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ORIGINAL REPORT

Phase III Trial of Carboplatin and Paclitaxel With or Without Sorafenib in Metastatic Melanoma

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ABSTRACT

Purpose
The primary objective of this study was to determine whether carboplatin, paclitaxel, and sorafenib (CPS) improve overall survival (OS) compared with carboplatin and paclitaxel (CP) in chemotherapy-naive patients with metastatic melanoma.

Patients and Methods
In this double-blind, randomized, placebo-controlled phase III study, all patients received carboplatin at area under the [concentration-time] curve 6 and paclitaxel 225 mg/m^2 intravenously once every 21 days with random assignment to sorafenib 400 mg orally twice per day on days 2 through 19 every 21 days or placebo. The primary end point was OS, and secondary end points included progression-free survival, objective tumor response, and toxicity.

Results
In all, 823 patients were enrolled over 34 months. At final analysis, the median OS was 11.3 months (95% CI, 9.8 to 12.2 months) for CP and 11.1 months (95% CI, 10.3 to 12.3 months) for CPS; the difference in the OS distribution was not statistically significant by the stratified log-rank test, stratified on American Joint Committee on Cancer (AJCC) stage, Eastern Cooperative Oncology Group (ECOG) performance status, and prior therapy ($P = .878$). Median progression-free survival was 4.9 months for CPS and 4.2 months for CP ($P = .092$, stratified log-rank test). Response rate was 20% for CPS and 18% for CP ($P = .427$). More patients on the CPS arm had grade 3 or higher toxicities (84% *v* 78%; $P = .027$), with increased rash, hand-foot syndrome, and thrombocytopenia accounting for most of the difference.

Conclusion
Sorafenib does not improve OS when given in combination with CP for chemotherapy-naive patients with metastatic melanoma. This study establishes benchmark end points for the CP regimen in first-line therapy of metastatic melanoma.

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INTRODUCTION

Until recently, advanced melanoma has been one of the cancer types most refractory to systemic therapy. Advances have been made with novel immunologic- and oncogene-directed therapies, but median survival remains less than 14 months with less than 20% long-term survival.[1,2] Thus, additional treatment approaches are needed. Inhibiting oncogenic BRAF with selective inhibitors has recently changed the therapeutic landscape for the approximately 50% of melanomas that harbor activating *BRAF* mutations. Targeted therapy approaches for *BRAF* wild-type tumors have not yet been developed. Vascular endothelial growth factor (VEGF)–targeted anti-antigenic therapy is an approach that has improved outcomes in several common cancer types, and emerging evidence suggests that a subset of patients with melanoma may benefit from this approach.[3-9]

Sorafenib is a small molecule kinase inhibitor with in vitro potency for VEGF receptors and RAF kinases (including both BRAF and CRAF).[10] In preclinical and clinical studies, sorafenib had antitumor effects that appeared to be, in part, mediated by antiangiogenic mechanisms.[11,12] Single-agent sorafenib trials in metastatic melanoma did not show significant efficacy.[13,14] The impact of sorafenib on MAP kinase pathway signaling, at the level of RAF kinases, remains uncertain.

A phase I/II clinical trial in which 105 patients with metastatic melanoma received a combination of carboplatin (at area under the [concentration-time] curve 6), paclitaxel 225 mg/m^2 intravenously once every 3 weeks, and sorafenib 400 mg twice daily orally showed promising response rate and

