

# A Randomized Phase 2 Study of Temozolomide and Bevacizumab or *nab*-Paclitaxel, Carboplatin, and Bevacizumab in Patients With Unresectable Stage IV Melanoma

A North Central Cancer Treatment Group Study, N0775

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**BACKGROUND:** Increasing evidence shows chemotherapy in combination with vascular endothelial growth factor (VEGF) inhibition is a clinically active therapy for patients with metastatic melanoma (MM). **METHODS:** A phase 2 trial was conducted in chemotherapy-naïve patients with unresectable stage IV MM who were randomized to temozolomide (200 mg/m<sup>2</sup> on days 1 through 5) and bevacizumab (10 mg/kg intravenously on days 1 and 15) every 28 days (Regimen TB) or *nab*-paclitaxel (100 mg/m<sup>2</sup>, or 80 mg/m<sup>2</sup> post-addendum 5 secondary to toxicity, on days 1, 8, and 15), bevacizumab (10 mg/kg on days 1 and 15), and carboplatin (area under the curve [AUC] 6 on day 1, or AUC 5 post-addendum 5) every 28 days (Regimen ABC). Accrual goal was 41 patients per regimen. The primary aim of this study was to estimate progression-free survival rate at 6 months (PFS6) in each regimen. A regimen would be considered promising if its PFS6 rate was > 60%. **RESULTS:** Ninety-three eligible patients (42 TB and 51 ABC) were enrolled. The majority of patients had M1c disease (20 TB and 26 ABC). The median PFS and overall survival times with ABC were 6.7 months and 13.9 months, respectively. Median PFS time and median overall survival with TB were 3.8 months and 12.3 months, respectively. The most common severe toxicities (≥ grade 3) in both regimens were cytopenias, fatigue, and thrombosis. Among the first 41 patients enrolled onto each regimen, PFS6 rate was 32.8% (95% confidence interval: 21.1%-51.2%) for TB and 56.1% (90% confidence interval: 44.7%-70.4%) for ABC. **CONCLUSIONS:** The addition of bevacizumab to *nab*-paclitaxel and carboplatin shows promising activity despite tolerability issues. *Cancer* 2013;119:586-92. © 2012 American Cancer Society.

**KEYWORDS:** metastatic melanoma, chemotherapy, vascular endothelial growth factor inhibition, combination therapy, unresectable metastatic melanoma.

## INTRODUCTION

Melanoma affected approximately 60,000 people in the United States in 2010,<sup>1</sup> with approximately 8000 deaths.<sup>1</sup> Until very recently, the US Food and Drug Administration (FDA) had only approved 2 drugs, dacarbazine (5-(3,3-dimethyl-1-triazenyl)imidazole-4-carboxamide [DTIC]) and interleukin-2 (IL-2) for clinical use in patients with metastatic melanoma (MM).<sup>2,3</sup> In 2011, two new agents received FDA approval for MM: ipilimumab (anti-CTLA4 antibody) and vemurafenib (BRAF V600E inhibitor). Both agents were approved in the United States based on completed phase 3

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clinical trials demonstrating superior survival endpoints of overall survival (OS) or progression-free survival (PFS). In the case of ipilimumab, an OS advantage was observed over that of a peptide vaccine (gp100)<sup>4</sup> and in the case of vemurafenib, a PFS advantage was observed over that of DTIC.<sup>5,6</sup>

Over the past several years, our research team has engaged in an effort to assess the clinical utility of combination therapeutics involving cytotoxic chemotherapy and inhibitors of angiogenesis in patients with MM. Vascular endothelial growth factor (VEGF) has been shown to play a significant role in the natural history of malignant melanoma.<sup>7,8</sup> In particular, the role of VEGF appears in the context of melanoma therapy with cytotoxic agents. Laboratory evidence demonstrates that malignant melanocytes exposed to conventional cytotoxic agents (DTIC) dramatically up-regulate VEGF production.<sup>9,10</sup> Thus, the addition of a VEGF-blocking agent in the context of systemic chemotherapy for MM may yield antitumor benefits beyond those of chemotherapy alone.

