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

A randomized double-blinded placebo controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with castration resistant prostate cancer (CALGB 90401)

Kelly, et al

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Includes Update #4

CANCER AND LEUKEMIA GROUP B

CALGB 90401

A RANDOMIZED DOUBLE-BLINDED PLACEBO CONTROLLED PHASE III TRIAL COMPARING DOCETAXEL AND PREDNISONE WITH AND WITHOUT BEVACIZUMAB (IND #7921, NSC #704865) IN MEN WITH HORMONE REFRACTORY PROSTATE CANCER

NCI-supplied agent(s): Bevacizumab/Placebo (NSC 704865, IND #7921)

Limited access companion study (for specified CALGB sites only): CALGB 70501

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).
Institutions not aligned with CALGB will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the CALGB. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to CALGB unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by CALGB. (generally via email but may be sent via fax or postal mail). Please send query responses and delinquent data to CALGB and do not copy the CTSU Data Operations. Query responses should be sent to CALGB via postal mail or fax (no transmittal form needs to accompany response). Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

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The pharmacogenomic component of this study is conducted as part of the NIH Pharmacogenomics Research Network, which is funded through a separate U01 mechanism (see http://www.nigms.nih.gov/pharmacogenomics/research_net.html for details

A RANDOMIZED DOUBLE-BLINDED PLACEBO CONTROLLED PHASE III TRIAL COMPARING DOCETAXEL AND PREDNISONE WITH AND WITHOUT BEVACIZUMAB (IND #7921, NSC #704865) IN MEN WITH HORMONE REFRACTORY PROSTATE CANCER

Patient Eligibility

Histologically documented hormone refractory prostate cancer with demonstrated evidence of progressive disease (see Sec 4.1)

Patients must have either:
- measurable disease, or
- non-measurable disease with PSA ≥ 5 ng/mL (see Sec. 4.2)

Patients must have demonstrated evidence of progressive disease since the most recent change in therapy (see Sec. 4.3)

Prior Treatment (see Sec. 4.4):
- Progression despite standard androgen deprivation therapy
- All antiandrogens must be discontinued at least 4 weeks prior to registration (see Sec. 4.4)
- ≥ 4 weeks since any other hormonal therapy, including ketoconazole and aminoglutethimide (see Sec. 4.4)
- No prior cytotoxic chemotherapy, including estramustine or suramin
- No prior anti-angiogenesis agents, including thalidomide and bevacizumab
- ≥ 4 weeks since any prior radiation (including palliative) or major surgery and fully recovered.
- ≥ 8 weeks since the last dose of Strontium-89 or Samarium

Patients receiving a bisphosphonate must be on a stable dose and must have started the bisphosphonate ≥ 4 weeks prior to initiating protocol treatment. Patients may initiate bisphosphonate therapy after completion of Cycle 1, if clinically indicated (see Sec. 4.5).

No known brain metastases (brain imaging (MRI/CT) is not required).

No current congestive heart failure (NYHA Class 2 or higher).

Patients with history of hypertension must be well controlled (<160/90).

Patients on full-dose anticoagulants must be on a stable dose of warfarin and have an in-range INR or be on a stable dose of LMW heparin (see Section 4.9).

No significant history of bleeding events (see Section 4.10).

No recent (within 12 months) arterial thrombotic events (see Section 4.11).

No serious or non-healing wound, ulcer or bone fracture.

No clinically significant peripheral neuropathy (grade ≥ 2).

No known hypersensitivity to Chinese hamster ovary cell products (see Section 4.14).

PC-Spes, Saw Palmetto, and St. John's Wort must be discontinued before registration (see Section 4.15).

ECOG Performance Status: 0-2.

Age ≥ 18.

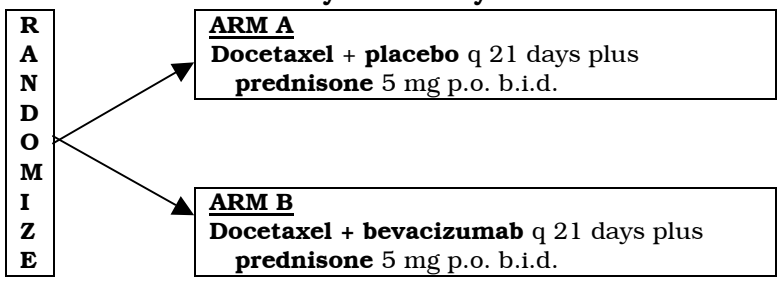
Required Initial Laboratory Values

ANC	≥ 1500/μL
Platelet Count	≥ 100,000/μL
Bilirubin	≤ 1.5 x ULN*
AST	≤ 1.5 x ULN
Creatinine	≤ 1.5 x ULN
UPC ratio	< 1.0*
PSA	≥ 5 ng/ml (If no measurable disease)
Testosterone	≤ 50 ng/dL (for those who have not had bilateral orchiectomy)

* See Section 4.18

SCHEMA

1 Cycle = 21 days



Continue treatment until disease progression or unacceptable toxicity for a maximum period of two years (see Sec.7.1).

Dexamethasone: During each cycle of therapy, all patients will undergo premedication with dexamethasone 8 mg orally approximately 12 hours, 3 hours, and 1 hour prior to docetaxel (i.e., 3 doses of 8 mg of dexamethasone the night before, the morning of, and just prior to the infusion of docetaxel).

Docetaxel: 75 mg/m^2 IV over 1 hour, every 21 days.

Bevacizumab/Placebo: 15 mg/kg IV every 21 days administered following docetaxel. The initial dose is to be given over 90 minutes, second dose over 60 minutes, and all subsequent doses over 30 minutes if prior infusions are tolerated without infusion-associated adverse events.

Prednisone: 5 mg p.o. b.i.d. beginning on Day 1 of the first cycle.

Aspririn: 81 mg daily p.o. is encouraged for all patients who are not already receiving daily aspirin (see Section 7.6).