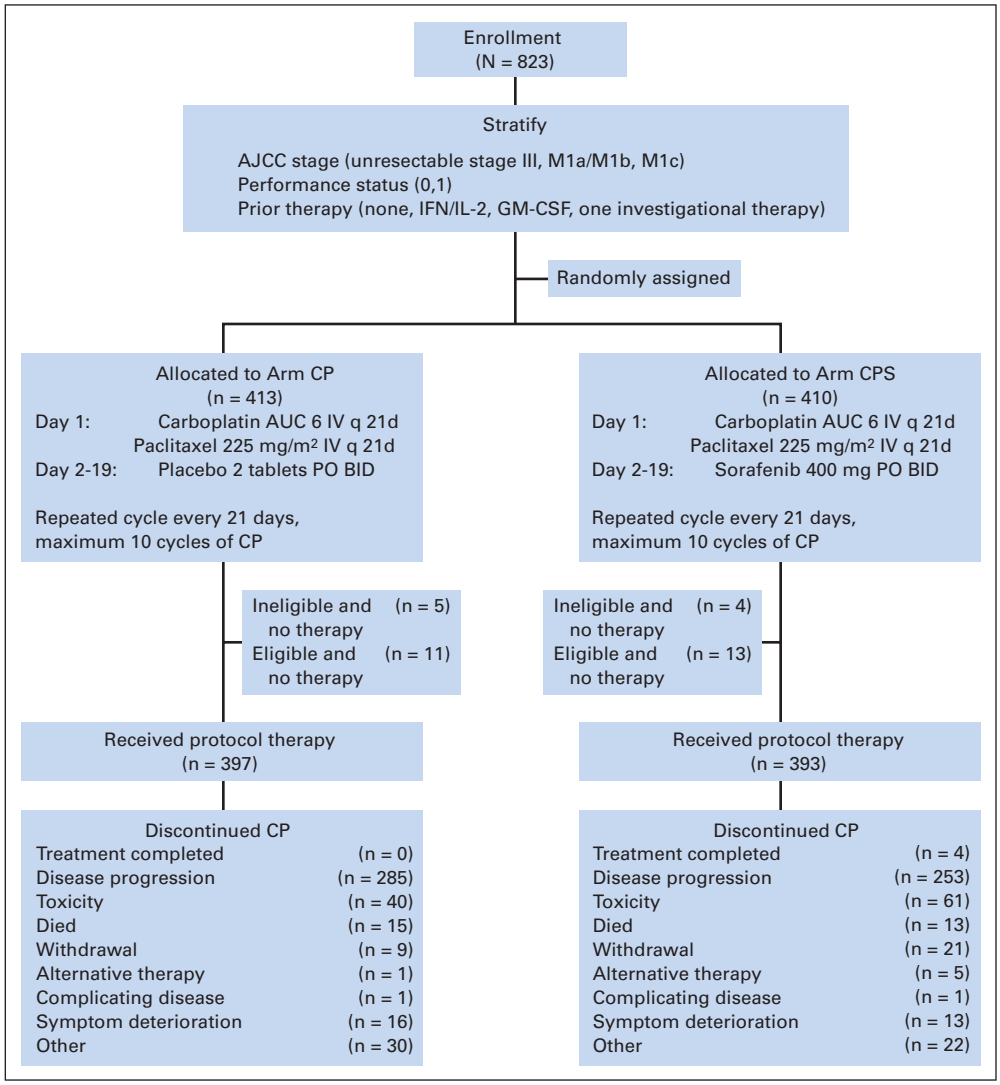

Fig 1. CONSORT diagram. AJCC, American Joint Committee on Cancer; AUC, area under the [concentration-time] curve; BID, twice per day; CP, carboplatin/paclitaxel; CPS, carboplatin/paclitaxel/sorafenib; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL-2, interleukin-2; IV, intravenously; PO, orally.

progression-free survival (PFS) in patients who were *BRAF* mutated as well as those who were *BRAF* wild-type.[15] This regimen was initially selected for development in various solid tumors, and the safe dose of sorafenib in combination with carboplatin at area under the curve 6 and paclitaxel at 225 mg/m^2 was sought to support further development in non–small-cell lung cancer in which this dose and schedule is the regulatory standard. On the basis of the results of the phase I/II trial, we proposed to evaluate in a phase III study (E2603; Carboplatin and Paclitaxel With or Without Sorafenib in Treating Patients With Unresectable Stage III or Stage IV Melanoma) the impact on overall survival (OS) of the addition of sorafenib to carboplatin and paclitaxel in patients with metastatic melanoma by using this same regimen (Figure 2). Patients were enrolled without determination of BRAF mutation status, given the lack of association between favorable treatment outcome and *BRAF* mutation status in the phase I/II trial.