Bevacizumab is a recombinant humanized murine monoclonal antibody to VEGF-A that blocks the binding of VEGF-A to its receptors, thereby inhibiting its biologic activity.<sup>11</sup> In 2009, we reported that the combination of bevacizumab with paclitaxel and carboplatin for patients with MM resulted in modest clinical benefit in a single-arm phase 2 clinical trial.<sup>12</sup> A randomized comparison of paclitaxel/carboplatin/bevacizumab (PCB) to paclitaxel/carboplatin (PC) in patients with MM reported a trend toward a survival benefit of PCB over PC,<sup>13,14</sup> even though the study did not reach its primary objective of statistically significant PFS advantage in the PCB arm. Thus, in an effort to improve on these observations, we sought to identify a more effective chemotherapy regimen that, in combination with bevacizumab, would yield greater clinical benefit. As such, we conducted a randomized phase 2 clinical trial in chemotherapy-naïve patients with MM to assess the antitumor activity and safety profiles of *nab*-paclitaxel (Abraxane; Celgene, Summit, NJ)/bevacizumab/carboplatin (ABC) and temozolomide/bevacizumab (TB) regimens.

## MATERIALS AND METHODS:

This phase 2 clinical trial randomized previously untreated patients with MM to either regimen TB (temozolomide 200 mg/m<sup>2</sup> orally on days 1 through 5 and bevacizumab 10 mg/kg intravenously [IV] on days 1 and 15 of a 28-day cycle repeated until disease progression) or regimen ABC (*nab*-paclitaxel 100 mg/m<sup>2</sup> IV on days 1, 8, and 15, bevacizumab 10 mg/kg IV on days 1 and 15, and

carboplatin at area under the curve [AUC] of 6 IV on day 1, of a 28-day cycle until disease progression). A stratified randomization procedure was employed (when both regimens were open to enrollment) using Eastern Cooperative Oncology Group performance status (PS) and M substage (M1a,b,c) to assign patients in equal number to the 2 regimens. The primary aim of this study was to independently assess the antitumor activity and safety profile of each regimen. The study was not designed to compare efficacy between the 2 regimens. The approach of conducting 2 concurrent phase 2 clinical trials (with randomization) in 1 study was done to streamline the protocol development process, eliminate potential selection bias, and ensure consistent evaluation and surveillance. This study was conducted as a multi-institution cooperative group trial through the North Central Cancer Treatment Group (NCCTG). All patients provided signed informed written consent. This study was approved by the institutional review boards of all participating institutions.

The study data safety monitoring plan included criteria for suspending enrollment to any given regimen for an unacceptable toxicity. For a given regimen, if 2 or more of the first 5 patients enrolled or 30% or more thereafter developed  $\geq$  grade 3 (Common Terminology Criteria for Adverse Events [CTCAE], version 3.0) non-hematologic or hematologic toxicity (excluding grade 3 neutropenia or thrombocytopenia) possibly, probably, or definitely related to treatment, enrollment would be suspended and a trial recommendation would be formulated and submitted for review to the Cancer Therapy Evaluation Program/National Cancer Institute (CTEP/NCI) and institutional review boards. Under these conditions, enrollment to regimen ABC was suspended from June 22, 2009 to August 14, 2009, when 9 of the first 28 patients randomized to regimen ABC developed severe thrombosis (3 patients), hypertension (2 patients), dyspnea and fatigue (2 patients), hemorrhage (1 patient), and oral mucositis (1 patient). The study was amended to reduce the starting dose of both *nab*-paclitaxel and carboplatin to 80 mg/m<sup>2</sup> and AUC 5, respectively.

Enrollment to regimen TB closed prior to that of regimen ABC due to suspension of accrual to regimen ABC, secondary to toxicity. As regimen ABC closed in on its accrual goal of 41 patients, proper notice was sent to the memberships stating that enrollment would close in 3 weeks. An unexpected jump in accrual rate occurred, leading to 52 total patients being enrolled to this regimen. The 23 patients who were enrolled to regimen ABC after addendum 5 was put into place will be referred to as the "post-addendum 5" patients (postadd5) for the purposes of this report.

