Original Article

A Phase II Trial of Nab-Paclitaxel (ABI-007) and Carboplatin in Patients With Unresectable Stage IV Melanoma

A North Central Cancer Treatment Group Study, N057E[1]

Lisa A. Kottschade, RN, CNP[1]; Vera J. Suman, PhD[1]; Thomas Amatruda, III, MD[2]; Robert R. McWilliams, MD[1]; Bassam I. Mattar, MD[3]; Daniel A. Nikcevich, MD[4]; Robert Behrens, MD[5]; Tom R. Fitch, MD[6]; Anthony J. Jaslowski, MD[7]; and Svetomir N. Markovic, MD, PhD[1]

BACKGROUND: There is increasing evidence that paclitaxel and carboplatin are clinically active in the treatment of metastatic melanoma (MM). ABI-007 is an albumin-bound formulation of paclitaxel that has demonstrated single-agent activity against metastatic melanoma. **METHODS:** A parallel phase II trial was conducted in patients with unresectable stage IV melanoma who were either chemotherapy naive (CN) or previously treated (PT). The treatment regimen consisted of ABI-007 (100 mg/m^2) and carboplatin area under the curve (AUC2) administered on days 1, 8, and 15 every 28 days. The primary aim of this study was objective response rate (RECIST). **RESULTS:** Seventy-six patients (41 CN and 35 PT) were enrolled between November 2006 and July 2007. Three patients withdrew consent prior to starting treatment. The median number of treatment cycles was 4. There were 10 (25.6%) responses (1 complete response [CR] and 9 partial responses [PRs]) in the CN cohort (90% CI, 16.7%-42.3%) and 3 (8.8%) responses (3 PRs) in the PT cohort (90% CI, 2.5%-21.3%). Median progression-free survival was 4.5 months in the CN cohort and 4.1 months in the PT cohort. Median overall survival (OS) was 11.1 months in the CN group and 10.9 months in the PT group. Severe toxicities in both groups (Common Terminology Criteria for Adverse Effects v.3.0 $\geq$grade 3) included neutropenia, thrombocytopenia, neurosensory problems, fatigue, nausea, and vomiting. **CONCLUSIONS:** The weekly combination of ABI-007 and carboplatin appears to be moderately well tolerated, with promising clinical activity as therapy in patients who are chemotherapy naive and with modest antitumor activity in those previously treated. *Cancer* 2011;117:1704–10. © *2010 American Cancer Society.*

KEYWORDS: metastatic melanoma, nab-paclitaxel, carboplatin, chemotherapy, stage IV, unresectable.

Patients diagnosed with metastatic (stage IV) melanoma face a poor prognosis, with a median overall survival (OS) time of 6-9 months and 5-year survival of approximately 5%.[1] Currently, dacarbazine remains the only Food and Drug Administration (FDA)-approved chemotherapy agent for stage IV melanoma, with response rates of less than 20% and no improvement in OS.[2] Several combination regimens have produced response rates of 30%-50% but with higher toxicity rates and no impact on OS.[3-6] Thus, the need for more effective therapy for metastatic melanoma remains.

Corresponding author: Lisa A. Kottschade, RN, CNP, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Fax: (507) 284-1803; kottschade.lisa@mayo.edu

[1]Mayo Clinic Rochester, Rochester, Minnesota; [2]Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, Minnesota; [3]Wichita Community Clinical Oncology, Wichita, Kansas; [4]Duluth CCOP, Duluth, Minnesota; [5]Iowa Oncology Research Association CCOP, Des Moines, Iowa; [6]Mayo Clinic Arizona, Scottsdale, Arizona; [7]St. Vincent Regional Cancer Center CCOP, Green Bay, Wisconsin

