

## **A Phase I Trial of the Oral, Multikinase Inhibitor Sorafenib in Combination with Carboplatin and Paclitaxel**

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**Abstract Purpose:** This study evaluated the safety, maximum tolerated dose, pharmacokinetics, and antitumor activity of sorafenib, a multikinase inhibitor, combined with paclitaxel and carboplatin in patients with solid tumors.

**Patients and Methods:** Thirty-nine patients with advanced cancer (24 with melanoma) received oral sorafenib 100, 200, or 400 mg twice daily on days 2 to 19 of a 21-day cycle. All patients received carboplatin corresponding to AUC<sub>6</sub> and 225 mg/m<sup>2</sup> paclitaxel on day 1. Pharmacokinetic analyses were done for sorafenib on days 2 and 19 of cycle 1 and for paclitaxel on day 1 of cycles 1 and 2. Pretreatment tumor samples from 17 melanoma patients were analyzed for *BRAF* mutations.

**Results:** Sorafenib was well tolerated at the doses evaluated. The most frequent severe adverse events were hematologic toxicities (grade 3 or 4 in 33 patients, 85%). Twenty-seven (69%) patients had sorafenib-related adverse events, the most frequent of which were dermatologic events (26 patients, 67%). Exposure to paclitaxel was not altered by intervening treatment with sorafenib. Treatment with sorafenib, paclitaxel, and carboplatin resulted in one complete response and nine partial responses, all among patients with melanoma. There was no correlation between *BRAF* mutational status and treatment responses in patients with melanoma.

**Conclusions:** The recommended phase II doses are oral 400 mg twice daily sorafenib, carboplatin at an AUC<sub>6</sub> dose, and 225 mg/m<sup>2</sup> paclitaxel. The tumor responses observed with this combined regimen in patients with melanoma warrant further investigation.

Sorafenib (BAY 43-9006; Nexavar) is a potent oral multikinase inhibitor that inhibits the activities of RAF kinase, vascular endothelial growth factor, c-Kit, Ret, and other growth factor receptor tyrosine kinases *in vitro* (1–3). *In vivo*, sorafenib

inhibited tumor growth in several xenograft models containing *BRAF* or *KRAS* mutations (1). In melanoma xenograft models, sorafenib slowed tumor development by inhibiting <sup>V600E</sup>BRAF activity, phosphorylation of MEK and extracellular signal-regulated kinase, and vascular development, similar to the effects obtained with small interfering RNA targeted against *BRAF* (4). In single-agent phase I/II trials, sorafenib showed a favorable toxicity profile and antitumor activity in patients with solid tumors (5, 6). Furthermore, a single-agent phase III trial in patients with renal cell carcinoma showed that treatment with sorafenib resulted in median progression-free survival of 24 weeks compared with 12 weeks in patients receiving placebo (7).

In preclinical studies, combinations of sorafenib with other chemotherapeutic agents inhibited the growth of human cancer cells *in vitro* (8) and in xenograft models (9). Combinations of sorafenib with other anticancer agents have yielded encouraging results in several clinical trials (10–13). However, in patients with advanced melanoma, sorafenib monotherapy displayed limited objective responses as determined by Response Evaluation Criteria in Solid Tumors and only 16% stable disease (14). Similarly, treatment of patients with advanced melanoma with single-agent carboplatin or paclitaxel yielded overall response rates of <20% (15–21). Combining carboplatin and paclitaxel did not appear to provide additional benefits with overall response rate of <10% and 17% in two

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**Table 1.** Baseline patient characteristics

Characteristic	No. patients (%)
Total patients	39 (100)
Gender	
Male	26 (67)
Female	13 (33)
Ethnicity	
Caucasian	37 (95)
Asian	1 (3)
Hispanic	1 (3)
Age (y)	
Mean (SD)	51.8 (12.9)
Median (range)	51 (25-75)
Primary carcinoma	
Malignant melanoma	24 (62)
Colon	4 (10)
Non-small cell lung cancer	4 (10)
Renal	2 (5)
Other*	5 (13)
Eastern Cooperative Oncology Group performance status	
0	22 (56)
1	17 (44)
Prior systemic regimens	
0	8 (21)
1	9 (23)
2	14 (36)
3	5 (13)
≥4	3 (8)
Prior treatment	
Taxane	3 (8)
Radiotherapy	12 (31)
Nondiagnostic surgery	29 (74)