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Background

Prostate cancer is the second-leading cause of cancer death in the United States (2). Though most advanced cancers initially are responsive to androgen ablation therapy, eventually all of these tumors become refractory to androgen deprivation. The prior assertion that chemotherapy is ineffective in the treatment of metastatic hormone refractory prostate cancer (HRPC) is being refuted. Currently, the combination of mitoxantrone and prednisone is FDA-approved for first line therapy for patients with progressive HRPC, based on the results of two randomized trials demonstrating superior palliation with the combination regimen compared with a corticosteroid alone (3,4). However, response proportions have been greatly improved with the use of anti-tubule agents. Docetaxel is one of the most active single agents with 41-46% of patients achieving ≥ 50% post-treatment declines in PSA and 24-40% of patients achieving regression of measurable disease in phase II studies (5).

1.2 Randomized studies with EMP based regimens

Estramustine-based regimens have been compared with mitoxantrone plus prednisone. In a randomized phase II study comparing two different schedules of docetaxel/estramustine phosphate/prednisone versus mitoxantrone and prednisone, Oudard et al., demonstrated ≥ 50% post-treatment declines in PSA in 62% and 67% in the docetaxel-based arms, versus 17% in the mitoxantrone arm (p = .00001) [Oudard, 2002 #14094]. Furthermore, patients treated on the docetaxel-based arms had longer time to PSA progression (9.1-9.5 mos. vs. 1.7 mos, p = .000001), improved pain index (56-79% vs. 41%, p = 0.007), and improved median survival (18-18.6 mos vs. 11.6 mos, p = 0.002).

To confirm the clinical benefits of the microtubule agents, docetaxel-based regimens were compared to mitoxantrone plus prednisone in two multicenter phase III randomized trials (SWOG 9916, TAX 327). SWOG 9916 is an intergroup trial led by Southwest Oncology Group comparing estramustine (280 mg p.o. t.i.d. days 1-5) and docetaxel (60 mg/m^2) every 3 weeks to mitoxantrone (12 mg/m^2) every 3 weeks and prednisone 5 mg p.o. b.i.d. There were 674 eligible patients randomized to the two arms in the SWOG trial. Progression free survival (6 months vs. 3 months, p < 0.0001) and overall survival (18 months vs. 16 months, p = 0.01) favored the docetaxel and EMP treated patients (67). TAX 327 is an industry-sponsored trial, that compared single agent docetaxel (75 mg/m^2) every 3 weeks plus prednisone 5 mg p.o. b.i.d. to docetaxel (30 mg/m^2) on a weekly schedule plus prednisone 5 mg p.o. b.i.d. to mitoxantrone (12 mg/m^2) every 3 weeks and prednisone 5 mg p.o. b.i.d. daily. There were 1006 patients randomized to one of the three arms in this trial. Overall survival was significantly improved in the patients treated with docetaxel + prednisone every 3 weeks compared to mitoxantrone and prednisone (18.9 months vs. 16.4 months, p = 0.009), however the weekly docetaxel arm failed to show any significant survival benefit (68). The proportion of patients that had pain response and post-therapy decline in PSA also significantly favored patients treated with docetaxel and prednisone every three weeks. Results from both of these trials suggest that docetaxel based regimens are superior to mitoxantrone and prednisone. The median survival distribution for taxane treated patients was approximately 18 months and the survival distribution for patients treated with mitoxantrone and prednisone was 16 months in both trials. While these trials did not address the relative contribution of EMP to docetaxel, the aggregate data from these and other trials suggests that EMP adds little to improve overall survival, increases morbidity and that docetaxel plus prednisone would be the most commonly used first line chemotherapeutic regimen in the community.

1.3 VEGF in Hormone Refractory Prostate Cancer

Vascular endothelial growth factor (VEGF) is a glycoprotein important in promoting tumor angiogenesis (13, 14). VEGF may play a role in the pathogenesis and progression of human prostate cancer. Flk-1/KDR receptors are expressed in human prostate cancer and their presence may correlate with higher grade lesions (15). In addition, vascular endothelial growth factor (VEGF) is present in both localized and metastatic prostate tumors as well as the plasma of patients with metastatic disease, and increasing expression may correlate with disease progression (16, 17). CALGB investigators have also recently demonstrated that both plasma and urine VEGF levels in HRPC patients are independent predictors of survival (18, 19), suggesting VEGF blockade may be a reasonable therapeutic approach. Finally, antibodies to VEGF have caused tumor regression in preclinical animal prostate tumor models (20-22). RhuMAb VEGF (bevacizumab) is a humanized murine monoclonal antibody that neutralizes VEGF activity and has shown promise in animal tumor models (23-25). The pharmacokinetics suggest a half-life of about 15 days. Co-administration of chemotherapy drugs did not affect the concentrations of the cytotoxic agents (26).

To evaluate the efficacy and safety of single-agent rhuMAb VEGF in metastatic hormone-refractory prostate cancer (HRPC), a single-center study of anti-VEGF antibody was undertaken at the University of California/San Francisco (27). Fifteen patients were treated with 10 mg/kg rhuMAb VEGF every 14 days for 6 infusions (one cycle) followed by additional treatment for selected patients exhibiting a response or stable disease. After one cycle, none of the 15 patients evaluable for tumor response had an objective complete or partial response. Three possible mixed responses were observed. No patient achieved a ≥ 50% decrease in serum PSA after one cycle, although 4 patients (27%) had a PSA decline of < 50%. The median time to objective progression was 3.9 months, and the median time to PSA progression was 2 months. Toxicity was generally mild with asthenia present in 6 of the 15 patients (40%). Two patients developed severe hyponatremia, although the association with rhuMAb VEGF was unclear. The conclusion was that single-agent rhuMAb VEGF in this dose and schedule did not produce significant objective responses in HRPC. However, this trial was not designed to test the cytostatic effect of the drug, which in retrospect, may be the most important feature of this class of agents.