### Eligibility

Eligible patients had to be  $\geq 18$  years of age with unresectable, histologically confirmed MM. Additional eligibility criteria included measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0); ECOG PS of 0 or 1; adequate hematologic, renal, and hepatic function; life expectancy of  $\geq 4$  months; and no prior chemotherapy for MM. Exclusion criteria included prior exposure to taxanes, agents disrupting VEGF activity in the adjuvant setting; peripheral neuropathy  $\geq$  grade 2; major surgical procedure, open biopsy, or significant trauma  $\leq 4$  weeks prior to randomization; brain metastases per magnetic resonance imaging (MRI); active infection requiring parenteral antibiotics; poorly controlled hypertension; New York Heart Association Class II-IV congestive heart failure; serious cardiac arrhythmia; myocardial infarction or unstable angina ( $\leq 6$  months); clinically significant peripheral vascular disease; deep venous thrombosis or pulmonary embolus within  $\leq 1$  year; need for full-dose anticoagulation therapy; active bleeding or known condition that carries a high risk of bleeding; non-healing wound; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within  $\leq 6$  months; central nervous system disease (primary brain tumor, vascular abnormalities); stroke or transient ischemic attack ( $\leq 6$  months); uncontrolled seizures; radiographically documented invasion of adjacent organs (duodenum, stomach) or tumor invading major blood vessels, known to be positive for human immunodeficiency virus or have hepatitis. Women who were pregnant or breast feeding were also not eligible for participation.

### Assessments

Within 14 days of registration, patients underwent a complete physical examination, assessment of performance status, complete blood counts with differential, comprehensive metabolic panel (including lactate dehydrogenase), urinalysis for proteinuria, and tumor assessment by conventional computed tomography (CT), spiral CT, or MRI. Within 28 days of registration, patients underwent MRI of the brain (CT if MRI was not able to be performed) to assess for the presence of brain metastasis. Prior to each cycle of treatment, patients underwent a physical examination, toxicity assessments (CTCAE, version 3.0) and laboratory (urine and blood) testing. Tumor status was assessed every 8 weeks until progression (RECIST, version 1.0). All patients received standard supportive care, including antiemetics, antibiotics, transfusions, and growth factor support as clinically appropriate.

For patients on regimen TB, treatment was held on day 1 of the cycle if their absolute neutrophil count (ANC) was  $< 1500 \text{ mm}^3$ , platelet count (PLT) was  $< 75,000 \text{ mm}^3$  or the patient experienced  $>$  grade 3 nonhematologic toxicity. Once blood counts recovered to above these levels and/or other nonhematologic adverse events resolved to  $\leq$  grade 1, patients were eligible for re-treatment at a lower dose level of temozolomide (reduction of  $50 \text{ mg/m}^2/\text{day}$ ). There were no dose reductions allowed on either regimen for toxicities related to bevacizumab. If a patient had a toxicity that was felt to be related to bevacizumab, further dosing was held or discontinued based on the specific toxicity. Treatment could be held for up to 4 weeks.

For patients on regimen ABC, treatment was held on day 1 of the cycle if ANC  $< 1500 \text{ mm}^3$ ; PLT  $< 75,000 \text{ mm}^3$ ;  $\geq$  grade 2 AST, alkaline phosphatase, or peripheral neuropathy; or any other  $\geq$  grade 3 nonhematologic toxicity. Patients could be retreated at a lower dose level (20% dose reduction of *nab*-paclitaxel and carboplatin decreased by 1 AUC). As with regimen TB, there were no dose reductions allowed for toxicities related to bevacizumab. If a patient had a toxicity that was felt to be related to bevacizumab, patients were to have their dose held or discontinued based on the specific toxicity. Treatment could be held for up to 4 weeks.

### Statistical Analysis

The primary endpoint for evaluating each regimen was the 6 month progression-free survival rate. Under the assumption that all 41 patients randomized to a given regimen will be followed at least 6 months (or until death), a 1-sided  $\alpha = 0.10$  one-sample test of proportions will have a 90% chance of detecting that the true 6-month PFS rate with that regimen is at least 60% when the true 6-month PFS rate for the regimen is greater than 40%. If any patients were lost to follow-up within 6 months of registration, the 6-month PFS rate would be estimated using the Kaplan-Meier method. If a patient died without documentation of progression, the patient was considered to have progressed at death.

