Original Article

A Phase 2 Clinical Trial of *nab*-Paclitaxel in Previously Treated and Chemotherapy-Naive Patients With Metastatic Melanoma

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BACKGROUND: *nab*-Paclitaxel (ABI-007, Abraxane), a 130-nM, albumin-bound (*nab*) particle form of Cremophor-free paclitaxel, is approved for metastatic breast cancer. In the current study, the efficacy and safety of *nab*-paclitaxel were evaluated in previously treated and chemotherapy-naive patients with metastatic melanoma (MM). **METHODS:** Patients with histologically or cytologically confirmed, measurable MM were enrolled. *nab*-Paclitaxel was administered intravenously weekly for 3 of 4 weeks at a dose of 100 mg/m^2 (in previously treated patients) or 150 mg/m^2 (in chemotherapy-naive patients). **RESULTS:** Thirty-seven patients were treated in each cohort. The response rate was 2.7% in the previously treated cohort and 21.6% in the chemotherapy-naive cohort; the response plus stable disease rate was 37.8% and 48.6% in the previously treated and chemotherapy-naive cohorts, respectively. The median progression-free survival (PFS) was 3.5 months and 4.5 months, and the median survival was 12.1 months and 9.6 months, respectively. The probability of being alive and free of disease progression at 6 months was 27% for the previously treated cohort and 34% for the chemotherapy-naive cohort; the probability of surviving 1 year was 49% and 41%, respectively, for the previously treated and chemotherapy-naive cohorts. Approximately 78% of the previously treated patients and 49% of the chemotherapy-naive patients were treated without dose reduction. Eight (22%) chemotherapy-naive patients discontinued therapy because of toxicities. Drug-related toxicities included grade 3 to 4 (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0]) neuropathy, alopecia, neutropenia, and fatigue. **CONCLUSIONS:** *nab*-Paclitaxel was found to be well tolerated and demonstrated activity in both previously treated and chemotherapy-naive patients with MM. The response rate, PFS, and survival compared favorably with current standard dacarbazine therapy and combination therapies for melanoma. *nab*-Paclitaxel therapy of MM should be investigated further in controlled clinical trials. ***Cancer*** **2010;116:155–63.** © *2010 American Cancer Society.*

KEYWORDS: ABI-007 (Abraxane), *nab*-paclitaxel, melanoma, overall survival.

There are approximately 8000 new patients diagnosed each year with stage IV metastatic melanoma (MM) in the United States.[1] The current treatment is unsatisfactory, and the long-term survival rate is approximately 10%.[2] For patients with solitary metastases in organs such as the lung and liver, metastasectomy alone is an option and, if complete, yields a median survival of 20 months and a 5-year survival rate of approximately 15%.[3] The accuracy of this conclusion needs to be confirmed by a prospective study, because the majority of the studies of this type are retrospective.

Chemotherapy and biologic therapy have been explored extensively in melanoma.[4] Dacarbazine is commonly used as a treatment for MM and remains the standard of care for the disease. Although not approved by the US Food and Drug Administration for melanoma, temozolomide is also widely used. In 2 recently conducted, large-scale, front-line phase 3 trials, dacarbazine alone, in the control arm of the studies, was compared with dacarbazine plus oblimersen sodium[5] and with temozolomide,[6] resulting in objective response rates of 6.8% and 12.1%, median progression-free survival (PFS)

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durations of 1.6 months and 1.5 months, and median overall survival (OS) durations of 7.8 months and 6.4 months, respectively.[5,6] To the best of our knowledge aldesleukin is the only other agent approved for the treatment of MM; it is not widely used because of toxicity and difficulty of administration.[7] Solvent-based taxanes have been reported to have some limited activity in malignant melanoma. Solvent-based paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) was reported to cause objective responses in 12% to 18% of patients in an initial study, but some subsequent trials were not as positive.[8-11] Solvent-based docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, NJ) demonstrated low response rates and high levels of toxicity, particularly grade 4 neutropenia, in phase 2 studies.[12,13]