1.4 Clinical Trials with Estramustine, Docetaxel and Bevacizumab in Hormone refractory Prostate Cancer

The CALGB was a participant in the SWOG 9916 intergroup trial, and simultaneously completed a series of phase II trials based on the estramustine and docetaxel backbone. One of these trials combined carboplatin with estramustine and docetaxel and most recently, another trial (CALGB 90006) investigated the role of the anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab, in combination with chemotherapy. The role of VEGF has been extensively studied in prostate cancer. Antibodies to vascular endothelial growth factors slow the growth in androgen independent prostate xenograft models (28-30). This effect is augmented with the addition of chemotherapy. Previously, plasma VEGF levels were shown to be significantly elevated in patients with castrate metastatic disease and have been associated with disease progression in other cancers (31). As noted above, the CALGB has prospectively studied the significance of VEGF in the plasma and the urine in patients with progressive castrate prostate cancer. VEGF levels were measured in plasma from patients enrolled in CALGB study 9480, an intergroup study of suramin in patients with progressive castrate metastatic disease. VEGF levels inversely correlated with survival time and in a multivariate model VEGF levels remained significant factors for survival at various cut points tested (19). Urine levels of VEGF and basic fibroblast growth factor (bFGF) were also studied in CALGB 9480. Bok, et al., reported that pre-treatment urine VEGF levels were predictive of survival and remained significant in multivariate analysis (18). No significant correlations between urine bFGF levels and survival were found (18).

Based on these data, the CALGB investigated the role of bevacizumab with estramustine and docetaxel in patients with progressive castrate metastatic prostate cancer in CALGB 90006 [Picus, ASCO 2003, updated personal communication]. Seventy-nine patients were treated with this combination (EMP: 280 mg p.o. TID on Days 1 -5; docetaxel: 70 mg/m^2 on Day 2; bevacizumab: 15 mg/kg over 30 min on Day 2). Typical premedication for docetaxel was given and coumadin 2 mg daily was administered to help prevent any thromboembolic disease related to the estramustine. Patients tolerated the therapy well. There was one death due to mesenteric vein thrombosis, one death due to a perforated sigmoid colon diverticulum, 2 patients with a CNS bleed, and 2 patients each with pulmonary embolism and deep venous thrombosis. While these thromboembolic events are of concern, the overall incidence was not dramatically higher than what has been observed with estramustine and docetaxel without bevacizumab. The other toxicities were similar to what was seen in published studies from Savarese and colleagues with estramustine\docetaxel\hydrocortisone. The addition of bevacizumab did not increase overall toxicities of docetaxel and it is expected that combining bevacizumab with higher doses of docetaxel as used in the pivotal trial of TAX 327 (75 mg/m^2) will not alter the toxicity profile. There is some data from the other randomized studies that daily aspirin can possibly reduce the incidence of thrombotic events.

Perhaps more importantly, the results observed with this combination compare favorably with other concurrent combinations tested by the CALGB. When compared to another CALGB triplet trial in which carboplatin was added to estramustine/docetaxel (CALGB 99813), the use of bevacizumab resulted in a post-therapy PSA decline in 58 out of 72 (81%) patients versus 68% of the patients treated with the carboplatin regimen, median time to objective disease progression of 9.7 months compared with 8.1, median time to PSA failure of 9.9 versus 9 months, and overall median survival of 21 months compared with 18 months. These results are encouraging and safety of this regimen would be enhanced with the elimination of estramustine, especially in light of the evolving data suggesting that estramustine adds little to the overall survival of patients.

1.5 Anti-angiogenesis Therapy and Cancer:

The role of anti-angiogenesis therapy in cancer is currently being defined. The results from a randomized phase III trial of 815 patients with untreated metastatic colon cancer comparing irinotecan, 5 fluorouracil and leucovorin with or without bevacizumab showed that the bevacizumab containing arm improved overall survival compared to the control arm (median 20.3 months vs. 15.6 months, p = 0.0003) (70). This trial helped to confirm that anti-angiogenesis therapy is a legitimate therapeutic target. What predicts a therapeutic benefit from anti-angiogenesis therapy is not known, but the pre-clinical activity of anti-VEGF antibodies in xenograft models, the correlation of plasma and urine VEGF levels in castrate metastatic prostate cancer to survival, and the encouraging results of the CALGB phase II study (90006) with estramustine and docetaxel with bevacizumab suggests that anti-angiogenesis therapy has a role in prostate cancer. Further trials are needed to investigate the impact of bevacizumab on survival in patients with HRPC.

1.6 Study Design

The combination of docetaxel and prednisone is becoming the standard of care for hormone refractory prostate cancer. There is a compelling biologic and clinical rationale for utilizing anti-VEGF antibody in patients with prostate cancer. It is possible that bevacizumab will exert cytostatic effects when used with chemotherapy impacting on the rate of disease progression and ultimately on survival. This will be a randomized double blinded placebo controlled phase III trial with an overall survival endpoint in patients with progressive hormone refractory prostate cancer. The blinded control arm will help eliminate investigator bias, which is critically important in drugs that may have cytostatic effects whose overall benefit will not be evident immediately. Because the FDA has approved the use of docetaxel (75 mg/m^2) along with prednisone 5 mg p.o. b.i.d. as the first line chemotherapy in HRPC, this will constitute our control arm. In this study, patients will be randomized to docetaxel 75 mg/m^2 IV repeated every 3 weeks plus prednisone 5 mg p.o. b.i.d. with either bevacizumab (15 mg/kg) IV or placebo every 3 weeks.

1.7 Inclusion of Minorities

Minorities will be eligible for this study without alteration in eligibility criteria. Based on previous data from advanced prostate cancer patients enrolled on CALGB 9594, the accrual targets in individual cells are not large enough to perform subgroup analysis by the two treatment groups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets. However, we plan to perform subset analyses within racial and ethnic groups.

2.0 OBJECTIVES

Primary Objective:

2.1 To determine if the addition of bevacizumab to docetaxel and prednisone increases overall survival compared to docetaxel and prednisone alone in patients with HRPC.

Secondary Objectives:

2.2 To compare the progression-free survival of these two regimens in patients with HRPC.

2.3 To compare the two regimens on the proportion of patients who experience a 50% post-therapy PSA decline from baseline.

2.4 To compare the two regimens with respect to the proportion of patients who experience grade 3 or higher toxicities.

3.0 ON-STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed any necessary therapy and are considered by their physician to be at less than 30% risk of relapse.
- Participants in this study must use adequate contraception for the duration of treatment and for at least three months following the completion of protocol therapy.