Additional participants: Carle Cancer Center CCOP, Urbana, Illinois (Kendrith M. Rowland, Jr., MD); Cedar Rapids Oncology Project CCOP, Cedar Rapids, Iowa (Martin Wiesenfeld, MD); Meritcare Hospital CCOP, Fargo, North Dakota (Preston D. Steen, MD); Michigan Cancer Research Consortium, Ann Arbor, Michigan (Philip J. Stella, MD); Rapid City Regional Oncology Group, Rapid City, South Dakota (Richard C. Tenglin, MD); CentraCare Clinic, St. Cloud, Minnesota (Donald Jurgens, MD); Siouxland Hematology-Oncology Associates, Sioux City, Iowa (Donald B. Wender, MD); Toledo Community Hospital Oncology Program CCOP, Toledo, Ohio (Paul L. Schaefer, MD); Upstate Carolina CCOP, Spartanburg, South Carolina (James D. Bearden, III, MD); Missouri Valley Cancer Consortium, Omaha, Nebraska (Gamini S. Soori, MD); Cancer Care Associates, Tulsa, Oklahoma (Allan Keller, MD); Montana Cancer Consortium, Billings, Montana 59101 (Benjamin T. Marchello, MD); Illinois Oncology Research Association, Peoria, Illinois (John W. Kugler, MD); Hematology & Oncology of Dayton, Inc., Dayton, Ohio (Howard M. Gross, MD); Medcenter One Health Systems, Bismarck, North Dakota (Edward J. Wos, MD); Mayo Clinic Florida, Jacksonville, Florida (Edith A. Perez, MD); Lehigh Valley Hospital, Allentown, Pennsylvania (Suresh Nair, MD).

The content is solely the responsibility of the authors and does not necessarily represent the views of the National Cancer Institute or the National Institutes of Health.

DOI: 10.1002/cncr.25659, **Received:** May 13, 2010; **Revised:** August 17, 2010; **Accepted:** August 18, 2010, **Published online** November 8, 2010 in Wiley Online Library (wileyonlinelibrary.com)

The combination of carboplatin and paclitaxel has been shown to be active in a wide range of malignancies including metastatic melanoma.[7-12] Response rates in a phase II trial setting and a retrospective review showed an objective response rate (ORR) of this combination of approximately 20%-25%,[7,8] with a third small randomized phase II trial showing no objective responses but stabilization of disease of approximately 20% in the combination paclitaxel + carboplatin arm.[9] In addition a recently reported randomized phase II trial utilizing paclitaxel and carboplatin ± bevacizumab/placebo showed a response rate for the control arm of approximately 16.4%.[10] Two phase III trials examining the impact of adding sorafenib to paclitaxel and carboplatin (in both chemotherapy-naive[11] and previously treated[12] settings) reported an ORR of 16% and 11%, respectively, in each of the paclitaxel/carboplatin arms, with progression-free survival (PFS) of 4.1 months[11] and 17.9 weeks, respectively.[12] Treatments were generally well tolerated, with cytopenias, neuropathy, nausea, vomiting and hypersensitivity reactions as the primary toxicities.

Given the modest clinical efficacy of the combination of paclitaxel and carboplatin for therapy of stage IV melanoma[7-12] and the development of ABI-007 (Abraxane, nab-paclitaxel), a solvent-free, albumin-bound formulation of paclitaxel designed to reduce the Cremophor vehicle-associated toxicity of paclitaxel suggested examining the antitumor effect of the combination of ABI-007 and carboplatin.

There are at least 2 potential advantages of the use of ABI-007 in place of paclitaxel in combination with carboplatin for patients with metastatic melanoma. First, ABI-007 has the ability to deliver a higher dose of paclitaxel. This was clearly demonstrated in the metastatic breast cancer setting in a randomized phase III study comparing ABI-007 at 260 mg/m^2 to paclitaxel at 175 mg/m^2 on a schedule of every 3 weeks.[13] The ABI-007 arm demonstrated significantly higher response rates and time to progression, as well as a significantly lower incidence of grade 3 or 4 neutropenia, despite the increased dose of paclitaxel administered in the ABI-007 arm.[13] There was an increased incidence of grade ≥3 peripheral neuropathy in the ABI-007 arm, but with a more rapid recovery. In addition, ABI-007 obviates "allergic" premedications and shortens infusion time relative to paclitaxel. Of particular interest for melanoma is the ability of ABI-007 (and not paclitaxel) to bind SPARC (secreted protein acidic and rich in cysteine), a protein highly expressed on malignant melanocytes.[14] This is a potentially important pathway in delivering ABI-007 to the tumor at high concentrations.[14,15] This may have explained the results of single-agent ABI-007 therapy in patients with previously treated stage IV melanoma, demonstrating clinical activity superior to prior studies of paclitaxel,[16] and as such, the substitution of ABI-007 for paclitaxel in combination with carboplatin for the treatment of metastatic melanoma may offer greater clinical benefit.

