The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

BEAM: A Randomized Phase II Study Evaluating the Activity of Bevacizumab in Combination with Carboplatin Plus Paclitaxel in Patients with Previously Untreated Advanced Melanoma

Kim et al

DOI: 10.1200/JCO.2011.34.6270

REDACTED PROTOCOL

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL EVALUATING THE EFFICACY AND SAFETY OF BEVACIZUMAB IN COMBINATION WITH CARBOPLATIN AND PACLITAXEL CHEMOTHERAPY FOR THE FIRST-LINE TREATMENT OF PATIENTS WITH METASTATIC MELANOMA**
PROTOCOL NUMBER:	AVF4096g
STUDY DRUG:	Bevacizumab
IND:	BB-IND 7023
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.

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I. SELECTION OF PATIENTS, INCLUDING BOTH ELIGIBILITY AND INELIGIBILITY CRITERIA

1. MATERIALS AND METHODS

1.1 PATIENTS

1.1.1 Patient Selection

Patients who have not previously received systemic treatment for Stage IV MM (excluding melanoma of ocular origin) may be eligible for this study. Patients may have received prior therapy in the adjuvant setting prior to Stage IV disease, including adjuvant systemic chemotherapy (if discontinued ≥ 4 months prior to Day 1) or biologic or experimental therapy (if discontinued ≥ 14 days prior to Day 1). Radiation therapy ≥ 14 days prior to Day 1 is allowed provided patients have recovered from any significant (Grade ≥ 3) acute toxicity. A history of BCG, GM-CSF, or vaccine therapy following complete surgical resection or complete irradiation/radiotherapy ablation of Stage IV disease prior to disease progression is also acceptable.

1.1.2 Inclusion Criteria

Subjects must meet the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Metastatic melanoma (Stage IV)
- Histologically confirmed malignant melanoma with measurable or non-measurable disease (including mucosal melanoma)
- ECOG performance status of 0 or 1
- Ability and willingness to comply with study and follow-up procedures

1.1.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

a. Disease-Specific Exclusions

- Prior treatment for Stage IV disease with chemotherapy or biologic therapy such as interferon and interleukin-2
    - Adjuvant systemic therapy is acceptable if it was used prior to Stage IV disease and was discontinued ≥ 4 months prior to Day 1; BCG, GM-CSF, or vaccine therapy following complete surgical resection or complete irradiation/radiofrequency ablation of Stage IV disease prior to disease progression is also acceptable.
- Complete surgical resection or irradiation of all identifiable sites of disease at randomization
- Radiation therapy within 14 days prior to Day 1
- Prior therapy with bevacizumab, sorafenib, sunitinib, or other VEGF pathway–targeted therapy
- Melanoma of ocular origin
- Known CNS disease/brain metastases (history of brain disease or active disease)

b. General Medical Exclusions

- Life expectancy of < 12 weeks
- Current, recent (within 4 weeks of Day 1), or planned participation in an experimental drug study other than a Genentech-sponsored bevacizumab cancer study
- Inadequate organ function, as evidence by any of the following laboratory values
    - Absolute neutrophil count (ANC) < 1500/μL
    - Platelet count < 100,000/μL
    - Total bilirubin > 1.5 mg/dL
    - Alkaline phosphatase, AST, and/or ALT > 2 × the upper limit of normal (ULN) (> 5 × ULN for patients with known liver involvement, or for alkaline phosphatase elevations, bone involvement)
    - Serum creatinine > 1.5 mg/dL

    - International normalized ratio (INR) > 1.5 × the ULN and/or activated partial thromboplastin time (aPTT) > 1.5 × the ULN (except for patients receiving anticoagulation therapy)
- History of other malignancies within 5 years of Day 1, except for tumors with a negligible risk for metastasis or death, such as adequately controlled basal cell carcinoma or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

c. Bevacizumab-Specific Exclusions

- Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg on anti-hypertensive medications)
- History of hypertensive crisis or hypertensive encephalopathy
- New York Heart Association (NYHA) Class II or greater CHF
- History of myocardial infarction or unstable angina within 6 months prior to Day 1
- History of stroke or transient ischemic attack within 6 months prior to Day 1
- Significant vascular disease (e.g., aortic aneurysm, aortic dissection) or recent peripheral arterial thrombosis within 6 months prior to Day 1
- History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 or anticipation of need for major surgical procedure during the course of the study