4.0 ELIGIBILITY CRITERIA

4.1 Histologic Documentation: Patients must have histologically documented adenocarcinoma of the prostate with progressive systemic (clinically metastatic disease documented on bone, CT or MRI scan) disease despite castrate levels of testosterone due to orchiectomy or LHRH agonist. Castrate levels of testosterone must be maintained.

All eligible patients must have a Gleason sum based on biopsy or TURP at the time of registration.

4.2 Disease Assessment:

At the time of enrollment, patients must have evidence of progressive metastatic disease, either:

- **Measurable disease** with any level of serum PSA (see Section 4.3.1)

  OR

- **Non-measurable disease** with PSA ≥ 5 ng/ml (see Sections 4.3.2 and 4.3.3). Patients with PSA ≥ 5 ng/ml only and no other radiographic evidence of metastatic prostate cancer are not eligible.

4.2.1 Definition of **Measurable Disease/Target Lesions**

Any lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques: 1) physical exam for clinically palpable lymph nodes and superficial skin lesions, 2) chest X-ray for clearly defined lung lesions surrounded by aerated lung **OR** those lesions measured as ≥ 10 mm with a spiral CT or MRI scan.

Measurable lesions (up to a maximum of 10 in number) representative of all organs involved to be identified as target lesions. The sum of the longest diameters (LD) for all target lesions will be calculated and reported as baseline sum LD.

- If measurable disease is confined to a solitary lesion and is not consistent with prostate cancer, then its neoplastic nature must be confirmed by histology.
- Ultrasound may not be used to measure tumor lesions that are not easily accessible clinically.

4.2.2 Definition of **Non-measurable Disease/Non-target Lesions**

Non-target lesions include all other lesions not included in Section 4.2.1, including small lesions with longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan and truly non-measurable lesions, which include:

- Bone lesions
- Pleural or pericardial effusions, ascites
- CNS lesions, leptomeningeal disease
- Irradiated lesions, unless progression documented after RT

4.3 Patients must have demonstrated evidence of progressive disease since the most recent change in therapy. Progressive disease is defined as **<u>any one</u>** of the following (measurable disease, bone scan, **or** PSA progression):

4.3.1 Measurable Disease Progression: Objective evidence of increase > 20% in the sum of the longest diameters (LD) of target lesions from the time of maximal regression or the appearance of one or more new lesions.

4.3.2 Bone Scan Progression: Appearance of one or more new lesions on bone scan attributable to prostate cancer along with a PSA ≥ 5 ng/ml will constitute progression.

4.3.3 PSA Progression: An elevated PSA (≥5 ng/mL) which has risen serially on at least two occasions after the discontinuation of antiandrogen therapy, each at least one week apart. If the confirmatory PSA (#3) value is less (i.e., #3b) than screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression (Figure 1).

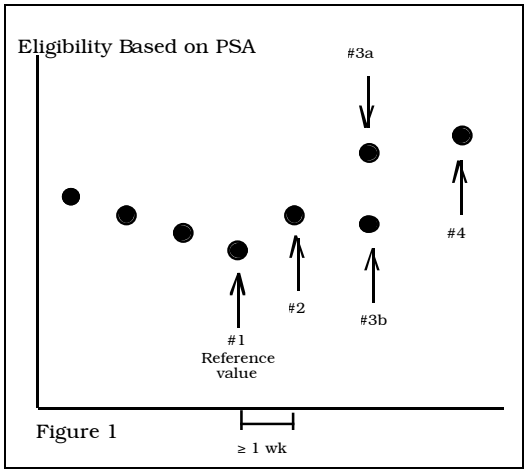


Figure 1

The reference PSA value (#1) must be measured at the time of the discontinuation of antiandrogen therapy; and at least 2 PSA measurements must be made following the end of antiandrogen therapy and prior to registration.

(For the purposes of the nomogram calculator, the last PSA value recorded prior to the initiation of treatment will be considered the baseline PSA.)

4.4 Prior Treatment:

- Progression despite standard androgen deprivation therapy (i.e., LHRH agonist and/or orchiectomy).
- All antiandrogens (e.g., flutamide, megestrol acetate [even if taken for hot flashes], bicalutamide and nilutamide) of any dose must be discontinued at least 4 weeks prior to registration. If improvement following antiandrogen withdrawal is noted, progression must be established using the criteria above.

  Primary testicular androgen suppression (e.g., with an LHRH agonist) should not be discontinued.
- At least 4 weeks since any other hormonal therapy, including ketoconazole and aminoglutethimide. The only exception to this time frame is that 5α-reductase inhibitors (e.g., finasteride, dutasteride) may be discontinued any time prior to registration.
- No prior cytotoxic chemotherapy, including estramustine or suramin.
- No prior anti-angiogenesis agents, including thalidomide and bevacizumab.
- ≥ 4 weeks since major surgery and fully recovered.
- ≥ 4 weeks since any prior radiation (including palliative) and fully recovered.
- ≥ 8 weeks since the last dose of Strontium-89 or Samarium.

4.5 Patients receiving a bisphosphonate must be on a stable dose and must have started the bisphosphonate ≥ 4 weeks prior to initiating protocol treatment. Patients do not have to be on a bisphosphonate to qualify for the study. Patients may initiate bisphosphonate therapy after completion of Cycle 1, if clinically indicated.

Patients enrolled on CALGB 90202 who have documented disease progression and have received at least 4 weeks of open label zoledronic acid treatment, are eligible for this study.

4.6 No known brain metastases (brain imaging (MRI/CT) is not required).

4.7 No current congestive heart failure (New York Heart Association Class II, III or IV).

4.8 Patients with history of hypertension must be well controlled (< 160/90) on a regimen of anti-hypertensive therapy.

4.9 Patients on full-dose anticoagulants must be on a stable dose of warfarin and have an in-range INR (usually between 2 and 3) **or be on a stable dose of LMW heparin**. Patients receiving anti-platelet agents are also eligible. In addition, patients who are on daily prophylactic aspirin or anticoagulation for atrial fibrillation are eligible (see also, Section 7.6 regarding daily aspirin).