\*Other tumors included mucinous adenocarcinoma of appendiceal wall, adenocarcinoma of distal esophagus, neuroendocrine tumor of esophagus, Ewing's sarcoma of right rib and lung, and basal cell carcinoma of right shoulder.

prospective trials with small cohorts (21, 22). In a retrospective analysis, 26% of patients with advanced melanoma treated with a carboplatin-paclitaxel combination had partial response (23).

The primary objectives of the present study were to evaluate safety and determine the maximum tolerated dose of sorafenib administered in combination with paclitaxel and carboplatin in patients with advanced cancer. Secondary objectives included evaluation of pharmacokinetics of all three compounds and preliminary efficacy analysis of the combination treatment. As sorafenib has been shown to inhibit the cytochrome P450 isoenzyme 3A4, *in vitro*, we were particularly interested in ruling out a significant increase in paclitaxel exposure when sorafenib is coadministered (24). Melanoma patients were preferentially accrued following the report of *BRAF* mutations early in the conduct of this trial.

## Patients and Methods

**Patients.** Eligible patients were at least 18 years old, had histologic or cytologic documented cancer, an Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease, adequate bone marrow, liver and renal function, and life expectancy of at least 12 weeks. After establishing maximum tolerated dose, additional patients were enrolled to evaluate pharmacokinetics and exclude significant differences in exposure to carboplatin and paclitaxel with intervening sorafenib

administration. Due to a change in the formulation of sorafenib from 50 to 200 mg tablets, an additional cohort of patients was enrolled to determine the bioequivalence of the two tablet sizes.

Patients were excluded if they had clinically evident congestive heart failure greater than New York Heart Association class 2 or had received anticancer chemotherapy or immunotherapy during the study or within 3 weeks of study entry or mitomycin C or nitrosoureas within 6 weeks of study entry. Prior adjuvant chemotherapy was permitted and patients were allowed to receive up to two prior chemotherapy regimens for metastatic disease (patients with three or more prior regimens could be enrolled after discussion with the sponsor). The use of concomitant investigational drugs was prohibited during or within 4 weeks of study entry. Use of ketoconazole, itraconazole, ritonavir, grapefruit products, and previous exposure to RAS pathway inhibitors was prohibited. Pregnant or nursing women were excluded. Women of childbearing potential were required to have a negative pregnancy test within 7 days of treatment initiation and to use adequate birth control measures during the study. Patients were excluded if they had a known or suspected allergy to any agent given in this study, had any condition that was unstable or could jeopardize their safety or ability to comply with study procedures, or could interfere with evaluation of the results.

All patients gave written, informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki, the Investigational New Drug and Bioresearch Regulations of the U.S. Food and Drug Administration, the Good Clinical Practice guidelines, and all applicable local laws and regulations. The study protocol and amendments were approved by each institutional review board or independent ethics committee.

**Study design and treatments.** In this three-center, open-label, non-placebo-controlled, dose-escalation trial, patients received paclitaxel i.v. over 3 h followed by carboplatin infusion over 30 min on day 1. Oral sorafenib was administered twice daily on days 2 to 19. No treatments were administered on days 20 and 21. Starting doses were 100 mg twice daily sorafenib, 225 mg/m<sup>2</sup> paclitaxel, and carboplatin corresponding to area under the curve of 6 (AUC<sub>6</sub>). Growth factor support was prohibited. Patients could continue to receive subsequent cycles until occurrence of unacceptable toxicity, tumor progression, or death. Patients with stable disease or a response who had received six cycles of combination therapy had the option to continue sorafenib monotherapy with reinitiation of chemotherapy if their disease progressed.

