2007;25:Abstract LBA1.
7. Moreno-Aspitia A, Morton RF, Hillman DW, et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. *J Clin Oncol.* 2009;27:11-15.
8. Hong DS, Camacho L, Ng C, et al. Phase I study of tipifarnib and sorafenib in patients with biopsiable advanced cancers (NCI protocol 7156 supported by NCI grant UO1 CA062461). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2007;25:Abstract 3549.
9. Dahut WL, Scripture C, Posadas E, et al. A phase II clinical trial of sorafenib in androgen-independent prostate cancer. *Clin Cancer Res.* 2008;14:209-214.
10. Ding Q, Huo L, Yang JY, et al. Down-regulation of myeloid cell leukemia-1 through inhibiting Erk/Pin 1 pathway by sorafenib facilitates chemosensitization in breast cancer. *Cancer Res*. 2008;68:6109-6117.
11. Gridelli C, Rossi A, Mongillo F, et al. A randomized phase II study of sorafenib/gemcitabine or sorafenib/erlotinib for advanced non-small-cell lung cancer in elderly patients or patients with a performance status of 2: treatment rationale and protocol dynamics. *Clin Lung Cancer.* 2007;8:396-398.
12. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol*. 2008;26:4714-4719.
13. Kupsch P, Henning BF, Passarge K, et al. Results of a phase I trial of sorafenib (BAY 43-9006) in combination with oxaliplatin in patients with refractory solid tumors, including colorectal cancer. *Clin Colorectal Cancer.* 2005;5:188-196.
14. Kumar S, Marks RS, Richardson R, et al. A phase I study of the raf kinase/VEGF-R inhibitor sorafenib in combination with bortezomib in patients with advanced malignancy. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2008;26:Abstract 2569.
15. Schiller JH, Flaherty KT, Redlinger M, et al. Sorafenib combined with carboplatin/paclitaxel for advanced non-small cell lung cancer: a phase I subset analysis. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2006;24:Abstract 7194.
16. Takimoto CH, Awada A. Safety and anti-tumor activity of sorafenib (Nexavar) in combination with other anti-cancer agents: a review of clinical trials. *Cancer Chemother Pharmacol.* 2008;61:535-548.
17. Tran MA, Smith CD, Kester M, et al. Combining nanoliposomal ceramide with sorafenib synergistically inhibits melanoma and breast cancer cell survival to decrease tumor development. *Clin Cancer Res.* 2008;14:3571-3581.
18. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
19. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004; 350:2335-2342.
20. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2006;24:2505-2512.
21. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006;355:2542-2550.