- Minor surgical procedures, fine-needle aspirations, or core biopsies within 7 days prior to Day 1
- History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1
- Serious, non-healing wound, active ulcer, or untreated bone fracture
    - Patients with fractures secondary to metastatic disease are eligible after appropriate radiotherapy
- Proteinuria at screening, as demonstrated by a urine protein/creatinine ratio of ≥ 1.0 at screening
- Known hypersensitivity to any component of bevacizumab
- Pregnancy (positive pregnancy test) or lactation
    - Patients of childbearing potential must use an effective means of contraception (men and women)
- Current, ongoing treatment with full-dose warfarin

II. SCHEMA AND TREATMENT PLAN, INCLUDING ADMINISTRATION SCHEDULE

2. STUDY DESIGN

2.1 DESCRIPTION OF THE STUDY

This Phase II, multicenter, randomized, double-blind, placebo-controlled trial is designed to estimate the efficacy and characterize the safety of bevacizumab when combined with carboplatin + paclitaxel chemotherapy compared with the carboplatin + paclitaxel chemotherapy alone in patients with previously untreated MM.

Patients must have histologically confirmed malignant melanoma, including cutaneous and mucosal origin, but excluding ocular region, with measurable or non-measurable metastatic disease at the time of randomization (patients may not have undergone complete surgical resection or complete irradiation/radiotherapy ablation without subsequent disease progression prior to enrollment). No prior systemic treatment for metastatic disease will be allowed.

Patients will be randomized in a 2:1 ratio to one of two treatment arms:

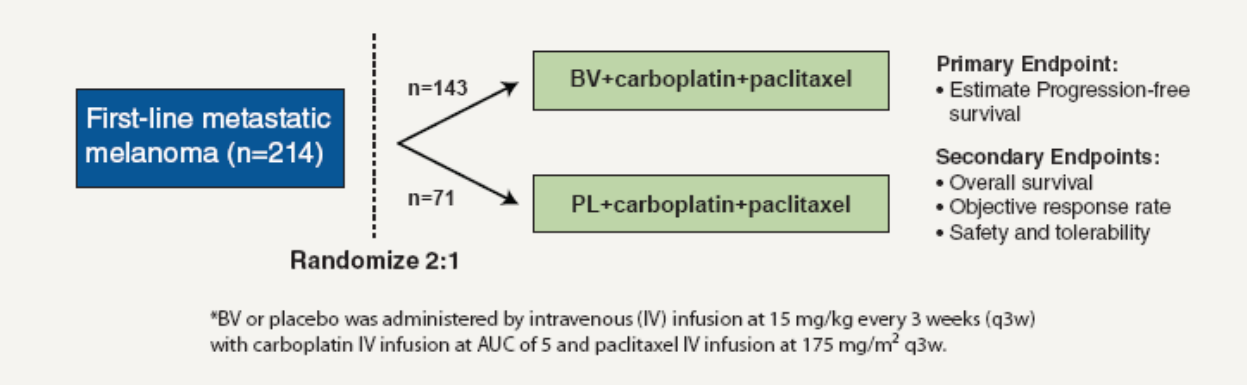
- Arm A (carboplatin + paclitaxel+ bevacizumab)
- Arm B (carboplatin + paclitaxel + placebo)

Randomization will be stratified by ECOG performance status (0 or 1) and disease stage (Stage IV M1a/b vs. Stage IV M1c). Patients will continue to receive study drug (bevacizumab or placebo) until disease progression, unacceptable toxicity, or patient choice, for a maximum of 102 weeks.