Although solvent-based taxanes are active, both their high rate of toxicity and their limited efficacy can be attributed to their water-insolubility, resulting in limited uptake and adverse reactions to the solvents used in each formulation. *nab*-Paclitaxel (ABI-007 [Abraxane], Abraxis BioScience, LLC, Los Angeles, Calif) is a solvent-free, 130-nM albumin-bound (*nab*) particle formulation of paclitaxel, in which stable albumin particles complex noncovalently with paclitaxel.[14] *nab*-Paclitaxel is highly and readily bioavailable in contrast to other water-insoluble chemotherapy drugs. In animal models, intratumoral paclitaxel concentrations were 33% higher after the administration of *nab*-paclitaxel compared with equal doses of solvent-based paclitaxel l.[15] In addition, compared with solvent-based paclitaxel, *nab*-paclitaxel was less toxic, allowing a 50% increase in the equitoxic dose in animals.[15] The maximum tolerated dose in humans (300 mg/m^2 every 3 weeks) was also higher than the maximum tolerated dose of solvent-based paclitaxel.[16,17]

These improvements in the delivery of *nab*-paclitaxel have been confirmed by the results of a randomized phase 3 trial. When compared with solvent-based paclitaxel in women with metastatic breast cancer, *nab*-paclitaxel was associated with higher objective response rates and longer PFS without increased toxicity.[18] Similar increased antitumor activity in metastatic breast cancer has recently been demonstrated versus solvent-based docetaxel.[19] These clinical data were predicted by preclinical models in which *nab*-paclitaxel demonstrated consistently better antitumor activity and was associated with a higher intratumoral concentration of drug when compared with solvent-based paclitaxel or docetaxel.[15]

In a phase 1 trial conducted in 39 patients with advanced solid tumors who received weekly *nab*-paclitaxel for 3 of 4 weeks, the maximum tolerated doses of *nab*-paclitaxel were 100 mg/m^2 and 150 mg/m^2, respectively, in heavily pretreated and chemotherapy-naive patients.[17] Prolonged disease stabilization was observed in 5 of the 14 patients with malignant melanoma, suggesting that *nab*-paclitaxel had antitumor activity in this disease. This, in addition to the novel mechanism of action and the results of the phase 3 trial mentioned earlier, was the basis for conducting the study reported herein.

MATERIALS AND METHODS

The study was conducted in compliance with the Good Clinical Practice guidelines of the International Conference on Harmonization and the Declaration of Helsinki. The protocol and all related materials were approved by the University of Arizona Human Subjects Committee as well as those of each participating institution, and in accord with the assurance filed with the US Department of Health and Human Services. Written informed consent was obtained from all patients before participation.

Patient Population

Eligible patients were men and nonpregnant, nonlactating women at least aged 18 years with histologically or cytologically confirmed malignant melanoma of any origin (skin, mucosal, uveal) with evidence of inoperable locoregional recurrence or distant metastasis and having a life expectancy of at least 12 weeks. Patients were required to have measurable disease, with no other current active malignancies and no brain metastases noted on screening assessments. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, hemoglobin $\geq$9 g/dL, an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, a platelet count $\geq 100 \times 10^9$/L, serum creatinine $\leq$1.5 mg/dL, total bilirubin $\leq$2 mg/dL, and hepatic transaminases $<2.5\times$ the upper limit of normal. If female, the patient must have been practicing adequate birth control methods.

Patients were excluded from the trial if they had evidence of brain metastases, had a preexisting grade 2 or higher peripheral neuropathy, had received prior radiation to a target lesion (unless there has been clear progression of the lesion since radiotherapy), had a history of allergy or hypersensitivity to the study drug, had a clinically significant concurrent illness, were unlikely to complete the study, or were enrolled in a different clinical study. A washout period from the last dose of any prior

therapy for melanoma of 28 days was required before initiation of therapy for the previously treated cohort.