A phase I trial of 3 different schedules of ABI-007 administered in combination with carboplatin in patients with solid tumors found a maximum tolerated dose for ABI-007 (MTD) of 300 mg/m^2 every 3 weeks, 100 mg/m^2 on days 1, 8, and 15 every 28 days, and 125 mg/m^2 on days 1 and 8 every 21 days, all with carboplatin AUC 6 on day 1.[17,18] This trial enrolled 10 (of 41) patients with metastatic melanoma, of whom 3 patients had a PR on the weekly regimen and 3 patients had stable disease (SD) on the every-3-weeks regimen.[17,18] There was a higher degree of severe (≥grade 3) neutropenia and thrombocytopenia with the weekly regimen.

Here we present the results of a phase II clinical trial utilizing a combination of carboplatin (AUC 2) and ABI-007 (100 mg/m^2) administered as a weekly regimen (on days 1, 8, and 15 of a 28-day treatment cycle) to both chemotherapy-naive and previously treated (no prior exposure to taxanes) patients with stage IV melanoma. We selected the weekly dosing regimen of carboplatin in the hope of decreasing the incidence of ≥grade 3 cytopenias, as was seen in the phase I trial.

PATIENTS AND METHODS

This study consisted of 2 parallel phase II clinical trials (cohorts) to assess the antitumor activity and safety profile of the combination of carboplatin and ABI-007 in patients with unresectable stage IV malignant melanoma who either were previously treated with chemotherapy in the metastatic setting (cohort 1) or were chemotherapy naive in the metastatic setting (cohort 2). This study was a multi-institution cooperative group study conducted through the North Central Cancer Treatment Group. All patients provided signed informed written consent. This study was approved by the institutional review boards of all participating institutions.

Eligible patients had to be ≥18 years of age with unresectable, histologically confirmed stage IV melanoma. Additional eligibility criteria included measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), Eastern Cooperative Oncology Group performance status (PS) of 0-2, life expectancy ≥3

months, adequate hematologic and hepatic function, and ≥4 weeks since the last chemotherapy (cohort 1 only), radiation therapy, or immunotherapy. Exclusion criteria included any prior treatment with platinum or taxanes (cohorts 1 and 2), any prior chemotherapy for metastatic disease (cohort 2), active infection, New York Heart Association Class III or IV, peripheral neuropathy ≥grade 2, other malignancy <5 years (except for nonmelanomatous skin cancer or carcinoma in situ of the cervix), or untreated metastatic melanoma to the brain or progression of brain metastasis within 3 months of study entry. Women who were pregnant or breastfeeding were not enrolled.

Study Design and Treatment

Eligible patients (both cohorts) were treated with 100 mg/m^2 of ABI-007 by intravenous infusion over 30 minutes, followed by carboplatin with a target AUC of 2 (by Calvert formula with Cockroft and Gault Equation and actual body weight) over 30 minutes on days 1, 8, and 15 of a 28-day cycle, for a maximum of 8 cycles. If patients did not develop excessive toxicity or progressive disease, treatment beyond 8 cycles was at the discretion of the treating physician.

Within 14 days of registration, patients underwent a complete physical exam, assessment of performance status, complete blood cell count, comprehensive metabolic panel including lactic dehydrogenase, and a tumor assessment by conventional CT or MRI or spiral CT. Prior to each cycle of treatment, patients underwent a physical exam, toxicity assessments, and blood draws for hematologic and chemistry groups. Tumor status was assessed every 8 weeks until progression using RECIST criteria.