4.10 No significant history of bleeding events or GI perforation.

- Patients with a history of significant bleeding episodes (e.g., hemoptysis, upper or lower GI bleeding) within 6 months of registration are not eligible.
- Patients with a history of GI perforation within 12 months of registration are not eligible.

4.11 No recent (within 12 months) arterial thrombotic events, including transient ischemic attack (TIA), cerebrovascular accident (CVA), unstable angina or angina requiring surgical or medical intervention in the past 12 months, or myocardial infarction (MI). Patients with clinically significant peripheral artery disease (i.e., claudication on less than one block) or any other arterial thrombotic event are also ineligible.

4.12 No serious or non-healing wound, ulcer or bone fracture.

4.13 No peripheral neuropathy ≥ grade 2.

4.14 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies are not eligible.

4.15 PC-Spes, Saw Palmetto, and St. John's Wort must be discontinued before registration. The discontinuation of other herbal medications and food supplements is strongly encouraged. Patients may continue on daily vitamins and calcium supplements.

4.16 ECOG performance status: 0-2

4.17 Age ≥ 18.

4.18 Required Initial Laboratory Values (other tests are required; see Section 6.0):

ANC	≥ 1500/μL
Platelet count	≥ 100,000/μL
Creatinine	≤ 1.5 x upper limits of normal
Bilirubin	≤ 1.5 x upper limits of normal**
AST	≤ 1.5 x upper limits of normal
PSA	≥ 5 ng/mL (if non-measurable disease)
Urine protein to creatinine ratio*	< 1.0
Serum Testosterone	≤ 50 ng/dL for patients who have not had bilateral orchiectomy

* See Appendix III for information regarding the calculation of UPC ratio.

** For patients with Gilbert's Disease, ≤ 2.5 X ULN is allowed.

5.0 REGISTRATION/RANDOMIZATION, STRATIFICATION, AND DATA AND SAMPLE SUBMISSION

5.1 Randomization Requirements

Informed Consent: the patient must be aware of the neoplastic nature of his disease and willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form are required.

5.2 CALGB Randomization Procedures

This study uses the CALGB on-line Patient Registration system. Randomization will be accepted only through CALGB Main Member institutions, selected affiliate institutions, and CCOPs using the on-line Patient Registration system. Randomization must occur prior to the initiation of therapy.

Confirm eligibility criteria (Section 4.0). Complete the Registration Worksheet. Access the on-line Patient Registration system via the patient registration icon on the CALGB Information Systems (IS) Application main menu. If the registering CRA requires assistance, he/she may consult the on-line help file located under the help menu of the CALGB IS Application. If further assistance is required, the registering CRA may call the CALGB Registrar (919-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time). Enter the following information:

Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Name of responsible contact (treating physician or responsible CRA)
CALGB patient ID #, if applicable
Patient's initials
Patient's Social Security # or hospital ID #
Patient's date of birth
Patient's gender
Patient's race and ethnicity
Patient's height in centimeters, weight in kilograms, and ECOG performance status
Type of insurance (method of payment)
Patient's postal code (if applicable)
Country of residence (if not USA)
Treatment start date
Date of signed consent
Date of signed HIPAA authorization
Companion study(s) (see Section 5.3)
Eligibility criteria met (no, yes)

When the patient is registered, a patient identification number will be generated. Please write the number in your records. Registration to any mandatory or optional companion studies will be done at the same time as registration to the treatment study. Registration to both treatment and companion studies will not be completed if eligibility requirements are not met for all selected trials (treatment and companions).

After registration is complete the patient may be randomized. The patient is randomized according to the stratification factors indicated in Section 5.4 below, which must be entered to obtain a treatment assignment. Treatment is to begin within 14 days of randomization.

Blinded, patient-specific clinical supplies of bevacizumab/placebo will be requested by the CALGB Statistical Center at the time of randomization and should arrive at

the clinical site within approximately seven to ten days of randomization (see Section 10.6).

The Main Member Institution and registering institution will receive a Confirmation of Randomization. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Data Operations, Hock Plaza, Suite 802, 2424 Erwin Road, Durham, NC 27705.

5.3 Registration to companion studies

5.3.1 Substudies

There are two substudies within CALGB 90401. These correlative science studies must be offered to all patients enrolled on CALGB 90401 (although patients may opt not to participate). The substudies included within CALGB 90401 are:

- PSA as a surrogate marker for survival and validation of novel biomarkers in HRPC, CALGB 150411 (Sections 9.1 and 9.2)
- Pharmacogenomic studies: CALGB 60404 (Section 9.3)

If a patient answers "yes" to "I agree that my blood may be used for research studies to learn about the effects that the experimental treatment may be having." (question #1) in the Model Consent, he has consented to participate in the PSA and novel biomarker studies described in Sections 9.1 and 9.2. The patient should be registered to CALGB 150411 at the same time that he is registered to the treatment trial (90401) and samples submitted per Sections 5.6.1 and 5.6.2.

If a patient answers "yes" to "I agree that my blood may be used for the genetic research studies described above" (question #2) in the Model Consent, he has consented to participate in the studies described in Section 9.3. Patients should be registered to CALGB 60404. Although it is preferable that patients are registered to 60404 at the same time that they are registered to 90401, registration to 60404 may occur up to 60 days following registration to the treatment trial. Samples should be submitted per Section 5.6.3.

5.3.2 Limited access companion study CALGB 70501

CALGB 70501, "Collection of patient-reported symptoms and performance status via the internet," is a separate limited access companion protocol available to a number of selected CALGB institutions. All patients enrolled or enrolling to CALGB 90401 at these specific institutions should be approached and invited to participate in CALGB 70501. Registration should occur simultaneously with the CALGB registration/randomization to CALGB 90401; however, registrations to CALGB 70501 may take place later. Please note that 70501 participants must be registered prior to receiving chemotherapy on Day 1 of Cycle 2 of this study.

5.4 Stratification Factors: Patients will be stratified by:

1. Using the 90401 nomogram developed by Halabi, et al (1), predicted 24 month survival probability:

   Group 1: < 10%; Group 2: 10-29.9%; Group 3: ≥ 30%.