PATIENTS AND METHODS

Eligibility

Eligible patients had pathologically confirmed cutaneous, mucosal, or unknown primary site melanoma, metastatic or unresectable disease, no evidence of CNS metastasis, and no prior treatment with either chemotherapy or MAP kinase pathway–targeted drugs. Other systemic therapies or radiation therapy must have been completed more than 4 weeks before enrollment. In addition, participants had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), were at least 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and had satisfactory baseline WBC, platelet count, serum creatinine, total bilirubin, AST/ALT, and international normalized ratio values. A history of invasive cancer within the previous 5 years was prohibited, as was a history of bleeding diathesis, severe intercurrent illness, use of cytochrome P450 enzyme-inducing medications, pregnancy, breast-feeding, or HIV infection. This protocol was approved by the National Cancer Institute central institutional review board and, where necessary, the local institutional review boards of participating institutions.

Treatment

Patients were randomly assigned in a double-blinded fashion to receive either carboplatin and paclitaxel (CP) or carboplatin, paclitaxel, and sorafenib (CPS; Fig 1). Additional information regarding treatment is provided in the Appendix (online only).

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3, was used to grade adverse events and to determine the need for dose modifications. The doses of carboplatin and paclitaxel were reduced following the occurrence of grade 4 neutropenia lasting more than 7 days, grade 4 neutropenia with fever (100.5°F or higher), grade

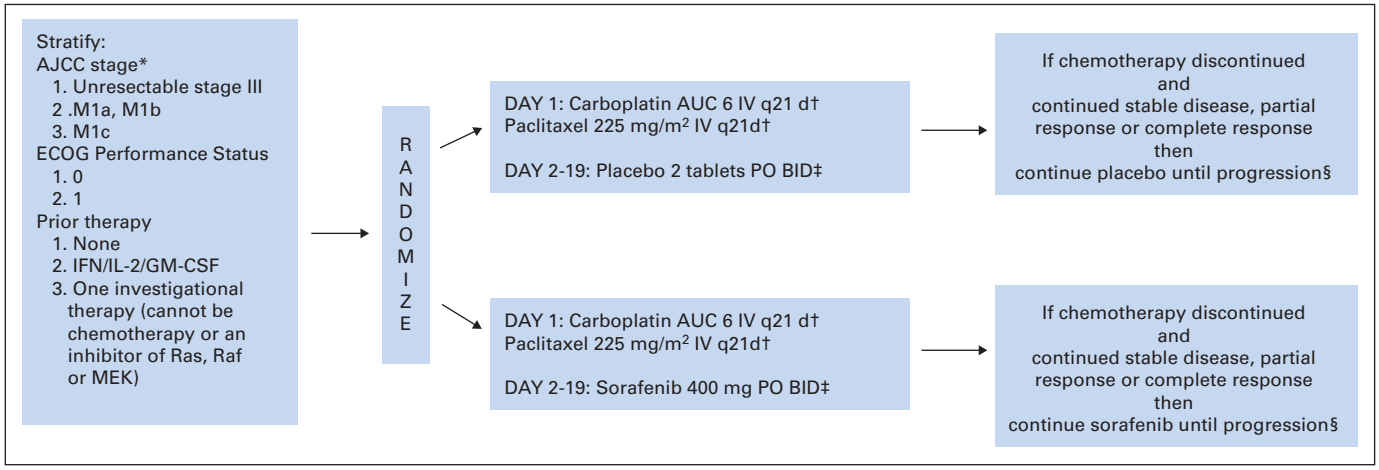

Fig 2. Trial schema. (*) Patients must have a history of melanoma of cutaneous, mucosal, or unknown primary site. Patients must not have ocular melanoma. (†) After four cycles of chemotherapy, the dose of both chemotherapy agents will be reduced by 25% for patients who have not yet had a dose reduction during earlier cycles. (‡) Sorafenib or placebo will be administered twice daily (approximately 12 hours between doses) from day 2 to day 19 of a 21-day cycle. If chemotherapy cannot be administered on schedule for any reason, patients will not be given sorafenib or placebo until day 2 of the next cycle. (§) Patients are eligible to continue sorafenib or placebo until progression after chemotherapy has been discontinued. For patients who are stable or continue to demonstrate partial or complete response, it is recommended that chemotherapy be discontinued after 10 cycles or sooner in the case of unacceptable toxicity. After the cessation of chemotherapy, sorafenib or placebo will be taken twice daily continuously throughout the cycle. AJCC, American Joint Committee on Cancer; AUC, area under the [concentration-time] curve; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL-2, interleukin-2; IV, intravenously; PO, orally.