Patients who are discontinued from treatment for reasons other than disease progression will be followed with tumor assessment every 6 weeks, until documented disease progression or the initiation of subsequent anti-cancer therapy, whichever is earlier. All patients, after either completing the study or discontinuing from treatment, will be followed for survival and subsequent anti-cancer therapy information until death,

loss to follow-up, or study termination by Genentech unless the patient requests to be withdrawn from study survival follow-up; this request must be documented in the patient's medical records and signed by the investigator.

Figure 1. Study Schema



2.2 STUDY TREATMENT

Patients in Arm A will receive bevacizumab administered by intravenous (IV) infusion at a dose of 15 mg/kg every 3 weeks in addition to carboplatin + paclitaxel every 3 weeks.

Patients in Arm B will receive placebo administered by IV infusion every 3 weeks, in addition to carboplatin + paclitaxel every 3 weeks.

Patients will receive study drug (bevacizumab or placebo) until disease progression or unacceptable toxicity, or for a maximum of 102 weeks, whichever occurs first. Carboplatin administration will stop after completion of 10 treatment cycles of carboplatin (Markman et al. 1999). Paclitaxel, if it is still ongoing, should continue along with study drug (bevacizumab or placebo) after carboplatin is discontinued. No reductions in the bevacizumab dose are allowed in this study. If adverse events occur that require holding study drug, the dose will remain unchanged once treatment resumes. Study drug may be held during suspension of chemotherapy for a transient chemotherapy-related toxicity. If chemotherapy is discontinued as the result of toxicity prior to disease progression, study drug should continue. Regardless of the reason for holding study drug, the maximum allowable length of treatment interruption is 60 days.

2.2.1 Dosage and Administration

The order of administration of study drug, carboplatin, and paclitaxel should be in accordance with institutional standards.

a. Study Drug

The dose of bevacizumab in this study is 15 mg/kg administered by IV infusion on the first day of each 21-day cycle; the interval between infusions must not be < 15 days. The bevacizumab dose will be based on the patient's weight at screening and will remain the same throughout the study. It is not necessary to correct dosing based on ideal weight. If a cycle of chemotherapy is delayed, study drug (bevacizumab or placebo) may also be delayed to allow same-day administration of chemotherapy and study drug.

The initial dose will be delivered over 90 ± 10 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 ± 10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes.

If a patient experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 ± 10 minutes as long as the patient continues to be premedicated. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 ± 10 minutes. Similarly, if a patient experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 ± 10 minutes.

b. Chemotherapy

Sites are instructed to follow institutional guidelines regarding the laboratory criteria required for administration of carboplatin and paclitaxel.

Carboplatin. Carboplatin will be dosed using the AUC based on the Calvert formula on Day 1 of every 3-week cycle for a maximum of 10 cycles. The carboplatin dose will be based on a patient's creatinine clearance and may be adjusted as needed because of changes in creatinine clearance or toxicity per institutional standard. Local laboratory draws within 48 hours of dosing are suggested to get the most updated creatinine clearance. The dose will be that needed to attain an AUC of 5 for carboplatin.

Total Dose (mg) = (target AUC) × (GFR + 25)

Note: With the Calvert formula, the total dose of carboplatin is calculated in milligrams, not milligrams per square meter.

Glomerular filtration rate (GFR) as creatinine clearance in milliliters per minute (mL/min) may be measured (preferably) by a 24-hour urine collection or may be calculated based on serum creatinine (creat) using institutional standard or the Cockcroft-Gault formula (Cockcroft and Gault 1976):

[(140 − age) × ideal weight (kg)]/[creat(mg/dL) × 72], multiplied by 0.85 for women

Ideal weight in kilograms (kg) may be calculated as follows, described by Robinson et al. (1983):

Men: 51.65 + {1.85 × [height (in inches) − 60]}
Women: 48.67 + {1.65 × [height (in inches) − 60]}

Paclitaxel. The dose of paclitaxel for this study is 175 mg/m2, administered by IV infusion on Day 1 of every 3-week cycle (the interval between infusions must not be < 17 days). Dosing will be based on a patient's weight and may be adjusted for weight

change at each cycle. Dose reductions for toxicity may be made per institutional standard and the Taxol® Package Insert. Paclitaxel, if it is still ongoing, should continue along with study drug (bevacizumab or placebo) after carboplatin is discontinued.