   Variables for the nomogram will include visceral disease (yes or no), initial Gleason score (2-7 or 8-10), ECOG performance status (0, 1 or 2), baseline PSA, LDH, alkaline phosphatase and hemoglobin (see Appendix IV).

2. Age:

   a) < 65 years, b) ≥ 65 years

3. Prior history of arterial events, defined as cardiac ischemia/infarction, CNS cerebrovascular ischemia, peripheral arterial ischemia or CNS hemorrhage (see Section 14.5):

   a) yes, b) no

5.5 Data Submission: Forms should be submitted to the CALGB Statistical Center, Data Operations in compliance with the data submission schedule below. There are two options for submitting forms that use the Teleform barcode and cornerstones:

- The forms may be faxed to the Statistical Center at 919-416-4990. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.
- The forms may be mailed to the CALGB Statistical Center, Data Operations, Hock Plaza, Suite 802, 2424 Erwin Road, Durham, NC 27705.Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

Data Submission: Submit forms to the CALGB Statistical Center, Data Operations at the following intervals:

	Form	Submission Schedule
C-1390 C-1302 C-660 C-1670	90401 Registration Worksheet 90401 Eligibility Checklist 90401 Pre-Study Form 90401 On-Study Form Solid Tumor Evaluation Form 90401 Medications Supplement Form *Baseline Scan Reports*	Within 1 week of the start of treatment
C-1325	90401 Specimen Submission Form*	When whole blood is submitted per protocol
C-1303	90401Treatment Form	At the end of each treatment cycle.
C-1304	90401 Adverse Event Form	After every cycle during treatment and at four weeks after the end of protocol treatment.†
C-1396	90401 Arterial Thromboembolic Event Report	FAX (919-668-9348) to the CALGB Statistical Center within 24 hours of knowledge of ≥ grade 3 thromboembolic event.†
C-1305	90401 Follow-Up Form	Every 3 cycles during protocol treatment; at the end of protocol treatment; then, every 3 months until progression; at 3 months after progression; when new primaries or secondary malignancies occur, and at death.**
C-714	CALGB Prostate Specific Antigen Form	After each cycle during protocol treatment. Thereafter, every 3 months until 5 years after registration or until PSA progression is confirmed.
C-660	Solid Tumor Evaluation Form	Every 3 cycles during protocol treatment starting with scan(s) prior to Cycle 4 until progression. If treatment ends before progression, submit whenever scans are done until non-protocol therapy starts or until progression or relapse.
	Scan reports	Submit for documentation of every non-PSA CR or PR and first non-PSA progression
C-900	CALGB Survival Data Form	Every 6 months from progression until death or 10 years after registration
C-260	CALGB Remarks Addenda	When needed

* Send original with blood sample to the Pathology Coordinating Office and send a copy to the Statistical Center, Data Operations

** If death is treatment related, also submit the CALGB C-1304 Adverse Event Form.

† **Institutions that do not submit adverse event forms in a timely manner may be denied future registrations to this study (see Sec. 14.5).**

Common Toxicity Criteria: This study will utilize the NCI Common Terminology Criteria for Adverse Events version 3.0 for toxicity and adverse event reporting.

5.6 Sample submission for correlative studies

All participating institutions must ask patients for their consent to participate in the correlative substudies planned for CALGB 90401, although patient participation is optional. Surrogate marker analysis for PSA, novel biomarker validation, and pharmacogenomic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 9.0. For patients who consent to participate, blood will be collected at the following time points for these studies:

	Prior to treatment	Prior to chemotherapy on Day 1 of each cycle, beginning with cycle 2*	After treatment, q 3 months until 5 yrs post-registration or progression
Blood[1] (10 mL/red-gray top)	X	X	X
Whole blood[2] (10 mL/purple top)	X (2 tubes)	X	
Whole blood[3] (10 mL/purple top)	X		

1 Serum to be used for surrogate marker analysis for PSA (150411)

2 Plasma to be used for novel biomarker validation (150411)

3 To be used for pharmacogenomic assays (60404). This sample may be submitted up to 60 days following registration to 90401.

* Samples may be collected up to 48 hours prior to chemotherapy

Sample registration and shipment via the LabTrak application is required for all CALGB institutions. For LabTrak assistance, contact the CALGB Help Desk at 1-877-44CALGB. All samples should be labeled with the CALGB treatment study number (90401), patient initials, patient ID number, sample type (i.e., serum or plasma), and the date of collection.

Instructions for the collection and shipping of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

All specimens should be sent to the following address:

CALGB Pathology Coordinating Office
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073 Fax: 614-293-7967

Copies of all forms and reports should also be sent to the CALGB Statistical Center, Data Operations.

5.6.1 Blood submission (for serum)

For patients who consent to participate, serum samples will be used for the surrogate marker analysis for PSA described in Section 9.1.

These samples will be collected prior to the initiation of treatment and prior to chemotherapy on Day 1 of each cycle beginning with cycle 2. Samples will also be collected every 3 months after the completion of treatment until 5 years after registration or until progression.

Collect 10 mL of whole blood in an serum separator tube (SST) (red/gray top). The tube should be inverted several times to mix clot activator with the blood. Allow the blood to clot for a minimum of 30 minutes in a vertical position. Observe a dense clot. Centrifuge clotted blood for 10 to 15 minutes at 1300 x g (or in accordance with manufacturer's instructions). The sample should be refrigerated until shipped on cool pack by overnight mail to the CALGB PCO. The sample should be shipped the same day that the blood is drawn.

5.6.2 Blood submission (for plasma)

For patients who consent to participate, plasma samples will be used for the novel biomarker analysis described in Section 9.2.

Collect two 10 mL tubes prior to the initiation of treatment, then one 10 mL tube prior to chemotherapy on Day 1 of each cycle beginning with cycle 2.

Collect peripheral venous blood in an EDTA (purple-top) tube(s). The tube(s) should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the CALGB PCO. The sample should be shipped the same day that the blood is drawn.