Determination of maximum tolerated dose was based on data from the first cycle; no intrasubject dose escalation was permitted. Dose-limiting toxicity (DLT) was defined as any one of the following: grade 4 neutropenia for at least 7 days, grade 4 neutropenia of any duration with sepsis or a fever >38.5°C, platelet count <25,000/μL, grade 3 or 4 nonhematologic toxicity (excluding nausea or vomiting not refractory to antiemetics and hypersensitivity reactions subsequently controlled by premedication), and any toxicity considered by the investigators to be related to the study drug and of sufficient severity to warrant such description. Data from the first treatment cycle were used to determine DLT. The next dose cohort was initiated if three patients enrolled at a given dose level reached day 21 without experiencing DLT. If one patient experienced DLT, three additional patients were added to that cohort. The maximum tolerated dose was considered to have been exceeded if two or more patients in any cohort experienced DLT. Dose cohorts were (a) 225 mg/m<sup>2</sup> paclitaxel, carboplatin AUC<sub>6</sub>, and 100 mg twice daily sorafenib; (b) 225 mg/m<sup>2</sup> paclitaxel, carboplatin AUC<sub>6</sub>, and 200 mg twice daily sorafenib; and (c) 225 mg/m<sup>2</sup> paclitaxel, carboplatin AUC<sub>6</sub>, and 400 mg twice daily sorafenib.

**Study assessments.** Before initiating treatment, each patient was evaluated for medical history, physical examination, tumor measurement using computer-assisted tomography or magnetic resonance imaging, Eastern Cooperative Oncology Group performance status, complete differential blood count, serum chemistries, urinalysis, and electrocardiogram. These assessments were also done before each subsequent cycle of treatment. All observations were recorded, including results of physical examinations, vital signs, adverse events,

concomitant medications, and laboratory tests. Complete blood counts were done twice weekly, and serum chemistries were done weekly during the first cycle, with more frequent monitoring in the event of severe myelosuppression. Patients were monitored every 3 weeks and as needed for adverse events. Tumor response and progression were assessed using Response Evaluation Criteria in Solid Tumors with imaging studies done after every two cycles of treatment. Blood samples were collected for analysis of plasma concentrations of sorafenib (days 2 and 19 of cycle 1), platinum (total and free), paclitaxel and 6-OH-paclitaxel (day 1 of cycles 1 and 2). Calculated pharmacokinetic variables included the geometric means and percent coefficient of variance (%CV) of area under the concentration-time curve between time 0 and time *t* (AUC<sub>0-t</sub>), maximum plasma concentration (C<sub>max</sub>), and half-life of drug in plasma (t<sub>1/2</sub>). Following the conclusion of this study, the U.S. Food and Drug Administration notified the sponsor that the independent contract laboratory (MDS Pharma, St. Laurent, and Blainsville sites) that performed the carboplatin assays used substandard methods in contemporaneous studies and cautioned that any results obtained from those sites should be considered unreliable. Hence, the carboplatin pharmacokinetics is excluded from this report.

All analyses, except pharmacokinetics, were descriptive. Attempts were made to obtain tumor samples from all melanoma patients for *BRAF* and *NRAS* mutational analyses. To confirm the presence of melanoma in at least 70% of the area of interest, genomic DNA was isolated from either paraffin-embedded tissue or frozen tissue using techniques described previously (25) and screened for *BRAF* mutations by direct sequencing of the amplified region of interest using an ABI 3100 automated sequencer. One patient with metastatic melanoma consented to serial 4-mm punch biopsies of cutaneous lesions done before and after 3 weeks of combined therapy. Samples were examined by H&E staining to confirm that the sample was predominantly melanoma. Activation of the mitogen-activated protein kinase cascade was determined by immunoblotting (26). Primary antibodies against phosphorylated and total MEK were obtained from Cell Signaling. Horseradish peroxidase-conjugated secondary antibodies were obtained from Jackson ImmunoResearch.

**Results**

*Patient disposition and baseline characteristics.* Baseline characteristics of the 39 patients enrolled in the dose-escalation

phase of the trial are shown in Table 1. The primary diagnoses for these patients were melanoma (cutaneous, *n* = 23; ocular, *n* = 1), colon cancer (*n* = 4), non-small cell lung cancer (*n* = 4), renal cell carcinoma (*n* = 2), or other tumors (*n* = 5). All patients received at least one dose of study medication and were included in both the safety and intent-to-treat analyses.