III. RULES FOR DOSE MODIFICATION

3. DOSAGE MODIFICATION

a. Bevacizumab

No reductions in bevacizumab dose are allowed in this study. Criteria for treatment modification and guidelines for the management of toxicities are summarized in Table 1. If adverse events occur that necessitate holding study drug, the dose will remain unchanged once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of approximately 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Patients should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to bevacizumab occurs at any time during the study, or if a patient experiences an adverse event that requires permanent discontinuation of bevacizumab (see Table 1), treatment with bevacizumab should be permanently discontinued. Patients who have been permanently discontinued from bevacizumab should be discontinued from the study, but will continue to be followed for disease progression and survival. If bevacizumab is held for ≥ 60 days, the patient must be permanently discontinued from this agent and the study.

Infusion Reaction. Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to ≤ 50% or interrupted for patients who experience any infusion-associated symptoms not specified above. When the patient's symptoms have completely resolved, the infusion may be continued at ≤ 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Table 1
Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension	
Grade 1 or 2	No bevacizumab dose modifications.
Grade 3	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
Grade 1 or 2 non-pulmonary and non-CNS events	No bevacizumab dose modifications.
Grade 3 non-pulmonary and non-CNS hemorrhage	All other patients will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4 non-pulmonary and non-CNS hemorrhage	Discontinue bevacizumab.
Any grade pulmonary or CNS hemorrhage	Discontinue bevacizumab.
Venous Thrombosis	
Grade 1 or 2	No bevacizumab dose modifications.
Grade 3 or asymptomatic Grade 4	Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over *(full-dose warfarin is excluded)*. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if the following criterion is met: • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Symptomatic Grade 4	Discontinue bevacizumab.

CNS=central nervous system; GI=gastrointestinal; INR=international normalized ratio; MRI=magnetic resonance imaging.

Table 1 (cont'd)
Bevacizumab Dose Management Due to Adverse Events

Arterial Thromboembolic Event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Congestive Heart Failure (left ventricular systolic dysfunction)	
Grade 1 or 2	No bevacizumab dose modifications.
Grade 3	Hold bevacizumab until resolution to Grade ≤1.
Grade 4	Discontinue bevacizumab.
Proteinuria	
Grade 1 or 2	No bevacizumab dose modifications.
Grade 3 (UPC ratio >3.5, urine collection >3.5 g/24 hr)	Hold bevacizumab treatment until Grade ≤2, as determined by either UPC ratio ≤3.5 or 24-hr collection ≤3.5 g.
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab.
GI Perforation	
Any grade	Discontinue bevacizumab.
Fistula	
Any grade (TE fistula)	*Discontinue bevacizumab.*
Grade 4 fistula	*Discontinue bevacizumab.*
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction not requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3 or 4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound Dehiscence	
Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab.
Reversible Posterior Leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events (excluding neutropenia)	
Grade 3	Hold bevacizumab until recovery to Grade ≤1.
Grade 4	Discontinue bevacizumab.

CNS=central nervous system; GI=gastrointestinal; INR=international normalized ratio; MRI=magnetic resonance imaging; UPC=urine protein/creatinine.

b. Chemotherapy

Dose reductions for carboplatin and/or paclitaxel should occur for the next cycle in the event of any of the following:

- Grade 4 neutropenia lasting > 7 days
- Febrile neutropenia
- Platelet count ≤ 50,000/μL
- Grade 3 or 4 toxicity attributed to carboplatin or paclitaxel (except for Grade 4 hypersensitivity reactions)

Dose reductions should be continued for the remainder of the study. A suggested schedule for doses reduction is as follows:

Paclitaxel 175 mg/m^2, carboplatin AUC 5 (starting dose)

↓

Paclitaxel 125 mg/m^2, carboplatin AUC 4

Grade 4 hypersensitivity to carboplatin or paclitaxel will lead to discontinuation of that agent only.