4 thrombocytopenia, lack of recovery of absolute neutrophil count or platelet count to pretreatment levels by day 28 of each cycle, or any grade 3 or 4 nonhematologic toxicity (including neuropathy) attributed to carboplatin or paclitaxel. Grade 4 hypersensitivity reactions led to permanent discontinuation of the responsible agent.

In the event of grade 3 toxicity believed to be secondary to sorafenib or placebo, they were discontinued until the toxicity resolved to grade 1 or lower. Treatment was resumed with a 50% dose reduction. For common grade 3 sorafenib-associated toxicities (eg, rash, hand-foot syndrome, stomatitis, or diarrhea), re-escalation of sorafenib dose was permitted after one full cycle of reduced dose and lack of significant toxicity. Dose reductions were permanent for grade 4 toxicity.

Statistical Design

The primary objective of this study was to determine whether the addition of sorafenib to carboplatin and paclitaxel could improve OS compared with CP. The primary comparison was performed as an intention-to-treat analysis (defining groups by assigned treatment) among all patients by using a two-sided log-rank test stratified on American Joint Committee on Cancer (AJCC) stage, ECOG PS, and prior therapy status and an overall type I error of 5%.

A total of 800 patients were planned and 677 deaths were anticipated to provide at least 90% power to detect a 22.5% difference in median OS while maintaining a significance level of 2.5% in a one-sided log-rank test, assuming exponential failure and a median survival of 9 months with CP and 11.6 months with CPS. The accrual rate was expected to be about 20 patients per month, and accrual was projected to be completed in 40 months. Additional statistical analysis information is provided in the Appendix.

RESULTS

This study accrued 823 patients between June 23, 2005, and April 22, 2008. The overall accrual rate was 24 patients per month, which exceeded the expected accrual rate of 20 patients per month. Four hundred thirteen patients were randomly assigned to CP and 410 patients were randomly assigned to CPS. The CONSORT diagram (Fig 1) provides the reasons for discontinuation of protocol therapy (Fig 2). The median number of cycles was five in both cohorts. Among the 823 patients, 96 were unblinded during the course of the study, with 90 (59, CP; 31, CPS) as a result of disease progression. Six patients were unblinded as a result of toxicity (five total: one, CP; four, CPS) or death (one, CPS).

Randomization resulted in good balance between the treatment groups for age, sex, race, AJCC stage, ECOG PS, and prior therapy (Table 1). Forty-two percent of patients receiving CP and 39% of patients receiving CPS had prior immunotherapy. Fifty-seven percent

Table 1. Patient Characteristics

Characteristic	Carboplatin/ Paclitaxel (%) (n = 413)	Carboplatin/Paclitaxel/ Sorafenib (%) (n = 410)
Male sex	61	66
Median age, years	59	61
AJCC stage		
Unresectable stage III	9	9
M1a/M1b	34	34
M1c	57	57
Serum LDH at baseline		
Normal	61	55
Above normal	39	45
ECOG performance status		
0	61	61
1	39	39
Prior systemic therapy		
None	58	59
Interferon, IL-2, GM-CSF	38	37
Investigational therapy	4	4

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-2, interleukin-2; LDH, lactate dehydrogenase.