Study Design

nab-Paclitaxel was supplied by Abraxis BioScience (Los Angeles, Calif) and was administered as intravenous infusions over 30 minutes weekly for 3 weeks followed by 1 week of rest (28-day cycles) on an outpatient basis. Patients who had been previously treated with cytotoxic chemotherapy were entered into the previously treated cohort, and patients with no previous chemotherapy treatment were entered into the chemotherapy-naive cohort. Patients with a history of bio- or immunotherapy as adjuvant treatment for their metastatic disease were accepted for treatment in both groups. Weekly doses were 100 mg/m^2 for the previously treated cohort and 150 mg/m^2 for the chemotherapy-naive cohort. A dose escalation of 25-mg/m^2 was permitted in Cycle 2 and onward for the previously treated cohort in the absence of dose-limiting toxicities. *nab*-Paclitaxel was initially administered without antiemetics, antihistamines, or corticosteroids, but the use of antiemetics was permitted at the investigator's discretion based on patient tolerance. Filgrastim (granulocyte colony-stimulating factor) treatment was permitted for neutropenic fever or sepsis.

Patients were withdrawn from the study in the event they developed progressive disease or unacceptable toxicity, if they refused therapy, or at the investigator's discretion.

Safety and efficacy analyses were performed on the treated population (ie, all randomized patients who received at least 1 dose of study drug).

For the evaluation of safety and tolerability, investigator-assessed incidences of treatment-emergent and treatment-related adverse events were reported as well as laboratory abnormalities; nadir of myelosuppression; and incidence of patients experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drug.

The confirmed overall response rate and disease control rate were summarized by the number and percentage of patients who achieved response as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Disease control was defined as having confirmed complete or partial overall response or stable disease for at least 16 weeks. PFS and OS were analyzed using Kaplan-Meier methods. For PFS, patients who did not develop disease progression and had not died were censored at the last known time the patient was free of disease progression. Patients who initiated new anticancer therapy before disease progression were censored at the time the new anticancer therapy was initiated. As a measure of duration of response, PFS was analyzed in patients with confirmed overall response. Exploratory comparisons of PFS and OS by baseline level of lactate dehydrogenase (LDH) were based on the log-rank test.

Assessments

Blood counts and chemistries were measured weekly to assess bone marrow and hepatic and renal function. In the case of myelosuppression, *nab*-paclitaxel was not administered until ANC and platelet counts had recovered to $\geq 1.5 \times 10^9$/L and $\geq 100 \times 10^9$/L, respectively. Before dosing within a treatment cycle (Weeks 2 and 3 of each cycle), ANC and platelet counts were required to be $\geq 1.0 \times 10^9$/L and $\geq 75 \times 10^9$/L, respectively. Tumor imaging studies were performed at baseline; with radiographic restaging performed every 8 weeks for the first 3 assessments, and every 12 weeks thereafter. Response was assessed using RECIST criteria.[20] Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Treatment-related toxicities were those toxicities considered by the investigators to be possibly, probably, or definitely related to *nab*-paclitaxel. PFS and OS were analyzed using Kaplan-Meier methods. Exploratory comparisons of PFS and OS by baseline level of LDH were based on the log-rank test.

RESULTS

Patient Characteristics

Seventy-four patients enrolled in the study and received at least 1 dose of *nab*-paclitaxel (Table 1). Of 37 patients in the previously treated group, 35 patients received prior chemotherapy, 1 patient received prior neoadjuvant therapy, 4 patients received prior adjuvant therapy, and 31 patients received prior metastatic therapy (mean number of prior metastatic chemotherapy regimens, 2.1 ± 1.48). Patients enrolled in this clinical trial had mainly visceral metastasis (70% among previously treated patients and 81% among chemotherapy-naive patients) and baseline LDH levels above the upper limit of normal (62% among previously treated patients and 51% among chemotherapy-naive patients), demonstrating a population of patients with poor prognosis. All patients had an ECOG performance status at baseline of ≤ 1.