Any additional dose modification should be based on institutional standards and guidelines (e.g., peripheral neuropathy could lead to dose reduction in paclitaxel alone). If one or both chemotherapy treatments are discontinued as the result of intolerable toxicities, study drug (bevacizumab or placebo) should continue to be administered until progressive disease or unacceptable toxicity. If chemotherapy is delayed for > 2 weeks, bevacizumab should be administered according to schedule. Carboplatin treatment should be discontinued after administration of the 10th treatment cycle (to prevent possible carboplatin hypersensitivity reactions due to prolonged exposure to carboplatin). Paclitaxel, if it is still ongoing, should continue along with study drug (bevacizumab or placebo) after carboplatin is discontinued.

IV. MEASUREMENT OF TREATMENT EFFECT INCLUDING RESPONSE CRITERIA, DEFINITION OF RESPONSE AND SURVIVAL, AND METHODS OF MEASUREMENT

4. OUTCOME MEASURES

4.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is PFS, defined as the time from randomization to documented disease progression or death on study, whichever occurs first, as determined by the investigator using RECIST. Death on study is defined as death from any cause occurring no later than 30 days after last dose of study treatment, either study drug or chemotherapy.

4.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Overall survival, defined as the time from randomization to death from any cause
- Objective response, as assessed by the investigator using RECIST, inclusive of complete response and partial response determined on two consecutive investigator assessments conducted ≥ 4 weeks apart
- Duration of objective response, as assessed by the investigator using RECIST, defined in those patients who achieve an objective response as the time from the initial response to documented disease progression or death from any cause, whichever occurs first
- Six-month landmark survival, defined as the number of patients surviving at 6 months following randomization
- Stable disease, as assessed by the investigator using RECIST, defined as the absence of disease progression, for ≥ 24 weeks from the time of randomization

4.3 Safety Outcome Measures

The safety outcome measures are as follows:

- Incidence of all adverse events

- Incidence of serious adverse events
- Incidence of adverse events leading to discontinuation of study drug or chemotherapy

Particular attention will be paid to the incidence of the following select adverse events:

- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Grade ≥ 3 wound dehiscence
- Grade ≥ 3 left ventricular systolic dysfunction
- Grade ≥ 3 bleeding other than pulmonary or CNS bleeding
- Grade ≥ 3 and neutropenia
- Arterial thromboembolic events (any grade)
- Gastrointestinal perforation (any grade)
- Pulmonary bleeding (any grade)
- CNS bleeding (any grade)
- Reversible posterior leukoencephalopathy (RPLS; any grade)

The incidence, nature, severity, and relatedness of adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v3.0.

V. REASONS FOR EARLY CESSATION OF TRIAL THERAPY

5.1 STUDY DRUG DISCONTINUATION

Patients may withdraw or be removed from study drug treatment at any time. Reasons for withdrawal from study drug treatment may include, but are not limited to, the following (all references to severity grade pertain to the NCI-CTCAE, v3.0):

- Patients who meet any of the following criteria should be discontinued from study drug treatment (see Table 1):
    - Grade 4 hypertension or Grade 3 hypertension not controlled with medication
    - Pulmonary or CNS hemorrhage (any grade) or any other Grade 4 hemorrhage
    - Symptomatic Grade 4 venous thrombosis
    - Arterial thromboembolic event (any grade)
    - Grade 4 left ventricular systolic dysfunction
    - Nephrotic syndrome
    - Gastrointestinal perforation (any grade)
    - Tracheoesophageal fistula (any grade) or Grade 4 fistula
    - Grade ≥ 2 bowel obstruction that has not fully recovered despite medical or surgical intervention
    - Wound dehiscence requiring medical or surgical intervention involving a body cavity
    - RPLS (any grade)
    - Any Grade 4 event thought to be related to bevacizumab by the investigator
- Determination by the investigator that it is no longer safe for the patient to continue therapy
- Patient's request to withdraw from study drug treatment
    - All patients will be followed at 3-month intervals for survival information unless the patient's request to be withdrawn from study survival follow-up is documented in the source documents and signed by the investigator.