*Dose-limiting toxicity.* Two patients who received 100 mg twice daily sorafenib had grade 3 or 4 toxicities during the first cycle of treatment (one grade 4 neutropenia lasting <7 days and one grade 3 rash considered related to sorafenib). Because the grade 3 rash was deemed a DLT, 4 additional patients were enrolled into this cohort. There were no DLT among the 3 patients receiving 200 mg twice daily sorafenib or among the first 3 patients receiving 400 and 50 mg tablets sorafenib. Of the additional 9 patients enrolled into the third cohort, 4 (44%) experienced grade 3 or 4 toxicities during the first cycle of treatment of which only one (grade 3 hand-foot skin reaction) was considered DLT. A fourth cohort was added in which 17 patients received 400 mg twice daily sorafenib using 200 mg tablets, 8 (47%) of whom had grade 3 toxicities during the first cycle of treatment, with 5 (29%) considered to be DLT (4 hand-foot skin reaction and 1 hypertension).

*Safety.* Treatment-related adverse events (Table 2) occurred in all patients, the most common of which were hematologic (95%), dermatologic (85%), fatigue (59%), sensory neuropathy (59%), nausea (56%), and arthralgia (26%). Grade 4 neutropenia occurred in 3 patients in the 100 mg twice daily cohort (43%), 1 patient in the 200 mg twice daily cohort (33%), and 20 patients in the 400 mg twice daily cohorts (69%). There were no cases of grade 4 thrombocytopenia. Rashes and plantar-palmar erythema were reported in 71%, 33%, and 59% of the patients in the 100, 200, and 400 mg twice daily cohorts, respectively. Of the 29 patients who received sorafenib 400 mg twice daily, hand-foot skin reaction grade ≥3 was reported in 5 (17%). However, there was no clear dose-dependent increment in treatment-related adverse events.

*Efficacy.* Of the 39 patients enrolled in this trial, there were nine partial response and one complete response by Response

**Table 2.** Treatment-related adverse events in first cycle

Adverse event	100 mg twice daily (n = 7)					200 mg twice daily (n = 3)					400 mg* twice daily (n = 29)				
	National Cancer Institute Common Toxicity Criteria grade (n)										1	2	3	4	All
	1	2	3	4	All	1	2	3	4	All					
<b>Hematologic</b>															
Neutrophils/granulocytes	0	1	3	3	7	0	0	2	1	3	0	2	2	20	24
Leukocytes	0	0	1	1	2	0	1	0	0	1	0	0	2	0	2
Platelets	1	0	1	0	2	0	0	3	0	3	2	5	12	0	19
Hemoglobin	0	0	0	0	0	0	1	0	0	1	1	9	5	1	16
<b>Dermatologic</b>															
Alopecia	0	5	0	0	5	0	1	0	0	1	2	10	0	0	12
Rash/desquamation	1	3	1	0	5	1	0	0	0	1	7	7	3	0	17
Hand-foot skin reaction	0	1	0	0	1	0	1	0	0	1	4	2	5	0	11
<b>Other</b>															
Fatigue	2	3	1	1	7	1	0	0	0	1	9	6	0	0	15
Nausea	3	3	0	0	6	2	0	0	0	2	5	5	4	0	14
Constipation	1	4	0	0	5	1	0	0	0	1	3	3	0	0	6
Sensory neuropathy	3	2	1	0	6	1	1	0	0	2	10	4	1	0	15
Arthralgia (joint pain)	1	1	0	0	2	1	0	0	0	1	4	3	0	0	7

\*Combined incidence of adverse events for the 4 × 50 mg and 2 × 200 mg tablet regimens.