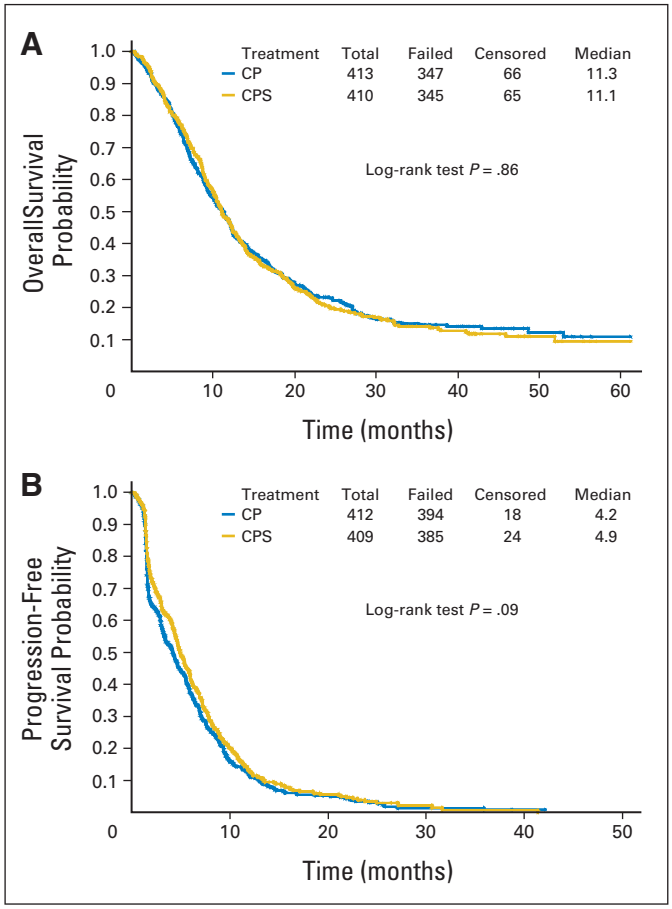

Fig 3. (A) Overall survival, determined by using the Kaplan-Meier method for the intention-to-treat population, from time of study registration. (B) Progression-free survival; two patients who were inevaluable for progression-free survival were excluded. CP, carboplatin/paclitaxel; CPS, carboplatin/paclitaxel/sorafenib.

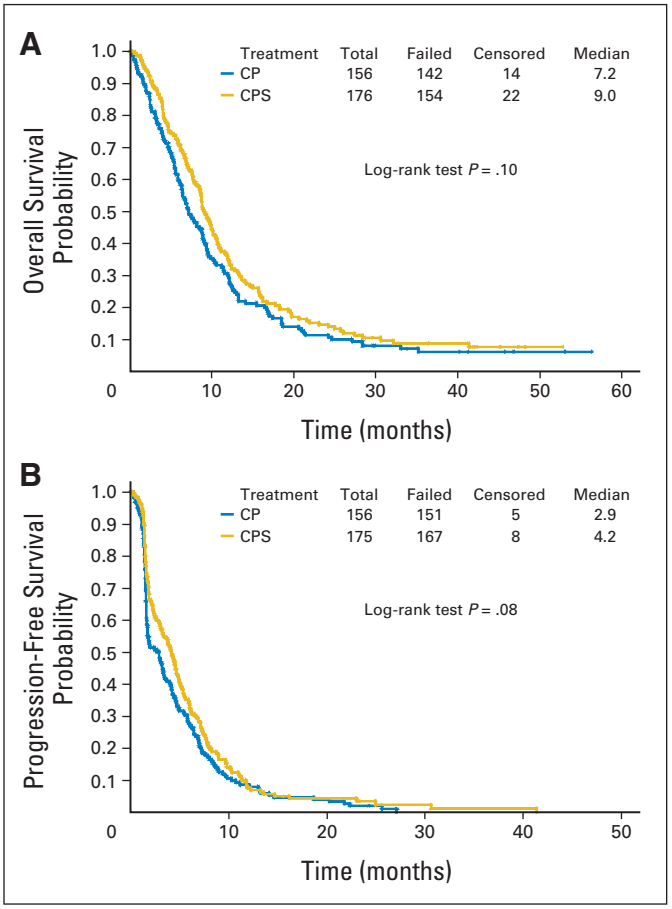

Fig 4. (A) Overall survival and (B) progression-free survival (PFS) for a subset of patients with increased lactate dehydrogenase at baseline from the time of study registration determined by using the Kaplan-Meier method. CP, carboplatin/paclitaxel; CPS, carboplatin/paclitaxel/sorafenib.

of patients on each arm were AJCC M1c. Serum lactate dehydrogenase (LDH) levels were increased in 39% of patients receiving CP and 45% of patients receiving CPS.

As of January 12, 2011, 692 patients had died (347, CP; 345, CPS), and full information (677 deaths) had been reached. The median OS was 11.3 months (95% CI, 9.8 to 12.2 months) for CP and 11.1 months (95% CI, 10.3 to 12.3 months) for CPS. Figure 3A displays the OS distribution by treatment arm estimated by the Kaplan-Meier method, and the two survival curves were not statistically different by the stratified log-rank test ($P = .863$). The hazard ratio (HR) for CPS versus CP was 1.01 for OS with the univariate Cox model, and the 95% repeated CI of Jennison-Turnbull was 0.87 to 1.18 (using the corresponding critical value of 2.03). The repeated CI did not contain the hypothesized alternative HR of 0.775 for CPS/CP.