- Unwillingness or inability of the patient to comply with study requirements
- Clinical need for concomitant or ancillary therapy that is not permitted in the study
- Unrelated intercurrent illness that, in the judgment of the investigator, will affect assessments of clinical status to a significant degree
- Unacceptable toxicity
- Disease progression

It is the right and duty of the investigator to interrupt the treatment of any patient whose health or well-being may be threatened by continuation in this study. Such patients should be withdrawn from the treatment phase of the study rather than continue in the study under a modified regimen.

5.2 Study Discontinuation

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete

VI. OBJECTIVES AND ENTIRE STATISTICAL SECTION (INCLUDING ENDPOINTS)

6.1 OBJECTIVES

The primary objective of this trial is to estimate the clinical benefit of the addition of bevacizumab to carboplatin + paclitaxel chemotherapy in patients with previously untreated metastatic melanoma, as measured by PFS.

The secondary objectives of this trial are as follows:

- To estimate the clinical benefit of the addition of bevacizumab to carboplatin + paclitaxel chemotherapy, as measured by overall survival, objective response, survival at 6 months, and stable disease of ≥ 6 months' duration in patients with previously untreated metastatic melanoma
- To further characterize the safety of bevacizumab in combination with carboplatin + paclitaxel chemotherapy in this patient population

6.2 STASTICAL METHODS

6.2.1 Analysis of the Conduct of the Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated.

6.2.2 Analysis of Treatment Group Comparability

Summaries of patient baseline characteristics will be presented by treatment arm in order to facilitate the assessment of comparability of treatment arms. The characteristics will include age, race, sex, LDH level, ECOG performance status, and disease stage. For continuous variables, such as age, summaries will include sample size, mean, standard deviation, median, minimum, and maximum. For categorical variables, such as sex, the summaries will include frequencies and percentages.

6.3.3 Efficacy Analyses

a. Analysis Populations

For efficacy, the analysis population will be the intent-to-treat (ITT) population, defined as all randomized patients. Treatment arm will be determined by randomization, i.e., “as randomized.” For safety, the analysis population will comprise all patients who receive any amount of study drug or chemotherapy. Treatment arm will be determined by actual treatment received, i.e., “as treated.”

b. Primary Endpoint

The primary efficacy outcome measure is PFS, defined as the time from randomization to disease progression or death on study, whichever occurs first. Disease progression will be determined by the investigator using RECIST. Death on study is defined as death from any cause occurring no later than 30 days after the last study treatment, either study drug or chemotherapy. For patients without documentation of disease progression or death on study, PFS will be censored at the time of the last tumor assessment.

The primary analysis of PFS will occur approximately 8 months after the last patient is enrolled. The number of PFS events (either disease progression or death on study) expected to be observed by this time is approximately 166.

For the primary analysis of PFS, a stratified Cox proportional hazards model will be used to obtain a point estimate of the hazard ratio for chemotherapy + bevacizumab relative to chemotherapy + placebo, along with a 95% confidence interval for the hazard ratio. The stratification factors, ECOG performance status and disease stage, will be included in the model. As a secondary analysis of PFS, Kaplan-Meier methods will be used to characterize the distribution of PFS for each treatment arm, including estimation of median PFS. A stratified log-rank test will be used for an exploratory analysis comparing PFS between the treatment arms.

c. Secondary Endpoints

Secondary efficacy endpoints include overall and 6-month landmark survival, objective response, duration of objective response, and stable disease. Objective response, duration of objective response, and stable disease will be based on investigator assessment using RECIST.