5.6.3 Blood submission (for pharmacogenomic studies)

For patients who consent to participate, whole blood samples will be used for the pharmacogenomic studies described in Section 9.3. This sample will be collected prior to the initiation of protocol treatment.

Collect 10 mL of peripheral venous blood in an EDTA (purple-top) tube. The tube should be inverted several times to mix the EDTA, refrigerated until shipped on cool pack by overnight mail to the CALGB PCO. The sample should be shipped the same day that the blood is drawn.

6.0 REQUIRED DATA

Guidelines for Pre-Study Testing

To be completed within 16 DAYS before registration:

- All blood work, EKG, history and physical.

To be completed within 28 DAYS before registration:

- Chest X-ray#
- CT scan or MRI of abdomen/pelvis

To be completed within 42 DAYS before registration:

- Bone scan

	Prior to Registration	Day 1 of each cycle*	Post Treatment Follow up**
Tests & Observations			
History and Progress Notes	X	X	X
Physical Examination	X	X	X
Pulse, Blood Pressure	X	X†	
Height	X		
Weight/BSA***	X	X	
Performance Status	X	X	
Tumor Measurements	X	A	X
EKG	X		
Drug Toxicity Assessment		X	
Laboratory Studies			
CBC, Differential, Platelets	X	X	
Serum Creatinine	X	X	
PSA	X∞	X	C
AST, Alk. Phos., Bili, LDH	X	X	
Serum Testosterone	X		
C-reactive protein, Albumin	X		
Urinalysis	X	F	
Staging			
Chest x-ray, PA & Lateral#	X	E	D
Bone Scan	X	B	D
CAT Scan **or** MRI of abdomen/pelvis	X	E	D
Correlative studies‡			
Whole blood (for serum & plasma)	*Baseline blood collection is to be completed prior to protocol treatment. See Sec. 5.6 for all collection time points.*		
Whole blood			

* Pre-registration tests, observations and laboratory studies completed within 14 days prior to the first day of treatment need not be repeated. Labs and physical exam may be obtained up to 48 hours prior to docetaxel for all other cycles.

** At least every 3 months until evidence of progression or relapse for a maximum of 5 years after registration.

*** The dose of chemotherapy need not be changed unless the calculated dose changes by ≥ 10%.

† Patients are to be encouraged to measure blood pressure weekly.

‡ For those patients who consent to participate in one or both companion substudies.

∞ Additional pre-registration PSA values are required for those patients demonstrating PSA progression for the purposes of eligibility (see Section 4.3.3). The last PSA value recorded prior to the initiation of treatment will be considered the baseline PSA for this study.

Patients who have received a chest CT (or MRI) need not have a chest x-ray.

A Within 2 days prior to each docetaxel treatment if accessible to physical examination.

B Every 3 cycles beginning prior to Cycle 4 until evidence of progression or relapse. Scans may be done up to 7 days prior to beginning a cycle.

C Every 3 months until PSA progression is confirmed for a maximum of 5 years after registration.

D Staging scans must be repeated after the end of protocol treatment unless performed within the prior 4 weeks. Thereafter, as indicated to follow for disease progression for a maximum of 5 years following registration.

E For patients with measurable disease at baseline, chest x-rays and/or CT scans/MRI are required every 3 cycles beginning prior to Cycle 4 until evidence of progression or relapse. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Sec. 12.1).

F Required only for patients receiving bevacizumab/placebo. All patients receiving bevacizumab/placebo will have a urinalysis performed within 48 hours prior to every bevacizumab/placebo dose; if urine protein is ≥ 2+, 24-hour urine collection or UPC ratio will be required (see Section 8.11).

7.0 TREATMENT PLAN

Protocol treatment is to begin within 14 days of randomization. **This is a randomized, double-blind trial.** Blinded, patient-specific clinical supplies of bevacizumab/placebo will be requested by the CALGB Statistical Center at the time of randomization and should arrive at the clinical site within approximately seven to ten days of randomization (see Section 10.6).

Each cycle is 21 days

RANDOMIZE

ARM A

Dexamethasone	8 mg p.o. 12 hours, 3 hours, and 1 hour prior to docetaxel
Docetaxel	75 mg/m^2 IV on Day 1 each cycle
Placebo	IV on Day 1 of each cycle
Prednisone	5 mg p.o. b.i.d.

ARM B

Dexamethasone	8 mg p.o. 12 hours, 3 hours, and 1 hour prior to docetaxel
Docetaxel	75 mg/m^2 IV on Day 1 of each cycle
Bevacizumab	15 mg/kg IV on Day 1 of each cycle
Prednisone	5 mg p.o. b.i.d.

7.1 Treatment will be continued until disease progression or unacceptable toxicity for a maximum period of two years. In the case of PSA progression, continue treatment until confirmation of PSA progression.

Patients should receive a minimum of 3 cycles of therapy (see Section 13.1.3).

7.2 **Dexamethasone:** During each cycle of therapy, all patients should undergo premedication with dexamethasone 8 mg orally approximately 12 hours, 3 hours, and 1 hour prior to docetaxel (i.e., 8 mg of dexamethasone the night before, the morning of, and just prior to the infusion of docetaxel).

Alternatively, dexamethasone may be given twice daily the day before, the day of, and the day after docetaxel (i.e., 6 doses of 8 mg of dexamethasone during each cycle of therapy).

Lastly, dexamethasone may also be given intravenously according to institutional guidelines.

7.3 **Docetaxel:** 75 mg/m^2 IV over 1 hour, every 21 days.

7.4 **Bevacizumab/Placebo:** 15 mg/kg IV every 21 days administered following docetaxel. The initial dose is to be given over 90 minutes, second dose over 60 minutes, and all subsequent doses over 30 minutes if prior infusions are tolerated without infusion-associated adverse events.

Allergic reactions may occur during or following administration of bevacizumab/placebo. Patients will be monitored for bevacizumab/placebo infusion reactions before, during and after the infusion. For the first cycle, vital signs will be checked prior to the administration of bevacizumab/placebo, midway through the infusion, and 30 minutes following the end of the infusion. Resuscitation equipment and other agents (prednisone, epinephrine, etc) should be available.