On day 1 of each treatment cycle, treatment was held if absolute neutrophil count (ANC) was <1500/mm^3 or platelet count (PLT) was <100,000/mm^3 or the patient developed a grade ≥2 aspartate aminotransferase, grade ≥2 neuropathy, or other grade ≥3 nonhematologic toxicity. When patients had recovered from these toxicities, treatment was restarted with a 20% dose reduction in both agents. On day 8 or 15 of each treatment cycle, treatment was omitted if ANC was <1000/mm^3 or PLT was <100,000/mm^3 or the patient developed either a grade ≥2 neuropathy or grade ≥3 nonhematologic toxicity. Study treatment was terminated if toxicities did not recover to acceptable levels within 4 weeks and/or if patients required a third dose reduction due to toxicity.

All patients received standard supportive care, including antiemetics, antibiotics, blood/platelet transfusions, erythropoietin, and colony-stimulating factors at the discretion of the treating physician.

Statistical Considerations

The primary endpoint for both trials was the clinical response rate, defined as the number of eligible patients whose disease met RECIST criteria 1.0 for response, that is, a complete response (CR) or partial response (PR) on 2 consecutive evaluations at least 8 weeks apart divided by the number of eligible patients who began treatment. For those patients whose disease responded to treatment, the duration of response was defined as the time from the first tumor evaluation, when an objective status of CR or PR was assigned, to date of disease progression.

For cohort 1 (prior chemotherapy, PT), a sample of 35 patients was to be enrolled so that a 1-sided alpha = 0.10 1-sample test of proportions would have at least a 90% chance of detecting whether the ORR was greater than 5% when it was at least 20%. If at least 4 patients of the 35 eligible patients enrolled had a tumor response without excessive toxicity, the regimen would be considered for further testing in this patient population.

For cohort 2 (chemotherapy naive, CN), a sample of 35 patients was to be enrolled so that a 1-sided alpha = 0.10 1-sample test of proportions would have at least a 90% chance of detecting whether the ORR was greater than 15% when it was at least 35%. If at least 9 patients of the 35 eligible patients enrolled had a tumor response without excessive toxicity, the regimen would be considered for further testing in this patient population.

A 90% confidence interval for the response rate was constructed using the properties of the binomial distribution. Progression-free survival time was defined as the time elapsed from registration to progression of disease or death without prior documentation of progressive disease. Survival time was defined as the time elapsed from registration to death due to any cause. Time-to-event distributions was estimated using the Kaplan-Meier method.[19] Toxicities were graded and attribution assigned by treating physicians using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

RESULTS

Patient Characteristics

Seventy six patients were accrued into this trial between November 15, 2006, and July 31, 2007. Three patients (1 PT and 2 CN) withdrew consent prior to the start of treatment. After the close of enrollment, 1 patient who

Table 1. Patient Characteristics

Patient Characteristics	Previously Treated Patients (Cohort 1), n=34	Chemotherapy Naive Patients (Cohort 2), n=39
Median age, y (range)	60 (28-84)	59 (23-91)
Male	23 (67.6%)	23 (59.0%)
M stage		
M1a	5 (14.7%)	7 (18.0%)
M1b	11 (32.4%)	13 (33.3%)
M1c	18 (52.9%)	19 (48.7%)
ECOG performance status		
0	22 (64.7%)	24 (61.5%)
1	11 (32.4%)	13 (33.3%)
2	1 (2.9%)	2 (5.1%)
Preexisting signs and symptoms		
Grade 3 fatigue	1 (2.9%)	—
Grade 2 fatigue	3 (8.8%)	4 (10.3%)
Grade 1 neurosensory difficulties	5 (14.7%)	5 (12.8%)
Prior therapies		
Radiation therapy	16 (47.1%)	8 (20.5%)
Immunologic therapy	8 (23.5%)	10 (25.6%)
Hormonal therapy	—	2 (5.1%)
Vaccine therapy	3 (8.8%)	2 (5.1%)
Chemotherapy[a]	34 (100%)	0
Temozolomide	23 (67.6%)	
Temozolomide + thalidomide	2 (5.8%)	
Everolimus	4 (11.8%)	
Dacarbazine	7 (20.5%)	
Elevated LDH at time of registration		
Yes	8 (24%)	16 (41%)
No	19 (56%)	18 (46%)
Baseline LDH not provided	7 (20%)	5 (13%)