Table 1. Patient Demographics

Patient Cohort	PT Patients	CN Patients
No. of patients treated	37	37
Mean age, y	55.9	61.2
<65	27 (73%)	22 (59%)
≥65	10 (27%)	15 (41%)
Men	21 (57%)	25 (68%)
Race		
Caucasian	35 (95%)	34 (92%)
Hispanic or Latino	1 (3%)	2 (5%)
Hawaiian/Pacific Islander	0	1 (3%)
Other	1 (3%)	0
Dominant site of metastasis/recurrence		
Visceral	26 (70%)	30 (81%)
Nonvisceral	10 (27%)	6 (16%)
Unknown	1 (3%)	1 (3%)
Baseline ECOG PS (0 or 1)	100%	100%
Baseline LDH (normal/elevated)	14/23	17/19*
Mean No. of prior treatments for metastatic disease	2.1	0

PT indicates previously treated; CN, chemotherapy-naive; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase.
*Baseline LDH level was unavailable for 1 patient.

Treatment Administration

Patients received a median of 4.0 cycles of *nab*-paclitaxel (range, 1-27 cycles); >50% of the patients in each cohort received ≥4 treatment cycles (21 [57%] of the patients in the previously treated cohort and 22 [59%] of the patients in the chemotherapy-naive cohort). Seventeen patients in the previously treated cohort had their dose increased to 125 mg/m^2 at Cycle 2 or later as permitted per protocol. There were 8 (22%) previously treated patients and 19 (51%) chemotherapy-naive patients with at least 1 dose reduction, and 10 (27%) previously treated patients and 19 (51%) chemotherapy-naive patients with at least 1 dose delay. There were no dose interruptions during the study. The mean percentage of protocol dose was 91.3% for previously treated patients and 84.9% for chemotherapy-naive patients.

Patients were not pretreated with antihistamines or steroids in either cohort, but 17 (46%) patients in the previously treated and 9 (24%) patients in the chemotherapy-naive group received antiemetics.

Safety

Treatment-emergent and treatment-related grade 3 and 4 toxicities are noted in Table 2. The most frequently reported toxicities were anemia (mostly grade 1), sensory neuropathy, fatigue, leukopenia, and neutropenia. These events were generally more prominent in patients in the chemotherapy-naive group receiving a dose of 150 mg/m^2 of the drug. Grade 3 or 4 neutropenia was experienced by 41% of the patients in the chemotherapy-naive group and 14% in the previously treated group. Only 1 patient in either group experienced febrile neutropenia.

nab-Paclitaxel was well tolerated in this patient population. Grade 3 sensory neuropathy was experienced by 2 patients in the previously treated group and 6 patients in the chemotherapy-naive group; 1 patient discontinued therapy because of the event, 1 patient was dose-reduced and then discontinued therapy after another grade 3 neuropathy, 3 patients were dose-reduced and continued therapy, and 3 patients discontinued therapy at the time of the neuropathy for other reasons (progressive disease or other toxicity). There was 1 instance of grade 4 sensory neuropathy in the chemotherapy-naive cohort. (The patient developed grade 3 neuropathy after 3 full cycles at full dose. Cycle 4 was initiated at a reduced dose, and the patient was dosed twice, but the neuropathy worsened to a grade 4 at 2 weeks after the 11th dose. The patient then discontinued therapy because of this event.) Overall, 19% percent of the patients in the chemotherapy-naive group had grade 3 or 4 sensory neuropathy, compared with 5% in the previously treated group.

None of the patients experienced a serious hypersensitivity reaction. Eight (22%) patients in the chemotherapy-naive group discontinued because of unacceptable toxicity, usually neuropathy or myelosuppression.