### Quantification of Plasma VEGF Levels

Plasma levels of VEGF-A and VEGF-D were measured using DuoSet antibodies from R&D Systems (Minneapolis, MN) as per manufacturer's instructions. Briefly, 96-well plates were coated overnight at  $4^\circ\text{C}$  with capture antibodies at  $1.0 \text{ }\mu\text{g/mL}$  and  $2.0 \text{ }\mu\text{g/mL}$  for VEGF-A and VEGF-D, respectively. The plates were washed and blocked for 1 hour at room temperature with reagent diluent, and  $50 \text{ }\mu\text{L}$  of undiluted plasma was added to wells in

duplicate and incubated for 2 hours at room temperature. The plates were washed with phosphate-buffered saline and 0.5% Tween-20, and 100 ng/mL VEGF-A and 200 ng/mL VEGF-D biotinylated detection antibodies were added for 1 hour at room temperature and was followed by incubation with a streptavidin horseradish peroxidase complex. Color was developed with tetramethylbenzidine

(TMB) substrate and optical density was measured at 450 nm wavelength. VEGF-A and VEGF-D concentration was determined using a standard curve ranging from 0 to 2000 pg/mL.

## RESULTS

### Patient Characteristics

Ninety-five patients (regimen TB: 43 patients; regimen ABC: 52 patients) were enrolled into this trial between August 15, 2008, and January 12, 2010 (Table 1). One patient randomized to regimen TB was found ineligible at the time of registration due to brain metastasis. One patient assigned to regimen ABC withdrew consent prior to study treatment. Therefore, regimen TB included 42 patients (57.1% male) aged 25 to 82 years (median age, 57 years). Regimen ABC included 51 patients (56.9% male) aged 22 to 83 years (median age, 57 years). The characteristics of the patients were well balanced between the treatment regimens (Table 1).

### Treatment Course and Toxicities

#### Regimen TB

At the time of this report, all but 1 patient had discontinued study treatment. The median number of cycles administered was 4 cycles (total  $\geq 247$  cycles; range, 1 to  $> 29$ ). There were 3 patients who had dose reductions of temozolomide due to hematologic adverse events. The most common severe ( $\geq$  grade 3) toxicities (possibly, probably, or definitely related to treatment) included: vomiting (12%), fatigue (10%), neutropenia (10%), and leukopenia (10%) (Table 2). Three patients discontinued treatment due to the following grade 3 adverse events: pulmonary embolism ( $n = 1$ ), dyspnea ( $n = 1$ ), and ileal obstruction with

**TABLE 1.** Demographic and Baseline Characteristics

Patient Characteristics	Regimen A (TB) n = 42	Regimen B (ABC) n = 51
Median age, y (range)	57 (25-82)	57 (22-83)
Sex, male	57.1%	56.9%
Prior radiation therapy	25.6%	17.6%
Prior systemic therapies		
None	65.1%	62.7%
Immunotherapy	32.6%	35.3%
Vaccine therapy	—	2.0%
Immuno- and vaccine therapy	2.3%	—
Eastern Cooperative Oncology Group performance status		
0	74.4%	64.7%
1	25.6%	35.3%
M1 substage		
M1a	23.3%	23.5%
M1b	30.2%	25.5%
M1c	46.5%	51.0%
Elevated lactate dehydrogenase ( $>$ upper limit of normal)	47%	51%
Preexisting signs and symptoms		
Grade 3 hypertension	—	2.0%
Grade 2 hypertension	4.7%	3.9%
Grade 2 fatigue	11.6%	5.9%
Grade 2 muscle pain	4.7%	5.9%
Grade 2 joint pain	0.0%	7.8%
Grade 2 anemia	2.3%	2.0%

Abbreviations: TB, temozolomide and bevacizumab; ABC, *nab*-paclitaxel, carboplatin, and bevacizumab.