[a] Two patients had received 2 prior chemotherapy regimens.

was registered as having had prior chemotherapy was found to have received immunotherapy not chemotherapy and as such was reassigned to the CN cohort. Thus, the PT cohort included the 34 patients (67.6% male) ages 28-84 years (median age, 60 years) who began study treatment, and the CN cohort included the 39 patients (59.0% male) ages 23-81 years (median age, 59 years) who began study treatment. The characteristics of these cohorts are presented in Table 1.

Treatment Course

Cohort 1 (PT)

At the time of this report, all patients have discontinued study treatment. The median number of cycles administered was 4 cycles (total, 135 cycles; range, 1-10 cycles). Fifteen patients (44.1%) received 85% or more of the total ABI-007 dose they should have received for their time on treatment. Twenty-one patients (61.8%) omitted day 8 and/or 15 of treatment (8 patients), had at least 1 dose reduction (3 patients), or both (10 patients), primarily because of severe neutropenia, fatigue, and neuropathy. The most common severe (≥grade 3) toxicities (possibly, probably, or definitely related to treatment) reported included neutropenia (41%), leukopenia (15%), lymphopenia (3%), vomiting (3%), nausea (3%), and peripheral nerve infection: herpes zoster (3%). Grade 2 neuromotor and neurosensory difficulties were reported in 3% and 9% of patients, respectively (Table 2). The reasons for treatment discontinuation included progression of disease (27 patients), excessive toxicity (need for a third dose reduction [3 patients], persistent fatigue [1 patient], and severe allergic reaction [1 patient]), and refusal to continue treatment (2 patients).

Table 2. Toxicities Reported to Be Possibly, Probably, or Definitely Related to Treatment by at Least 10% of Those Who Began Treatment

Toxicity	Previously Treated Patients (Cohort 1), n=34		Chemotherapy Naive Patients (Cohort 2), n=39	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic				
Neutropenia	59%	41%	59%	28%
Thrombocytopenia	41%	0%	44%	5%
Leukopenia	26%	15%	21%	3%
Lymphopenia	6%	3%	8%	0%
Anemia	68%	0%	72%	0%
Nonhematologic				
Fatigue	56%	3%	72%	3%
Nausea	56%	3%	46%	3%
Neurosensory	47%	0%	33%	5%
Vomiting	26%	3%	15%	3%
Arthralgia	9%	0%	10%	0%
Myalgia	18%	0%	8%	0%
Peripheral nerve infection	3%	3%	—	—

Cohort 2 (CN)

At the time of this report, all but 1 of 39 patients have discontinued study treatment. The median number of cycles administered was 4 cycles (total, 194 cycles; range, 1-26 cycles). Twenty-four patients (65.1%) received 85% or more of the total ABI-007 dose they should have

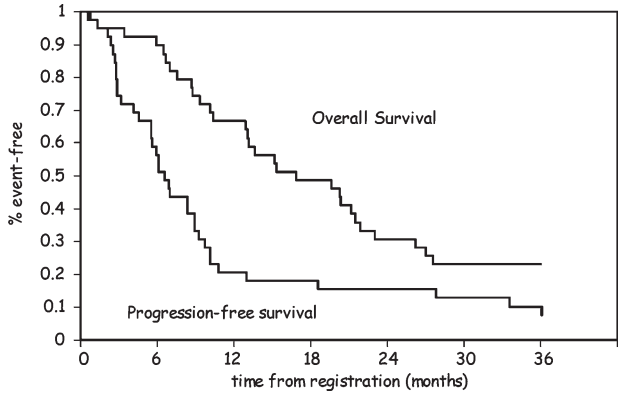

Figure 1. Distribution of progression-free and overall survival times among the patients who did not have prior chemotherapy in the metastatic setting is shown.