Activity

The confirmed complete or partial overall response rate was 2.7% (1 of 37 patients) for the previously treated cohort (95% confidence interval [95% CI], 0.1-14.2%) and 21.6% (8 of 37 patients) for the chemotherapy-naive cohort (95% CI, 8.4%-34.9%) (Table 3). All responses were partial responses. The duration of response for the previously treated patient was 12.9 months; for the chemotherapy-naive patients, the median duration of response was 24.9 months, and the individual values for the 8 patients in months were 3.9 (censored), 10.0 (censored), 10.8, 13.6, 18.7, 25.5 (censored), 26.8 (censored), and 31.2 months, respectively. The sites of disease in the responders were lung, lymph node with or without soft tissue, abdomen, brain, liver, and peritoneum.

An additional 13 (35%) of the previously treated patients and 10 (27%) of the chemotherapy-naive patients

Table 2. Most Common Grade 3 and Grade 4 Treatment-Emergent and Treatment-Related Toxicities*

	PT Patients (N = 37)		CN Patients (N = 37)	
	Grade 3	Grade 4	Grade 3	Grade 4
Patients with at least 1 treatment-emergent toxicity†	18 (49%)	3 (8%)	21 (57%)	4 (11%)
Neutrophils‡	4 (11%)	1 (3%)	13 (35%)	2 (5%)
Lymphopenia	6 (16%)	0	4 (11%)	0
Sensory neuropathy	2 (5%)	0	6 (16%)	1 (3%)
Leukocytes‡	2 (5%)	0	6 (16%)	1 (3%)
Fatigue	5 (14%)	0	3 (8%)	0
Rash/desquamation	0	0	2 (5%)	0
Dyspnea	5 (14%)	0	1 (3%)	0
Pain: other extremity	2 (5%)	0	0	0
Patients with at least 1 treatment-related toxicity	12 (32%)	1 (3%)	18 (49%)	4 (11%)
Neutrophils‡	4 (11%)	1 (3%)	13 (35%)	2 (5%)
Lymphopenia	4 (11%)	0	3 (8%)	0
Sensory neuropathy	2 (5%)	0	6 (16%)	1 (3%)
Leukocytes‡	2 (5%)	0	6 (16%)	1 (3%)
Fatigue	3 (8%)	0	2 (5%)	0
Lymphatics: other	2 (5%)	1 (3%)	0	1 (3%)
Blood/bone marrow: other	0	0	3 (8%)	0
Rash/desquamation	0	0	2 (5%)	0
Hyponatremia	2 (5%)	0	0	0
Hemoglobin‡	1 (3%)	1 (3%)	0	0
Pruritus/itching	1 (3%)	0	0	0
Platelets‡	1 (3%)	0	0	0
Motor neuropathy	1 (3%)	0	1 (3%)	0
Febrile neutropenia	0	0	1 (3%)	0

PT indicates previously treated; CN, chemotherapy-naive.
*Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).
†The incidence of grade 5 (death) was 3 (8%) and 4 (11%) for the PT and CN cohorts, respectively. All grade 5 events were found to be unrelated to study therapy.
‡Based on clinical laboratory values.

had stable disease for at least 16 weeks. A large proportion of patients in this clinical trial had a confirmed response or stable disease for $\geq$16 weeks while receiving *nab*-paclitaxel (37.8% of patients in the previously treated group and 48.6% of patients in the chemotherapy-naive group [95% CI, 22.2-53.5% and 32.5-64.8%, respectively]). The median PFS was 3.5 months for the previously treated cohort (95% CI, 1.7-5.6 months) and 4.5 months for the chemotherapy-naive cohort (95% CI, 3.4-6.7 months) (Table 3) (Fig. 1). The PFS probabilities at 16 weeks were .3784 for the previously treated group, .5392 for the chemotherapy-naive group, and .4726 across all patients. The median OS was 12.1 months for previously treated patients and 9.6 months for chemotherapy-naive patients (95% CI, 6.5-17.5 months and 6.7-23.7 months, respectively) (Table 3) (Fig. 2). The probability of being alive and free of disease progression at 6 months was 27% for the previously treated cohort and 34% for the chemotherapy-naive cohort; the probability of surviving 1 year was 49% and 41% for the previously treated and chemotherapy-naive cohorts, respectively.