**TABLE 2.** More Common Toxicities Reported to Be Probably, Possibly, or Definitely Related to Study Treatment

Toxicity	Regimen A (TB) (n = 42)		Regimen B (ABC), Pre-Add5 (n = 28)		Regimen B (ABC), Post-Add5 (n = 23)	
	Any Grade	$\geq$ Grade 3	Any Grade	$\geq$ Grade 3	Any Grade	$\geq$ Grade 3
Anemia	57%	5%	96%	21%	83%	17%
Leukopenia	36%	10%	75%	29%	74%	26%
Neutropenia	19%	10%	75%	54%	65%	43%
Thrombocytopenia	48%	5%	57%	21%	65%	17%
Dyspnea	2%	2%	18%	14%	9%	0%
Fatigue	88%	10%	93%	21%	87%	9%
Hypertension	52%	2%	29%	7%	17%	0%
Nausea	76%	7%	57%	0%	57%	4%
Thrombosis	5%	5%	18%	14%	9%	9%
Vomiting	43%	12%	11%	4%	30%	0%
Neuropathy-sensory	10%	0%	54%	0%	35%	0%

Abbreviations: ABC, *nab*-paclitaxel, carboplatin, and bevacizumab; Add5, Addendum 5; TB, temozolomide and bevacizumab.



abdominal hemorrhage ( $n = 1$ ). Two patients died while on study treatment, including a 72-year-old woman with bone metastases previously treated with radiation who died during cycle 1 from complications of bone marrow suppression and a 47-year-old woman who died during cycle 1 due to rapid disease progression. The reasons for treatment discontinuation among the remaining 36 patients are disease progression ( $n = 32$ ), refusal ( $n = 3$ ), and other medical condition ( $n = 1$ ).

### Regimen ABC

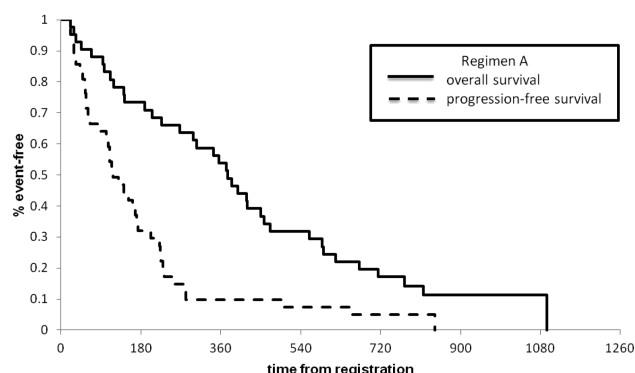
At the time of this report, all but 1 patient had discontinued study treatment. The median number of cycles administered is 4 cycles (total > 310 cycles; range, 1 to > 33). The most common severe ( $\geq$  grade 3) toxicities reported included: neutropenia (49%), leukopenia (27%), thrombocytopenia (20%), anemia (20%), fatigue (16%), and thrombosis (12%) as shown in Table 2. Twelve patients (8 pre-addendum 5 and 4 post-addendum 5) discontinued study treatment due to the following  $\geq$  grade 3 adverse events: thrombosis/thrombus/embolism (preadd5 = 5 patients; postadd5 = 1 patient) neutropenia, thrombocytopenia, leukopenia, with renal failure (preadd5 = 1 patient), pleural effusion and pancreatitis (preadd5 = 1 patient), thrombocytopenia (preadd5 = 1 patient), infection (postadd5 = 2 patients), and persistent fatigue (postadd5 = 1 patient). The reasons for treatment discontinuation among the other 38 patients were disease progression ( $n = 28$ ), patient refusal ( $n = 3$ ), desire for alternative therapy ( $n = 6$ ), and unacceptable treatment delay secondary to Port-A-Cath placement ( $n = 1$ ).

### Clinical Efficacy

#### Regimen TB

All but one patient (who refused further follow-up) were followed for a minimum of 16 months or until death. At last contact, 3 patients were alive without disease progression, 5 patients were alive with disease progression, and 34 patients had died of their disease.

Among the first 41 eligible patients randomized to TB, the Kaplan-Meier estimate for the 6 month PFS rate was 32.8% (95% confidence interval [CI]: 21.1%-51.2%); thus, ruling out a 6-month PFS rate of 60% or more. Considering all 42 eligible patients randomized to Regimen TB, the tumor response rate (TRR) was 23.8% (95% CI: 12.1%-39.5%), with 9 partial responses and 1 complete response. The median PFS and OS times were estimated to be 3.8 months (95% CI: 3.0-6.2 months) and 12.3 months (95% CI: 9.3-15.3 months), respectively (Fig. 1).