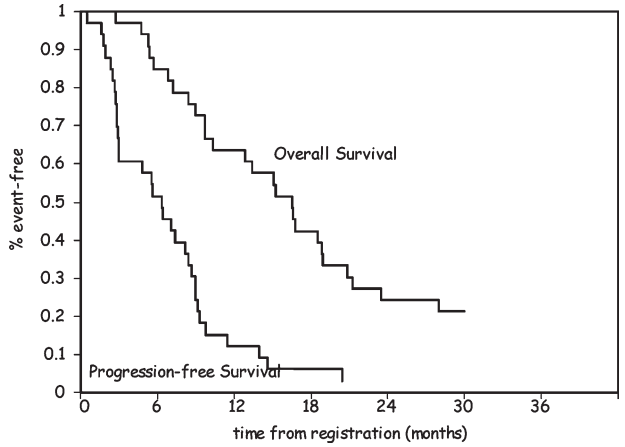

Figure 2. Distribution of progression-free and overall survival times among the patients who did have prior chemotherapy in the metastatic setting is shown.

received for their time on treatment. Twenty-five patients (64.1%) omitted day 8 and/or 15 of treatment (12 patients), had at least 1 dose reduction (4 patients), or both (9 patients), primarily because of severe neutropenia and neuropathy. The primary reason for study discontinuation was progression of disease (28 patients). There was 1 treatment-related death in this cohort. This was a 79-year-old man with M1b stage disease who died 26 days after enrolling, having completed 1 cycle of treatment. He developed grade 4 febrile neutropenia, diarrhea, infectious colitis, and hypotension. The most common severe (≥grade 3) toxicities (possibly, probably, or definitely related to treatment) reported included neutropenia (28%), thrombocytopenia (5%), neurosensory difficulties (5%), vomiting (3%), nausea (3%), fatigue (3%), and leukopenia (3%). Grade 2 neurosensory difficulties were reported in 3% of patients. (Table 2) The reasons for treatment discontinuation included progression of disease (28 patients), excessive toxicity (need for a third dose reduction [1 patient], neuropathies [2 patients], and severe allergic reaction [1 patient], severe nausea and vomiting [1 patient]), death (1 patient), and refusal to continue treatment (1 patient), desire for alternative treatment (1 patient), and completion of 8 cycles of treatment (3 patients).

Clinical Efficacy

Cohort 1 (PT)

All but 1 patient (who refused further follow-up) were followed for a minimum of 9.0 months or until death. Three patients had a partial tumor response lasting 3.2, 3.5, and 11.6 months, respectively. No CRs were reported. Thus, the tumor response rate was 8.8% (90% CI, 2.5-21.3%). At last contact, 1 patient was alive without disease progression, 6 patients were alive with disease progression, and 27 patients had died of their disease. The median PFS was 4.2 months, and the median OS was 10.9 months (Fig. 1).

Cohort 2 (CN)

All patients were followed for a minimum of 1.7 years or until death. Among the first 35 patients enrolled, there were 9 patients (25.7%; 90% CI, 14.1%-40.6%) who had a tumor response (1 CR and 8 PRs). Among all 39 patients enrolled, there were 10 patients (25.6%; 90% CI, 14.6%-39.6%) who had a tumor response (1 CR and 9 PRs) lasting 4.0 to 30.6+ months (median, 12.1 months). Thus, the tumor response rate was 25.6% (90% CI, 14.6%-39.6%). At last contact, 3 patients were alive without disease progression, 4 patients were alive with disease progression, and 32 patients had died of their disease. The median PFS was 4.3 months, and the median OS was 11.1 months (Fig. 2).