Among the 821 patients with PFS data, there were 779 PFS events (394, CP; 385, CPS). The major explanation for missing PFS data was removal from study for toxicity or there was no explanation provided and no reporting of subsequent radiographic follow-up (Fig 2). The median PFS was 4.2 months (95% CI, 3.4 to 4.7 months) for CP and 4.9 months (95% CI, 4.5 to 5.6 months) for CPS (stratified log-rank $P = .092$). The HR for CPS versus CP was 0.90 (95% CI, 0.78 to 1.03) for PFS from the univariate Cox model (Fig 3B).

Subgroup analyses were performed on the basis of stratification factors used for random assignment because these are known prognostic factors in metastatic melanoma. LDH is a well described prognostic factor in metastatic melanoma. The median OS was 8.7 months (95% CI, 7.6 to 9.3 months) for patients with increased LDH and 13.8 months (95% CI, 12.3 to 14.9 months) for patients with normal LDH (log-rank test $P < .001$). We explored the possibility that sorafenib might exert a treatment effect within these LDH-defined subgroups. The 791 patients with known LDH level at registration were included in the analysis and were stratified into two groups: 459 patients had normal LDH (243, CP; 216, CPS), and 332 patients had increased LDH (156, CP; 176, CPS). In patients with increased LDH level, the median OS was 7.2 months (95% CI, 6.3 to 8.9 months) for CP and 9.0 months (95% CI, 8.4 to 10.1 months) for CPS (log-rank $P = .095$; Fig 4A). The median PFS was 2.8 months (95% CI, 1.7 to 3.4 months) for CP and 4.2 months (95% CI, 3.0 to 4.8 months) for CPS, and the two PFS curves were not significantly different (log-rank $P = .078$; Fig 4B). No differences in outcome were detected in the normal LDH subgroup.

Clinical response was assessed by using RECIST 1.0 criteria (Table 2). The overall response rate for the CP group was 18.2% (95% CI, 14.6% to 22.2%; 75 of 413) compared with an overall response rate of 20.5% (95% CI, 16.7% to 24.7%; 84 of 410) for the CPS group

Table 2. Radiographic Response by Treatment Group

Response	Carboplatin/Paclitaxel (n = 413) No.	%	Carboplatin/Paclitaxel/Sorafenib (n = 410) No.	%
CR	5	1.2	3	0.7
PR	70	17.0	81	19.8
SD	160	38.7	166	40.5
PD	119	28.8	101	24.6
Unevaluable*	59	14.3	59	14.4

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
*The two most common reasons for patients being unevaluable were failure to start assigned therapy and death prior to radiographic restaging.

(Fisher's exact test $P = .427$). The median duration of overall response in the 159 responders (complete response plus partial response) was 6.7 months (95% CI, 4.9 to 8.3 months) for the CP group and 6.3 months (95% CI, 5.1 to 7.8 months) for the CPS group (log-rank $P = .519$).

The incidence rates of grade 3 or higher toxicity were 78.3% (95% CI, 74.0% to 82.3%) and 84.5% (95% CI, 80.5% to 87.9%) for the CP and CPS groups, respectively (Table 3). CPS had a significantly higher toxicity rate than CP (Fisher's exact test $P = .027$). The most common types of grade 3 or higher toxicity are listed in Table 3. These included neutropenia, leukopenia, fatigue, sensory neuropathy, anemia, thrombocytopenia, rash/desquamation, hand-foot syndrome, and hypertension. CPS was associated with a significantly higher rate of rash/desquamation, thrombocytopenia, hand-foot syndrome, sensory neuropathy, hypertension, diarrhea, anorexia, and hyponatremia than CP (Fisher's exact test $P < .05$). A single case of cutaneous squamous cell carcinoma was diagnosed and was identified in a patient receiving sorafenib. There were 17 treatment-related deaths as determined by the treating physician: eight on the CP arm and nine on the CPS arm. Concomitant disease progression was documented in only one patient.