As anticipated from other recent studies,[4] an exploratory analysis indicated that the baseline level of LDH was associated with longer PFS and OS in the chemotherapy-naive patients with normal baseline LDH compared with those with an elevated baseline LDH ($P = .027$ and $P = .018$, respectively) (Table 3). For example, the OS of the chemotherapy-naive patients with normal LDH was 26.5 months, compared with 5.6 months in patients with elevated LDH. In the previously treated cohort, PFS was also found to be significantly longer in patients with normal baseline LDH compared with patients with elevated LDH ($P = .012$).

Table 3. Efficacy, Progression-Free Survival, and Overall Survival

Patient Cohort	PT Patients	CN Patients	Total
No. of patients	37	37	74
Confirmed CR or PR			
No. of patients	1 (PR)	8 (PR)	9 (PR)
% of patients	2.7	21.6	12.2
95% CI	0.1-14.2	8.4-34.9	4.7-19.6
SD ≥16 wk + PR			
No. of patients	14	18	32
% of patients	37.8	48.6	43.2
95% CI	22.2-53.5	32.5-64.8	32-54.5
Type of response	1 PR, 13 SD	8 PR, 10 SD	9 PR, 23 SD
PFS			
No. with disease progression or death	37 (100%)	31 (84%)	68 (92%)
Median PFS, mo	3.5	4.5	3.8
95% CI	1.7-5.6	3.4-6.7	3.4-5.3
Patient OS			
No. of patient deaths	30 (81%)	27 (73%)	57 (77%)
Median OS, mo	12.1	9.6	9.7
95% CI	6.5-17.5	6.7-23.7	7.3-15.6
PFS and OS by baseline LDH level			
PFS with normal LDH	3.6 (2.2-9.0)	8.1 (4.5-18.7)	
PFS with elevated LDH	1.8 (1.6-4.6)	3.5 (1.9-4.7)	
OS with normal LDH	17.8 (9.3 to >30.6)	26.5 (9.6-31.4)	
OS with elevated LDH	8.5 (3.5-14.8)	5.6 (3.9-12.0)	

PT indicates previously treated; CN, chemotherapy-naive; CR, complete response; PR, partial response; 95% CI, 95% confidence interval; SD, stable disease; PFS, progression-free survival; OS, overall survival; LDH, lactate dehydrogenase.

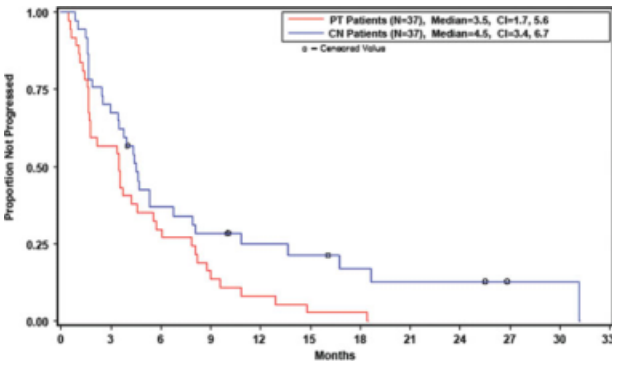

Figure 1. Progression-free survival is shown in the treated population. PT indicates previously treated; CI, confidence interval; CN, chemotherapy naive.