For overall survival, a stratified Cox proportional hazards model will be used to obtain a point estimate of the hazard ratio for chemotherapy + bevacizumab relative to chemotherapy + placebo, along with a 95% confidence interval for the hazard ratio. Kaplan-Meier methods will be used to characterize the distribution of overall survival for each treatment arm, including estimation of median survival and 6-month landmark survival.

For objective response, a 95% confidence interval for the difference between treatment arms in the proportion of responders will be calculated, using the normal approximation to the binomial distribution. A stratified Cochran-Mantel-Haenszel test will be used to compare the proportion of responders in each treatment arms. Only patients with measurable disease will be included in the analysis of objective response.

For duration of objective response, Kaplan-Meier methods will be used to characterize the distribution for each treatment arm, including estimation of median duration. Only patients with measurable disease who achieve a response (either partial or complete) will be included in the analysis of duration of response.

For stable disease, Kaplan-Meier methods will be used to estimate the proportion of patients with stable disease for each treatment arm, i.e., the proportion of patients who have not experienced disease progression by 24 weeks from the time of randomization.

6.3.4 Safety Analyses

All adverse events will be collected and summarized for both treatment arms, with special emphasis on the occurrence of select adverse events, Grade 3 and 4 adverse events, serious adverse events, and all adverse events leading to discontinuation of

study drug or chemotherapy. Select adverse events of interest for both treatment arms are as follows:

- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Grade ≥ 3 wound dehiscence
- Grade ≥ 3 left ventricular systolic dysfunction
- Grade ≥ 3 bleeding other than pulmonary or CNS bleeding
- Grade ≥ 3 and neutropenia
- Arterial thromboembolic events (any grade)
- Gastrointestinal perforation (any grade)
- Pulmonary bleeding (any grade)
- CNS bleeding (any grade)
- RPLS (any grade)

The safety analysis population will comprise all patients who receive any amount of study drug or chemotherapy. Adverse events will be summarized by treatment arm. Frequencies and percentages of patients experiencing each select adverse event will be tabulated. Adverse events will also be tabulated by severity grade. Each adverse event will be characterized by the worst grade during the reporting period. There will be separate tabulations of select adverse events, serious adverse events, fatal adverse events, adverse events leading to discontinuation of study drug (bevacizumab or placebo), and adverse events leading to discontinuation of the treatment regimen (study drug and/or chemotherapy). There will also be a tabulation of all deaths on study not due to disease progression.

6.3.5 Missing Data

For patients without documentation of disease progression or death on study, PFS will be censored at the time of the last tumor assessment. For patients without documentation of death, overall survival will be censored at the time of the last known contact. For patients who achieve a response and have no documentation of disease

progression, duration of response will be censored at the time of the last tumor assessment.

6.3.6 Determination of Sample Size

Approximately 200 patients will be randomized in a 2:1 ratio to the chemotherapy + bevacizumab arm or the chemotherapy + placebo arm. Accrual is expected to be approximately 12 months, following a 3-month ramp-up period. The primary analysis of PFS will occur approximately 8 months after the last patient is enrolled. The expected number of PFS events (either disease progression or death) to be observed by this time is approximately 166. Assuming median PFS of 4 months for the chemotherapy + placebo arm and 6 months for the chemotherapy + bevacizumab arm (which yields a hazard ratio of 0.67), out of 166 PFS events observed, 106 would be expected to occur in the chemotherapy + bevacizumab arm and 60 in the chemotherapy + placebo arm. The expected 95% confidence interval for the hazard ratio is approximately 0.49 to 0.92).

With 133 patients receiving chemotherapy + bevacizumab, there will be a 93% probability of observing at least one occurrence of any adverse event that has an incidence of 2% in bevacizumab-treated patients.

VII. REFERENCES

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

Markman M, Kennedy A, Webster K, et al. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol 1999;17:1141.

Robinson JD, Lupkiewicz SM, Palenik L, Lopez LM, Ariet M. Determination of ideal body weight for drug dosage calculations. Am J Hospital Pharm 1983;40(6):1016–9.