**Figure 1.** Survival and progression curves are shown for Regimen A.

### Regimen ABC

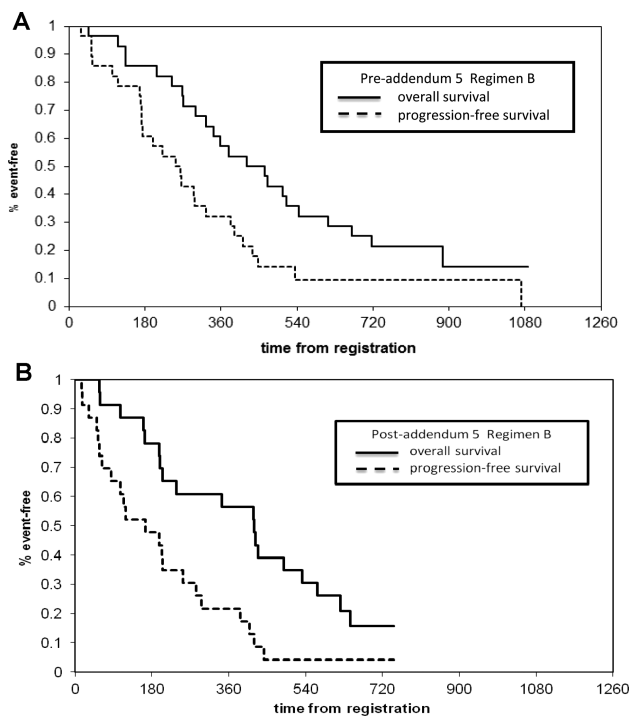
All 51 patients were followed for a minimum of 16.5 months or until death. At last contact, 4 patients were alive without disease progression, 9 patients were alive with disease progression, and 37 patients had died of their disease.

Among the first 41 eligible patients randomized to ABC, the Kaplan-Meier estimate for the 6-month PFS rate was 56.1% (90% CI: 44.7%-70.4%), thereby not excluding a 6-month PFS rate of 60% or more. Considering all 51 eligible patients randomized to Regimen ABC, the overall 6-month PFS rate was 54.9% (90% CI: 42.8-70.4%) with a PFS6 in the preadd5 and postadd5 cohorts of 60.7% (90% CI: 47.3%-78.0%) and 47.8% (90% CI: 33.4%-68.4%), respectively. There were 17 partial responses and no complete responses, yielding an overall TRR of 33.3% (95% CI: 20.8%-47.9%). The TRR among the preadd5 and postadd5 cohorts was 35.7% (95% CI: 18.6%-55.9%) and 30.4% (95% CI: 13.2%-52.9%), respectively.

The overall median PFS time was estimated to be 6.7 months (95% CI: 5.6-9.5 months). In addition, the median PFS in the preadd5 and postadd5 cohorts was 9.4 months (95% CI: 5.7-11.6 months) and 5.4 months (95% CI: 3.1-8.8 months), respectively. The overall median OS was estimated to be 13.9 months (95% CI: 10.7-17.5 months). Finally, the preadd5 and postadd5 OS rates were 14.5 months (95% CI: 9.9-22.0 months) and 13.8 months (95% CI: 6.5-18.7 months), respectively (Fig. 2).

### Changes in Plasma VEGF-A and VEGF-D Levels

Serial measurements of plasma VEGF-A and VEGF-D levels were obtained prior to each treatment as well as at time of progression. Bevacizumab is a primarily VEGF-A-neutralizing antibody, and we sought to understand whether its use affected the levels of VEGF-D as well. Emerging evidence suggests that VEGF-D plays a central