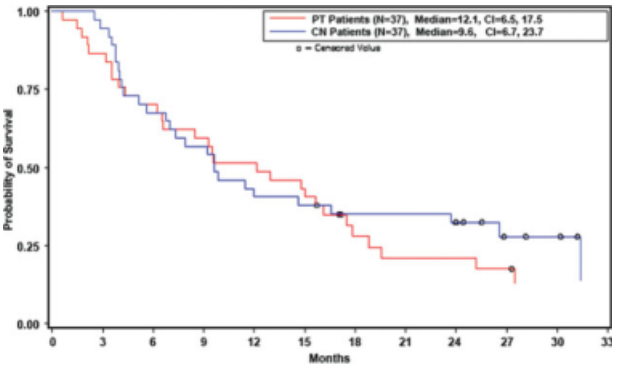

Figure 2. Overall survival is shown in the treated population. PT indicates previously treated; CI, confidence interval; CN, chemotherapy naive.

The time to the initiation of the next program of therapy after cessation of *nab*-paclitaxel therapy was examined. In the chemotherapy-naive group, 43% of patients went for ≥2 months without new therapy, 19% went for ≥6 months, and 11% went ≥12 months (Fig. 3). Overall, 10 previously treated and 16 chemotherapy-naive patients had remarkably slow progression after disease recurrence, ranging from 2 to 23 months.

DISCUSSION

MM remains a very challenging entity for treatment with a known short survival. Thus, in several large studies, the overall median survival has ranged from 6.2 to 7.8 months, and disease progression is usually rapid and unrelenting. In a recent meta-analysis of a large number of

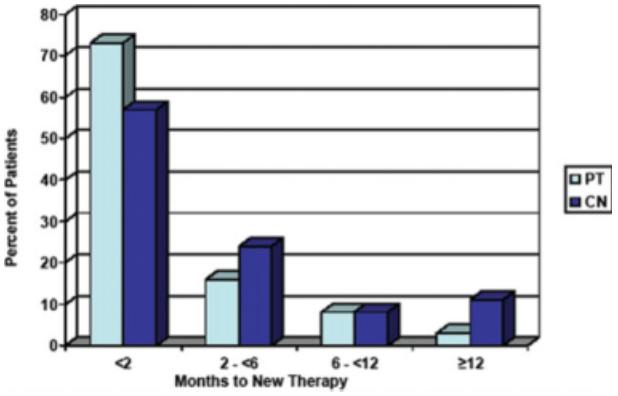

Figure 3. Time to new therapy is shown according to the percentage of patients who did not start a new therapy after the cessation of treatment with *nab*-paclitaxel. PT indicates previously treated; CN, chemotherapy naive.

phase 2 cooperative group trials, the median OS in patients with MM was 6.2 months, and the median PFS was 1.7 months.[21]

nab-Paclitaxel was investigated in the current study because, in a phase 1 study of this formulation given on the schedule of weekly for 3 of 4 weeks, hints of activity including tumor shrinkage and declines in an initially elevated serum LDH value were noted. In addition, *nab*-paclitaxel is at least as active against a variety of metastatic cancers as Cremophor-formulated paclitaxel.[14] It is approved for the treatment of metastatic breast cancer and is currently under study for other cancers, including lung cancer, head and neck cancer, pancreatic cancer, and others.

The current clinical trial enrolled a majority of patients with poor-prognosis MM, as determined by elevated LDH and metastasis to visceral organs. Despite this, in both the previously treated and the chemotherapy-naive groups of patients, the PFS and the OS were longer than would have been anticipated from prior studies of other chemotherapeutic agents. The PFS was 3.5 months and 4.5 months, respectively, in the previously treated and chemotherapy-naive patients, whereas in the literature the PFS in MM patients treated with dacarbazine or temozolomide has been reported to be approximately 1.6 months.[5,6] Similarly, the OS was 12.1 months for previously treated patients and 9.6 months for chemotherapy-naive patients, which is considerably longer than the median survival of <8 months reported for patients treated with dacarbazine or temozolomide. In this small study, the PFS at 6 months and the OS at 1 year were higher compared with the results of a recent review of 42 clinical trials including greater than 2100 patients with MM participating in studies from cooperative groups between 1975 and 2005.[21] It has been proposed that single-arm clinical trials that demonstrate either a PFS at 6 months >30% or an OS at 1 year >45% are useful endpoints for the selection of regimens to be then tested in phase 3 clinical trials.[21]