Table 3. Most Common Grade 3, 4, and 5 Adverse Events by Treatment Arm

Adverse Event	Carboplatin/Paclitaxel Arm (%) (n = 397)	Carboplatin/Paclitaxel/Sorafenib Arm (%) (n = 393)	*P*
Neutrophils	49.1	48.9	.943
Hemoglobin	7.1	7.6	.786
Leukocytes	22.9	27.2	.164
Platelets	8.8	23.4	< .001
Hypertension	1.3	4.6	.004
Fatigue	14.1	16.0	.487
Rash/desquamation	2.0	14.8	< .001
Hand-foot syndrome	0.3	12.0	< .001
Sensory neuropathy	14.9	20.6	.040
Febrile neutropenia	4.0	6.1	.064
Diarrhea without prior colostomy	3.8	7.1	.042
Anorexia	2.3	5.3	.026
Allergic reaction	2.8	5.1	.102
Lymphopenia	4.3	5.1	.617
Dehydration	4.8	5.3	.748
Hyponatremia	2.3	5.3	.026
Hyperglycemia	4.8	4.3	.865
Muscle pain	5.5	4.6	.627
Worst			.071
Grade 3	34.2	41.7	
Grade 4	41.6	40.4	
Grade 5	2.5	2.3	
Grades 3 to 5	78.2	84.4	.027

Note. Table lists adverse events whose incidence proportion was ≥ 3% in either treatment arm. Fisher's exact test was used for the comparison between the two treatment arms.

DISCUSSION

Despite the promising antitumor activity of sorafenib and chemotherapy combinations in patients with unresectable stage III or stage IV melanoma reported in previous clinical trials, this double-blind randomized phase III trial failed to demonstrate statistically significant benefits in OS for CPS therapy compared with CP and placebo therapy. There was a 1.8-month difference in median OS and a 1.4-month difference in median PFS between the two regimens in patients with increased LDH at baseline; however, these differences were not statistically significant ($P = .094$ and $P = .078$, respectively). This subgroup analysis was not prospectively powered. In retrospect, we had 49% power to detect a difference of this magnitude in OS with a two-sided type I error of 5% without interim analysis. A sample size of 770 patients would be needed to have 80% power for the OS analysis of this subgroup under the original design.

Previous trials of single-agent sorafenib in patients with metastatic melanoma have shown low response rates and no clear improvement in PFS compared with historical controls.[13,14] The subset of patients with evidence of disease control were not more or less likely to have *BRAF*-mutated tumors. A separately conducted and previously reported randomized trial was initiated after this study.[16] Two hundred seventy patients with metastatic melanoma that was refractory to chemotherapy regimens containing dacarbazine or temozolomide were randomly assigned to receive carboplatin and paclitaxel with or without sorafenib. PFS was the primary end point, and the trial was not powered for OS. A PFS advantage was not observed. The median PFS was 4.1 months for the CP plus placebo arm and 4.0 months for the CP plus sorafenib arm (HR, 0.91; 99% CI, 0.63 to 1.31; two-sided log-rank $P = .49$). In the chemotherapy-naive setting, we observed similar PFS durations of 4.2 and 4.9 months in the respective arms. Sorafenib in combination with dacarbazine did appear to improve PFS compared with dacarbazine alone (4.9 months *v* 2.7 months; HR, 0.665; $P = .068$); however, this randomized phase II result has not been followed up with a phase III trial.[17]

This trial rules out a clinical benefit from sorafenib in combination with carboplatin and paclitaxel in unselected patients. The possibility remains that sorafenib could provide benefit in a small, biomarker-defined subpopulation. Had we stratified patients on the basis of *BRAF* mutation status, a more definitive statement could be made about the effect of sorafenib in the *BRAF*-mutant population. Our results suggest that patients with an increased LDH may contain a subpopulation that derives a treatment benefit. If so, this would add to observations made with vatalanib (PTK787) in colon cancer and bevacizumab in metastatic melanoma[9,18] and further suggests that the

mechanism of this benefit may relate to its anti-VEGF effects. Furthermore, two small-molecule VEGF receptor (VEGFR) inhibitors with more potent and selective anti-VEGFR inhibition than sorafenib have shown significant single-agent activity in patients with metastatic melanoma.[19,20] Given this information and the fact that sorafenib is relatively inactive as a single agent in patients with melanoma, investigation of other anti-VEGF strategies in combination with chemotherapy in patients with increased LDH would appear to offer more promise than the CPS regimen.