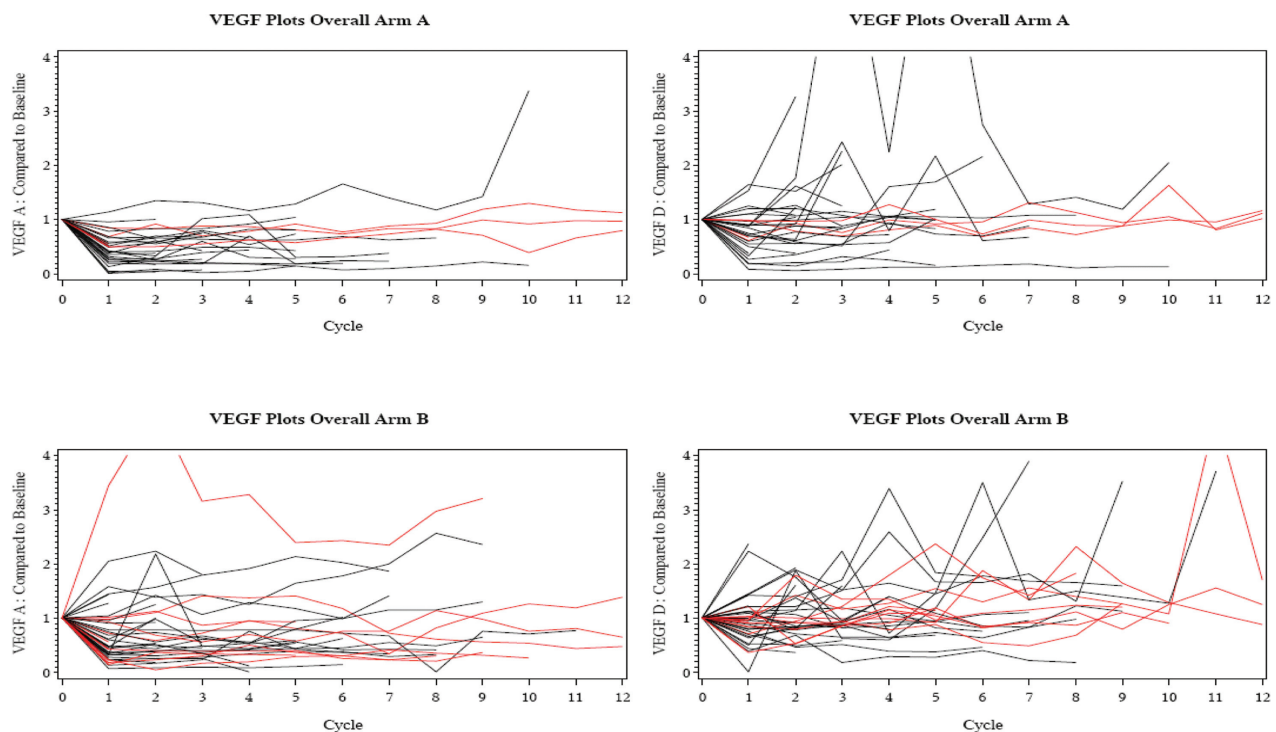


**Figure 2.** Survival and progression curves are shown for Regimen B.

role in intratumoral endothelial cell survival.<sup>15</sup> Our data demonstrated that among the 30 patients on regimen TBand 44 patients on regimen ABC who had at least 1 postregistration determination of VEGF-A and VEGF-D, there were decrements in VEGF-A levels in a majority of the patients after 1 cycle of treatment (Fig. 3). However, changes in VEGF-A or VEGF-D levels during treatment did not correlate with clinical response to treatment.

## DISCUSSION

The current study trial was primarily built on the findings from our previous phase 2 trial of *nab*-paclitaxel and carboplatin (study N057E) that reported a median PFS time of 4.3 months and median OS of 11.1 months among chemotherapy-naïve patients, and 4.2 months and 10.9 months, respectively, among those previously treated.<sup>16</sup> Toxicities encountered included nausea, vomiting, peripheral neuropathy, and cytopenias necessitating the lower starting doses of *nab*-paclitaxel and carboplatin. In the current trial, the addition of bevacizumab to *nab*-paclitaxel and carboplatin (ABC regimen) shows promising activity in both PFS (6.7 months) and OS (13.9 months) despite tolerability issues, relative to N057E as well as historical benchmarks of other therapies for MM