The transcytosis of *nab*-paclitaxel across the endothelial membrane of the blood vessel to the site of the tumor is facilitated by the binding of albumin to the gp60 receptor and caveolar transport.[15,22,23] After entering the interstitial space adjacent to tumors, the accumulation of *nab*-paclitaxel is possibly mediated by SPARC (Secreted Protein, Acidic and Rich in Cysteine),[24-26] an albumin-binding protein with significant homology to gp60, which, when overexpressed, is associated with a poor prognosis in a large number of cancers, including melanoma.[26,27] This may be in part responsible for an increase in intratumoral concentration of paclitaxel,[28,29] with resultant improved efficacy.

Another interesting feature of the course of patients treated with *nab*-paclitaxel is the slow progression or long stabilization of disease in a substantial number of patients. Ten previously treated and 16 chemotherapy-naive patients had remarkably slow progression after disease recurrence (range, 2-23 months). This might indicate a change in the biology of the tumor. Approximately 11% of the chemotherapy-naive patients were stable for at least 12 months, and for as long as 23 months, after cessation of therapy, despite having radiographically documented persistence of disease.

Taxanes have demonstrated moderate activity in melanoma in several previously reported studies, with response rates reported to range from 12% to 16%.[8-13] In addition, preliminary results of a large phase 2 randomized clinical trial testing a combined regimen of paclitaxel and carboplatin, with or without sorafenib, in patients with previously treated MM yielded a response rate of 11% to 12%,[30] thereby confirming some antitumor activity of taxane-containing regimens in patients with this disease. Indeed, the OS of the patients receiving the combination of carboplatin and paclitaxel in the above-mentioned study was similar to that of patients in the current study. The toxicity of Cremophor, particularly the 14% incidence of acute hypersensitivity reactions, is a well-known, dose-limiting toxicity. The albumin-bound particle formulation of the drug avoids this toxicity, and the drug can be given without any premedication.

The most common and most severe toxicities noted with the drug are neuropathy and neutropenia,

although the majority of patients develop alopecia as well. Toxicity in terms of neuropathy was greater in the chemotherapy-naive group, presumably because of the higher dose of drug administered compared with the previously treated group. At the current time, dose interruption and dose reduction are effective interventions for neuropathy, although therapy eventually needs to be terminated in a small fraction of the patients. If neutropenia of grade $\geq$3 develops, it can be managed with filgrastim treatment on Days 2 to 5 or Days 2 to 6 after each dose of *nab*-paclitaxel. Because thrombocytopenia was not a problem with this agent, and because the neutropenia is modest and can usually be reversed with growth-factor treatment, we believe an important pathway for the further development of this drug is in combination with other therapies for melanoma, including those that may be myelosuppressive.

Overall, *nab*-paclitaxel was well tolerated and active in patients with MM. Both the response rate and PFS compared favorably with standard dacarbazine therapy, prior reports of single-agent paclitaxel therapy, other regimens such as combination chemotherapy, and various other therapies for previously treated patients.

nab-Paclitaxel should be evaluated further in both chemotherapy-naive and previously treated patients with MM as both single-agent therapy and in combination with other chemotherapy, biologic therapy, and targeted therapy. Because the PFS and OS of the patients in the previously treated group who received 100 mg/m^2 of *nab*-paclitaxel was similar to that of the chemotherapy-naive group receiving 150 mg/m^2 of *nab*-paclitaxel, it may be that future randomized clinical trials of *nab*-paclitaxel should use the dose of 100 mg/m^2.

CONFLICT OF INTEREST DISCLOSURES

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