**Table 3.** Characteristics and tumor responses of patients with melanoma

Gender	Age (y)	Eastern Cooperative Oncology Group status	American Joint Committee on Cancer metastasis stage	Elevated lactate dehydrogenase	Disease sites	Prior therapy	Mutations	Response	Treatment duration (mo)
M	50	0	C	No	Liver, lung	0	<i>BRAF</i>	Progressive disease	>1
M	26	0	C	No	Adrenal, lymph node	1	<i>BRAF</i>	Partial response	29
F	50	0	B	No	Lung, skin	0	<i>BRAF</i>	Stable disease	3
F	52	0	B	No	Lung, skin	2	<i>BRAF</i>	Partial response	10
M	34	1	C	Yes	Liver	1	<i>NRAS</i>	Stable disease	5
F	53	1	C	Yes	Liver	2	<i>BRAF</i>	Stable disease	>1
M	69	1	C	Yes	Lymph node	1	Not available	Not evaluable	<1
F	39	0	C	Yes	Abdomen, adrenal, bowel, skin	0	Wild-type	Partial response	>12
M	53	0	C	Yes	Liver	1	<i>BRAF</i>	Partial response	17
M	46	0	A	No	Lymph node	1	<i>BRAF</i>	Partial response	15
M	33	0	C	No	Lung, pelvis	1	<i>BRAF</i>	Stable disease	>2
M	61	0	B	No	Lung, skin	1	<i>NRAS</i>	Partial response	10
M	47	0	C	No	Adrenal, lung, skin	1	<i>BRAF</i>	Complete response	21
F	51	0	C	Yes	Liver, lung	1	Not available	Stable disease	>3
F	51	0	B	No	Lung, skin	0	<i>BRAF</i>	Stable disease	>12
F	75	1	A	No	Skin	1	Not available	Stable disease	>11
F	49	1	C	Yes	Lymph node, pancreas, spleen	2	<i>BRAF</i>	Partial response	23
M	54	1	C	Yes	Kidney, liver, lymph node, vertebrae	1	Not available	Stable disease	4
M	33	0	B	No	Lung	0	Wild-type	Partial response	10
F	52	0	A	No	Lymph node	0	Wild-type	Partial response	>15
F	45	0	C	Yes	Adrenal, liver, lung, skin, uterus	0	Not available	Stable disease	6
F	55	1	C	Yes	Liver, pancreas, skin	3	Wild-type	Stable disease	6
M*	37	1	C	Yes	Bone, liver	Not available	Not available	Progressive disease	>1
M	56	0	C	Yes	Liver, lung, lymph node	Not available	Not available	Stable disease	3

\*Patient had ocular melanoma.

Evaluation Criteria in Solid Tumors criteria, all in patients with melanoma (overall response rate, 26%). One responding patient received 100 mg twice daily sorafenib, another received 200 mg twice daily, and all others received 400 mg twice daily. Eight melanoma patients had received prior cisplatin for the treatment of metastatic disease, with 3 patients who achieved a partial response on this study. In addition, 19 patients had stable disease and 5 had progressive disease. Five patients were removed from study before a response assessment due to clinical deterioration. At the time of first assessment, 29 (74%)

patients were progression-free. The American Joint Committee on Cancer stage, demographic characteristics, and number of cycles of therapy administered in patients with melanoma are shown in Table 3. One complete response occurred in a male with melanoma that had metastasized to s.c. sites, lung and adrenal gland, who have received previously temozolomide. The median duration of response was 467 days (range, 81-575 days) and did not differ significantly by dose level. Median progression-free survival was 307 days (range, 27-658 days) in the 24 patients with melanoma compared with

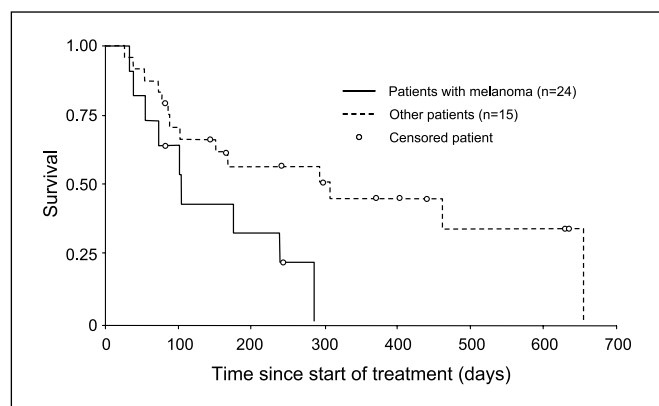


Fig. 1. Progression-free survival (PFS) in patients with melanoma or other tumors.

104 days (range, 34-286 days) in patients with other tumor types (Fig. 1).