**Figure 3.** Graphs show vascular endothelial growth factor A (VEGF-A) and VEGF-D levels.

tested in the National Cancer Institute Cooperative Groups.<sup>17</sup> Notably, the initial dosing schedule of *nab*-paclitaxel 100 mg/m<sup>2</sup> IV on days 1, 8, and 15, carboplatin at AUC of 6 IV on day 1, and bevacizumab 10 mg/kg IV days 1 and 15 of a 28-day cycle induced higher incidence of cytopenias, fatigue, hypertension, nausea, thrombosis, and neuropathy than expected, which required lower starting doses of *nab*-paclitaxel and carboplatin to 80 mg/m<sup>2</sup> and AUC 5, respectively. Although there was some difference in PFS (9.4 months for the preadd5 group and 5.4 months for the postadd5 group), OS was largely unaffected (14.5 months for preadd5 and 13.8 months for postadd5). The ABC regimen of our current study also compares favorably to 2 prior phase 2 studies evaluating bevacizumab combinations with paclitaxel and carboplatin, which demonstrated median PFS and OS times in the 5- and 12-month range, respectively.<sup>12,13</sup>

In this study, we also evaluated the utility of the addition of bevacizumab to temozolomide (regimen TB), a commonly used chemotherapeutic agent in MM. The TB regimen resulted in a median PFS time of 3.8 months, which is similar to the median PFS of 4.2 months reported by von Moos et al,<sup>18</sup> thus confirming their observation. The TB regimen was well tolerated in both trial populations.

In conclusion, the last several years have witnessed a tremendous effort in developmental therapeutics for MM, resulting in the FDA approval of 2 new agents, ipilimumab and vemurafenib, in 2011.<sup>5,19</sup> Our current study found that the addition of bevacizumab to *nab*-paclitaxel and carboplatin (regimen ABC) shows promising activity in terms of both PFS and OS that is comparable to that of ipilimumab and vemurafenib. Toxicity on this regimen was somewhat higher than was seen on the TB arm with more grade 3 toxicities, but with careful monitoring, this is still a generally acceptable safety profile. Its place in the treatment armamentarium for metastatic melanoma should be explored in the phase 3 clinical trial setting.

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## CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

## REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2010. Atlanta, GA: American Cancer Society. <http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-and-figures-2010>. Accessed January 25, 2011.
2. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999;17:2105-2116.
3. 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.
4. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723.
5. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507-2516.
6. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med*. 2010;363:809-819.
7. Salven P, Heikkilä P, Joensuu H. Enhanced expression of vascular endothelial growth factor in metastatic melanoma. *Br J Cancer*. 1997;76:930-934.
8. Ugurel S, Rappel G, Tilgen W, Reinhold U. Increased serum concentration of angiogenic factors in malignant melanoma patients correlates with tumor progression and survival. *J Clin Oncol*. 2001;19:577-583.
9. Lev DC, Onn A, Melinkova VO, et al. Exposure of melanoma cells to dacarbazine results in enhanced tumor growth and metastasis in vivo. *J Clin Oncol*. 2004;22:2092-2100.
10. Lev DC, Ruiz M, Mills L, McGary EC, Price JE, Bar-Eli M. Dacarbazine causes transcriptional up-regulation of interleukin 8 and vascular endothelial growth factor in melanoma cells: a possible escape mechanism from chemotherapy. *Mol Cancer Ther*. 2003;2:753-763.
11. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov*. 2004;3:391-400.
12. Perez DG, Suman VJ, Fitch TR, 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.
13. O'Day SK, Sosman J, Peterson A, et al. 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;7:13.
14. Kim KB, Sosman JA, Fruehauf JB, et al. BEAM: a randomized phase II study evaluating the activity of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced melanoma. *J Clin Oncol*. 2012;30:34-41.
15. Papiewska-Pajak I, Boncela J, Przygodzka P, Cierniewski CS. Autocrine effects of VEGF-D on endothelial cells after transduction with AD-VEGF-D(DeltaNDeltaC). *Exp Cell Res*. 2010;316:907-914.
16. Kottschade LA, Suman VJ, Amatruda T, 3rd et al. 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, N057E1. *Cancer*. 2011;117:1704-1710.
17. Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol*. 2008;26:527-534.
18. von Moos R, Seifert B, Simcock M, et al; Swiss Group for Clinical Cancer Research (SAKK). First-line temozolomide combined with bevacizumab in metastatic melanoma: a multicenter phase II trial (SAKK 50/07). *Ann Oncol*. 2012;23:531-536.
19. 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.