DISCUSSION

The results of the presented study in patients with metastatic melanoma demonstrate that the combination of ABI-007 and carboplatin has promising clinical activity for patients who are chemotherapy naive but fail to meet/exceed the study threshold for promising clinical activity in patients who have been previously treated in the metastatic setting. Overall, treatment was moderately well tolerated, with the main toxicities being nausea,

vomiting, peripheral neuropathy, and cytopenias (neutropenia, thrombocytopenia, leukopenia).

Previous studies have shown that a taxane-based regimen in combination with carboplatin has some activity in melanoma.[7-12] Hodi et al[7] reported the results of a small phase II pilot study utilizing an every-3-week regimen of paclitaxel 175 mg/m^2 and carboplatin AUC 7.5 on day 1. Of the 15 patients enrolled, 3 had PRs, and 7 had stable disease, with a median survival of 9 months. Zimpfer-Rechner et al conducted a randomized phase II study utilizing single-agent paclitaxel (100 mg/m^2 per day) versus the paclitaxel (80 mg/m^2 per day) and carboplatin (200 mg/m^2 per day). The dosing on this regimen was quite different with paclitaxel $\pm$ carboplatin being utilized weekly for 6 weeks on and 2 weeks off. Forty patients were enrolled, with 32 being evaluable. There were no responses reported in the combination arm, but the SD rate was 20%.[9] Rao et al,[8] in a single-institution retrospective review of 31 patients treated with the combination as second-line therapy primarily administered as a weekly regimen (paclitaxel 100 mg/m^2 and carboplatin AUC 2 on days 1, 8, and 15 every 28 days), reported a 26% PR rate and a 19% SD rate.[8] Finally, 2 randomized phase III trials examining the impact of adding sorafenib to paclitaxel and carboplatin found ORRs of 11%[12] and 16%[11] in the paclitaxel/carboplatin arms. Replacing paclitaxel with ABI-007 in the hope of improving the toxicity profile and thus increasing the amount of drug given resulted in promising antitumor activity (ORR, 25.6%) among CN patients but not among PT patients. The toxicity profile of this study showed less toxicity than that of the 2 PRISM studies,[11,12] with less overall grade 3 or 4 cytopenias, fatigue, and sensory neuropathy. The etiology of this is not completely clear but most likely is a result of replacing paclitaxel with ABI-007 and a lower weekly carboplatin dosing. However, allergic reactions were significantly reduced with the use of ABI-007. The present study also showed slightly better survival rates compared with that of ipilumimab (PFS, 2.9 months; OS, 10.1 months).[20] In summary, the presented data confirm that ABI-007 approximates the efficacy and toxicity of paclitaxel when combined with carboplatin for the treatment of patients with metastatic melanoma. Although such regimens have not been formally compared in a randomized controlled study, the combination of ABI-007 and carboplatin is a viable option when CN patients cannot tolerate conventional paclitaxel therapy. In addition, recent evidence of the combination of bevacizumab with paclitaxel and carboplatin, although not definitive, seems to suggest a better clinical outcome compared with prior FDA-approved therapies.[10,21] Whether the addition of bevacizumab to the combination of ABI-007 and carboplatin will yield similar (or superior) results to those of paclitaxel/carboplatin is the subject of an ongoing study.

CONFLICT OF INTEREST DISCLOSURES

This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic. Supported in part by Public Health Service grants CA-25224, CA-37404, CA-35113, CA-35101, CA-35431, CA-35269, CA-35195, CA-52352, CA-37417, CA-35267, CA-63848, CA-35090, CA-35103, CA-35415, CA-35119, and CA-63849.