**Pharmacokinetics.** As expected from the long mean half-life (23.73-34.83 h on day 19), there was significant accumulation of sorafenib observed at all doses (Table 4). The fold increase in mean values of AUC<sub>0-12</sub> did not vary by dose level. Steady-state C<sub>max</sub> values (day 19) for the three sorafenib dose cohorts were 3.6, 3.1, and 6.25 mg/L, respectively. The increases in mean C<sub>max</sub> were consistent with increases observed in AUC<sub>0-12</sub> from days 2 to 19. The pharmacokinetic profile of paclitaxel in cycle 1 (before sorafenib) and cycle 2 (after 18 days of sorafenib) was not notably different (data not shown). Mean paclitaxel C<sub>max</sub> and AUC<sub>0-∞</sub> values were 8.2 to 10.8 mg/L and 28.5 to 31.7 mg h/L, respectively, in cycle 1 compared with 6.6 to 9.4 mg/L and 23.4 to 28.1 mg h/L, respectively, following sorafenib across dose levels. Mean 6-OH-paclitaxel C<sub>max</sub> and AUC<sub>0-∞</sub> values were 0.74 to 1.05 mg/L and 1.95 to 2.7 mg h/L, respectively, in cycle 1 compared with 0.74 to 1.15 mg/L and 2.1 to 3.0 mg h/L,

respectively, following sorafenib across dose levels (Table 4). These data show no clinically significant change in C<sub>max</sub> and AUC values of paclitaxel indicating no clinically relevant interaction between sorafenib and paclitaxel at any of the studied sorafenib doses.

**Correlative studies.** Eleven of 17 (65%) melanoma patients harbored the V600E BRAF mutation, with 6 (55%) of these patients achieving objective responses. One of 2 (50%) patients with a mutation in NRAS had a partial response. Three of 4 (75%) patients with wild-type NRAS and BRAF responded to treatment. Tumor samples from 7 patients could not be obtained for analysis, but none of these patients had an objective response. Melanoma samples from the patient who underwent serial biopsy of cutaneous lesions also harbored the V600E BRAF mutation. Immunoblot analyses revealed no change in MEK protein level following 3 weeks of treatment, but phosphorylated MEK was markedly decreased (Fig. 2).

### Discussion

This dose-escalation trial was designed to determine the safety and maximum tolerated dose of sorafenib in combination with carboplatin and paclitaxel to identify a regimen suitable for further phase II/III evaluations. The incidence of severe myelosuppression observed in this trial was comparable with that reported with similar doses of carboplatin and paclitaxel (27). Dermatologic adverse events (most frequently rash) were the principal sorafenib-associated toxicities. In most patients, symptoms began within the first cycle and typically resolved by the end of the second cycle despite persistent dosing. Rash tended to be maculopapular, observed on the head, trunk, or extremities, and associated with pruritus when large areas of skin were involved. Severe hypertension was less frequently observed in our study than in other recent reports. This may be attributable to the fact that sorafenib was not administered for

**Table 4.** Comparison of plasma pharmacokinetics of sorafenib, paclitaxel and 6-OH-paclitaxel on the second day of cycle 1 and after 18 d of sorafenib dosing (day 19, cycle 1)