The combination of carboplatin and paclitaxel has never been compared with single-agent chemotherapy in a randomized trial in patients with melanoma, but it has been included in the treatment guidelines of the National Comprehensive Cancer Network melanoma panel. In this phase III trial, we observed a response rate of 18%, median PFS of 4.1 months, and median OS of 11.3 months for CP. Among dacarbazine- or temozolomide-refractory patients in the trial previously reported by Hauschild et al,[16] the response rate was 11%, median PFS was 4.0 months, and median OS was 9.7 months. These results compare favorably to the same end points for dacarbazine as reported in the last three published phase III trials[21-23] using dacarbazine as a control arm: response rate of 7.5% to 13.5%, median PFS of 1.6 months (reported in only one trial), and median OS of 6.4 to 7.8 months. By the criteria in the analysis of Korn et al,[24] this regimen might be worthy of further evaluation as a potentially superior disease-controlling regimen than dacarbazine, the single-agent chemotherapy standard in melanoma. Ipilimumab has a relatively low response rate (11%) and short median time to progression (2.9 months) when administered as a single agent in patients for whom prior therapy failed. However, responding patients and some with disease stabilization have durable benefit that confers a survival benefit. Conversely, vemurafenib has a high response rate (48%) and more prolonged median PFS (5.3 months) as a single agent in a phase III trial and clearly represents the preferred drug therapy for patients whose tumors bear *BRAF* mutations.

The ability of sorafenib to significantly inhibit the MAP kinase pathway in melanoma remains unproven. Approximately 50% of melanomas harbor *BRAF* mutations and another 20% harbor activating *NRAS* mutations.[25,26] Preclinical data have shown that sorafenib can inhibit the MAP kinase pathway and inhibit the proliferation of cells with either *BRAF* or *NRAS* mutations in vitro.[11] If sorafenib mediated antitumor effects in these subpopulations, we would have expected our study to be positive, given that approximately 70% of patients enrolled would be expected to have either a *BRAF* or *NRAS* mutation. Given the recent evidence that selective BRAF inhibitors produce substantial efficacy in patients with melanomas that harbor activating *BRAF* mutations, it appears that sorafenib is unable to achieve similar degrees of MAP kinase pathway inhibition in vivo.[2] This lack of biologic effect likely accounts for the inability of sorafenib to improve outcomes in comparison to vemurafenib, which is markedly more active. The most likely explanation for lack of molecular efficacy of sorafenib in BRAF- or NRAS-driven tumors is the fact that maximum-tolerated dose of sorafenib is defined by toxicities that appear unrelated to BRAF or CRAF antagonism and are more likely related to inhibition of VEGFR. Although this has not been directly proven, the toxicity profile of sorafenib has more in common with those of sunitinib and pazopanib,[27,28] two potent inhibitors of VEGFR, than with vemurafenib. These presumed off-target effects likely prohibit administration of effective BRAF/CRAF inhibitory doses.

The inability to corroborate the earlier findings of a large, uncontrolled trial of sorafenib, carboplatin, and paclitaxel in patients with melanoma likely relates to patient selection. Although the eligibility criteria for the previously reported, uncontrolled trial were nearly identical to those used in this phase III trial, subjective elements of patient selection can substantially influence patients' prognostic factors and time-to-event end points.[15] Notably, the objective response rate of 26% is only slightly higher than the 18% response rate observed in this phase III trial. PFS was the most divergent end point and could relate to differences in prognostic factors. The OS estimate from the previous trial appeared far superior to that in previous phase III trials. And, in this phase III trial, median OS for both arms was substantially longer than that for cohorts treated within the previous decade.

In conclusion, sorafenib does not improve OS, PFS, or response rate in combination with carboplatin and paclitaxel in chemotherapy-naive patients with metastatic melanoma. Sorafenib appeared to be the best available MAP kinase pathway inhibitor when this study was initiated and was demonstrated to be an effective anti-antigenic therapy in other cancer types. In the intervening years, more active MAP kinase pathway inhibitors (targeting BRAF and MEK) and antiangiogenic drugs have emerged that appear to be of higher priority for further evaluation, particularly in subsets of patients with melanoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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