REFERENCES

1. Barth A, Wanek LA, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg*. 1995;181:193-201.
2. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol*. 2000;18:158-166.
3. Legha SS, Ring S, Papadopoulos N, Plager C, Chawla S, Benjamin R. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. *Cancer*. 1989;64:2024-2029.
4. Middleton MR, Lorigan P, Owen J, et al. A randomized phase III study comparing dacarbazine, BCNU, cisplatin and tamoxifen with dacarbazine and interferon in advanced melanoma. *Br J Cancer*. 2000;82:1158-1162.
5. Del Prete SA, Maurer LH, O'Donnell J, Forcier RJ, LeMarbre P. Combination chemotherapy with cisplatin, carmustine, dacarbazine, and tamoxifen in metastatic melanoma. *Cancer Treat Rep*. 1984;68:1403-1405.
6. Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol*. 1999;17:2745-2751.
7. Hodi FS, Soiffer RJ, Clark J, Finkelstein DM, Haluska FG. Phase II study of paclitaxel and carboplatin for malignant melanoma. *Am J Clin Oncol*. 2002;25:283-286.
8. Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. *Cancer*. 2006;106:375-382.
9. Zimpfer-Rechner C, Hofmann U, Figl R, et al. Randomized phase II study of weekly paclitaxel versus paclitaxel and carboplatin as second-line therapy in disseminated melanoma: a multicentre trial of the Dermatologic Co-operative Oncology Group (DeCOG). *Melanoma Res*. 2003;13:531-536.
10. O'Day SK, Kim KB, Sosman J, et al. 23LBA BEAM: a randomized phase II study evaluating the activity of BEvacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated Advanced Melanoma. *Eur J Cancer Suppl*. 2009;7(3):13.
11. Flaherty KTL, Lee SJ, Schuchter LM, et al. Final results of E2603: a double-blind, randomized phase III trial comparing carboplatin (C) /paclitaxel (P) with or without sorafenib (S) in metastatic melanoma. *J Clin Oncol*. 2010;28:15s.Abstract 8511.

12. Hauschild A, Agarwala SS, Trefzer U, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J Clin Oncol*. 2009;27:2823-2830.
13. Gradishar WJ, Tjulandin S, Davidson N, et al. Superior efficacy of albumin-bound paclitaxel, ABI-007, compared with polyethylated castor oil-based paclitaxel in women with metastatic breast cancer: results of a phase III trial. *J Clin Oncol*. 2005;23:7794-7803.
14. Ledda F, Bravo AI, Adris S, Bover L, Mordoh J, Podhajcer OL. The expression of the secreted protein acidic and rich in cysteine (SPARC) is associated with the neoplastic progression of human melanoma. *J Invest Dermatol*. 1997;108:210-214.
15. Desai NT, Trieu V, Yao R, Frankel T, Soon-Shiong P. SPARC expression in breast tumors may correlate to increased tumor distribution of nanoparticle albumin-bound paclitaxel (ABI-007) vs taxol. *San Antonio Breast Cancer Symposium*; 2004.
16. Hersh EM, O'Day SJ, Ribas A, Samlowski WE, Gordon MS, Shechter DE, et al. A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naive patients with metastatic melanoma. *Cancer*. 116:155-163.
17. Stinchcombe TE, Socinski MA, Walko CM, et al. Phase I and pharmacokinetic trial of carboplatin and albumin-bound paclitaxel, ABI-007 (Abraxane) on three treatment schedules in patients with solid tumors. *Cancer Chemother Pharmacol*. 2007;60:759-766.
18. Stinchcombe TW, Lindley C, Collichio F, et al. Preliminary results of phase I trial of carboplatin (CP) in combination with ABI-007 administered weekly or every 3 weeks in patients with solid tumors. *San Antonio Breast Cancer Symposium*; 2005.
19. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
20. O'Day SH, McDermott DF, Weber RW, et al. A phase III, randomized, double-blind, multicenter study comparing monotherapy with ipilimumab or gp100 peptide vaccine and the combination in patients with previously treated, unresectable stage III or IV melanoma. *ASCO Annual Meeting*. 2010;28:18s.
21. Perez DG, Suman VJ, Fitch TR, Amatruda T, 3rd, Morton RF, Jilani SZ, et al. Phase 2 trial of carboplatin, weekly paclitaxel, and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study, N047A. *Cancer*. 2009;115:119-127.