Sorafenib dose	Patient no.		t <sub>1/2</sub> (h) mean (%CV)		C <sub>max</sub> (mg/L)			AUC <sub>0-12</sub> (mg h/L)		
	Day A*	Day B*	Day A*	Day B*	Day A* mean (%CV)	Day B* mean (%CV)	Day B* to day A* ratio (90% confidence interval)	Day A* mean (%CV)	Day B* mean (%CV)	Day B* to day A* ratio (90% confidence interval)
Sorafenib (mg twice daily)										
100	7	4	ND	24.96 (35)	2.01 (31)	3.59 (32)	ND	7.87 (36)	29.03 (24)	ND
200	3	2	ND	23.66 (11)	2.14 (52)	3.09 (15)	ND	8.91 (47)	25.03 (20)	ND
400	25	19	ND	30.9 (56)	3.36 (58)	6.25 (40)	ND	17.5 (77)	51.6 (40)	ND
Paclitaxel (mg twice daily)										
100	6	4	10.79 (13)	11.4 (10)	10.8 (46)	8.7 (48)	1.06 (0.68-1.63) <sup>†</sup>	31.7 (35)	26.5 (38)	1.01 (0.79-1.29) <sup>†</sup>
200	3	2	10.04 (15)	9.91 (29)	9.4 (90)	6.6 (21)	0.66 (0.31-1.40) <sup>†‡</sup>	28.5 (64)	23.4 (25)	0.88 (0.56-1.40) <sup>†‡</sup>
400	25	17	9.64 (26)	10.12 (32)	8.2 (37)	9.4 (52)	1.24 (1.04-1.49) <sup>†</sup>	28.6 (39)	28.1 (42)	1.09 (0.95-1.25) <sup>†</sup>
6-OH-paclitaxel (mg twice daily)										
100	6	4	ND	ND	1.05 (32)	0.74 (59)	0.71 (0.58-0.88) <sup>†</sup>	2.7 (49)	2.1 (49)	0.81 (0.61-1.06) <sup>†</sup>
200	3	2	ND	ND	0.74 (66)	1.02 (79)	1.92 (1.49-2.47) <sup>†‡</sup>	1.95 (62)	2.35 (61)	1.66 (1.45-1.91) <sup>†‡</sup>
400	23	15	ND	ND	0.99 (66)	1.15 (65)	1.32 (1.12-1.55) <sup>†</sup>	2.7 (68)	3.0 (77)	1.25 (1.01-1.54) <sup>†</sup>

\*Samples for pharmacokinetic analyses were obtain on (a) day 2 (A) and day 19 (B) for sorafenib and (b) on day 1 (A) and day 22 (B) for paclitaxel and 6-OH-paclitaxel.

<sup>†</sup> Mean ratio corrected for dose differences between cycles.

<sup>‡</sup> As there were only two paired observations at 200 mg twice daily sorafenib, both calculated ratios are provided.

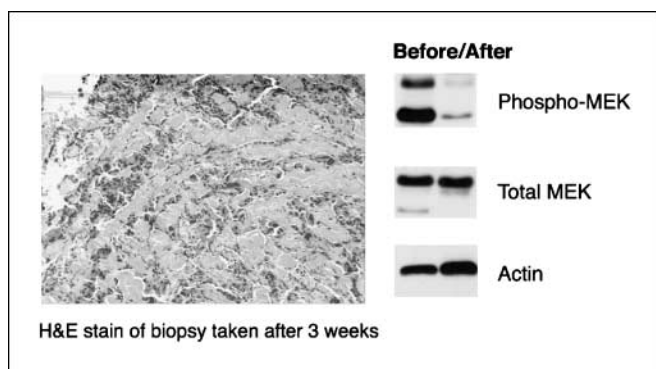


Fig. 2. Serial biopsies from responding patient with *BRAF* mutation.

2 days before the day 21 blood pressure assessments. There was no evidence of cumulative toxicity related to sorafenib. Neuropathy was typically mild and occurred with a frequency and severity expected with this dose and schedule of carboplatin and paclitaxel (27). Therefore, no effect of sorafenib on the toxicity of the chemotherapy was discernible.

The pharmacokinetics of sorafenib described here are comparable with previously reported results (5, 28, 29). Consistent with its long half-life, multiple dosing resulted in sorafenib accumulation but, as in earlier studies, the increase was not dose-related (5, 28, 29). Importantly, administration of 400 mg twice daily sorafenib had no apparent effect on the pharmacokinetics of paclitaxel. These data indicate that there may be no interaction between sorafenib and paclitaxel when sorafenib dosing is discontinued for at least 24 h before administration of paclitaxel. Our primary concern was that sorafenib may inhibit cytochrome *P450* enzymes responsible for the clearance of paclitaxel. We had less concern that sorafenib would inhibit the clearance of carboplatin, a process mediated by direct renal clearance. A phase I trial combining sorafenib with oxaliplatin showed no pharmacokinetic interaction (10). Ongoing clinical trials, including one in which sorafenib is dosed continuously, will establish the effect of sorafenib on carboplatin pharmacokinetics.

Although one study with sorafenib monotherapy in patients with melanoma yielded a low response rate, other clinical trials have shown that sorafenib is effective when used in combination with other anticancer agents, including taxanes and platinum-containing drugs (10–13). Patients with melanoma were preferentially accrued due to the observation of objective responses in several of the initial patients accrued. This combination yielded promising results, with one complete response and nine partial responses among the 24 patients with melanoma. In addition, there were 24 (62%) patients with stable disease or objective responses in the whole study population. Interestingly, the complete response and all partial response occurred in patients with melanoma and appear to be durable because these patients remained free of progression for a median duration of at least 6 months beyond discontinuation of chemotherapy. These results have led to the conduct of two randomized phase III trials in melanoma comparing sorafenib, carboplatin, and paclitaxel with carboplatin and paclitaxel. The smaller of the two trials randomized 270 patients who had failed dacarbazine- or temozolomide-containing chemotherapy regimens (30). This trial failed to show an improvement in

progression-free survival for the sorafenib. Whereas the median progression-free survival with the chemotherapy alone was prolonged in comparison with single-agent chemotherapy trials in melanoma, sorafenib does not appear to have a role in the treatment of chemotherapy-refractory melanoma. The larger of the two randomized trials (E2603) is currently randomizing 800 patients who have not previously received chemotherapy to sorafenib, carboplatin, and paclitaxel or carboplatin and paclitaxel. Overall survival is the primary endpoint and more than 500 patients have been accrued. Given the availability of another vascular endothelial growth factor targeted therapy, bevacizumab, to improve outcomes in chemotherapy-naïve but not chemotherapy-refractory patients with metastatic breast cancer, there is reason to believe that sorafenib may show similar properties in melanoma.

A high frequency of activating mutations in *BRAF* has been reported in melanoma cell lines and primary tumors suggesting a role for this oncogene in melanoma progression (25, 31). However, mutational analysis, available from 17 of the 24 melanoma patients, showed no correlation between clinical response and *BRAF* status. It is possible that activated gene product, causing phosphorylation of MEK and extracellular signal-regulated kinase, is more relevant to the cancer phenotype than merely the mutation of the gene. Although data from a single patient cannot be generalized, this patient showed significant reduction in MEK phosphorylation in serial biopsies of the cutaneous lesions 3 weeks after initiation of treatment, thus appearing to support this hypothesis. Obviously, more data will be needed before any inferences can be drawn. The apparent discordance between *BRAF* mutational status and response to treatment maybe due to the small sample size. It is also possible that the antitumor activity of sorafenib is through inhibition of tumor vasculature. This effect has been observed in preclinical models and presumably relates to effects on vascular endothelial growth factor and platelet-derived growth factor signaling (1), although one study suggests that *RAF* inhibition in endothelial cells may be responsible for antiangiogenic effects with sorafenib (32). Supporting this hypothesis is the observation that some of the responding patients developed extensive central necrosis by computed tomography early in the course of therapy, an observation also seen in renal cell carcinoma with sorafenib and other vascular endothelial growth factor signaling inhibitors.

In conclusion, this dose-escalation trial shows that sorafenib can be safely combined with carboplatin and paclitaxel. Based on these results, the recommended phase II doses for the treatment of melanoma are 400 mg orally twice daily sorafenib, carboplatin AUC6, and 225 mg/m<sup>2</sup> paclitaxel. This regimen is also well suited for evaluation in non-small cell lung cancer, ovarian cancer, and head and neck cancer, as carboplatin and paclitaxel are standard treatments for these tumor types. The responses seen in patients with melanoma warrant further investigation in a larger patient population and may help clarify the relationship between response to treatment and *BRAF* mutational status.

#### Disclosure of Potential Conflicts of Interest

K.T. Flaherty, consultant for Bayer and Onyx Pharmaceuticals; J. Schiller, speakers' bureau for Genentech, M. Redlinger, honorarium from Bayer and Onyx Pharmaceuticals; C. Lathia, C. Xia, and O. Penetrunciu, employed by Bayer Pharmaceuticals; B.L. Weber, employed by GlaxoSmithKline.

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