7.5 **Prednisone:** 5 mg p.o. b.i.d. beginning on Day 1 of the first cycle.

7.6 The use of **primary, prophylactic G-CSF, pegfilgrastim, or GM-CSF** should be considered for patients predisposed to complications from neutropenia. Predisposing factors include medical history, disease characteristics, age, and performance status (see also, Section 11.5).

7.7 **Aspirin:** 81 mg daily p.o. is encouraged for all patients who are not already receiving daily aspirin. Aspirin is recommended because of the increased risk of arterial thromboembolic events from bevacizumab. Patients who cannot tolerate aspirin or in whom it is contraindicated should not receive it.

7.8 Appropriate prophylactic anti-emetics of the physician's choice may be used.

7.9 Treatment with an LHRH agonist will be continued for patients who have not had bilateral orchiectomy.

8.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

Base dose adjustments on clinical assessment on Day 1 of each treatment cycle.

Docetaxel will not be re-escalated once reduced. If dose reduction for docetaxel beyond –2 is required or if docetaxel is held for more than six weeks (from the date of last docetaxel treatment), docetaxel and prednisone should be discontinued. If docetaxel and prednisone are discontinued, bevacizumab/placebo should be continued until disease progression or unacceptable toxicity.

Dose Levels for Docetaxel

Dose Level	Docetaxel
Level 0	75 mg/m^2
Level -1	65 mg/m^2
Level -2	55 mg/m^2

Bevacizumab/placebo dose is always 15 mg/kg. Bevacizumab/placebo may be held or discontinued as described below, but the dose is not reduced. If bevacizumab/placebo is held for more than six weeks (from the date of last bevacizumab/placebo treatment), bevacizumab/placebo should be discontinued. If bevacizumab/placebo are discontinued, docetaxel and prednisone should be continued until disease progression or unacceptable toxicity.

8.1 Hematologic toxicities

8.1.1 Docetaxel dose modifications for hematologic toxicity

Blood counts on Day 1 of each cycle

ANC/μL		Platelets/μL	Docetaxel
≥ 1,500	and	≥ 100,000	100%
< 1,500	or	< 100,000	Hold*

* Hold docetaxel and bevacizumab/placebo. Repeat counts weekly and resume all therapy when ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. If therapy is held for more than one week, resume with docetaxel at one lower dose level.

Following episodes of grade 3 or 4 neutropenia (ANC < 1000 /mm^2), consideration should be given to the use of granulocyte growth factors (i.e., G-CSF, pegfilgrastim, GM-CSF) for subsequent cycles.

For febrile neutropenia during any cycle, defined as ANC < 500 and T ≥ 38.2°C (100.8°F), docetaxel should be decreased one dose level for all subsequent cycles (see also, Section 11.5.2).

8.1.2 No bevacizumab/placebo dose modifications will be made for hematologic toxicity.

8.2 Hepatic Dysfunction

8.2.1 Dose adjustments for hepatic dysfunction

Bili		AST	Docetaxel
≤ 1.5 x ULN	**and**	> 1.5 – 5 x ULN	Decrease by one dose level
> 1.5 x ULN	**or**	> 5 x ULN	Hold*

- Hold docetaxel and bevacizumab/placebo until bilirubin ≤ 1.5 x ULN or AST ≤ 1.5 – 5 x ULN. Resume with docetaxel at one lower dose level.

8.2.2 If bilirubin > 1.5 x ULN **or** AST > 5 x ULN recurs despite docetaxel dose reduction, bevacizumab/placebo should be discontinued.

8.3 Dose modifications for neurotoxicity

For grade 3 or 4 neurotoxicity, hold both docetaxel and bevacizumab/placebo until the toxicity resolves to grade 2 or less and then resume therapy with docetaxel at one lower dose level. If the disability persists or worsens despite dose reduction, hold both docetaxel and bevacizumab/placebo until toxicity clears to grade 2 or less then resume with docetaxel at one more lower dose level. If therapy is held for more than six weeks (from the date of last docetaxel treatment) or if disability persists after 2 dose reductions, discontinue docetaxel/prednisone.

8.4 Docetaxel dose modifications for gastrointestinal toxicity

For ≥ grade 3 oral ulceration, dysphagia, diarrhea, nausea or vomiting, hold both docetaxel and bevacizumab/placebo. Resume with docetaxel at one lower dose level once symptoms resolve to grade 1 or less.

8.5 Docetaxel and prednisone dose modifications for fluid retention

If symptomatic, treat the patient early with diuretics of the physician's choice. If the patient is not responsive to diuretics, continue docetaxel and bevacizumab/placebo therapy without prednisone. If fluid retention remains refractory, remove patient from all protocol therapy.

8.6 Bevacizumab/placebo dose modifications for hypertension

- **For hypertension controlled with medication (to < 160/90):** Continue therapy.
- **For persistent or symptomatic hypertension:** Hold bevacizumab\placebo therapy. If treatment is delayed for more than one cycle due to uncontrolled hypertension, discontinue bevacizumab/placebo.
- **Grade 4 hypertension:** Occurrence of grade 4 hypertension should lead to permanent discontinuation of bevacizumab/placebo.

Patients who hold or discontinue therapy with bevacizumab/placebo due to hypertension may continue docetaxel/prednisone.

8.7 Bevacizumab/placebo dose modifications for reversible posterior leukoencephalopathy syndrome (RPLS)

For signs and symptoms suggestive of RPLS (e.g., confusion headache, seizures, cortical blindness) skip bevacizumab/placebo. Suspected RPLS should be investigated with MRI as described in Section 10.6. If diagnosis of RPLS is confirmed, bevacizumab/placebo should be permanently discontinued.

If RPLS is ruled out via MRI, the decision on resuming bevacizumab/placebo should be based on the nature of the signs/symptoms: For grade 4 events with likely relationship to bevacizumab, discontinue bevacizumab/placebo; for grade 3 events, bevacizumab/placebo may be resumed if toxicities completely resume within 4 weeks.

Docetaxel/prednisone may be continued at the discretion of the treating physician.

8.8 Bevacizumab/placebo dose modifications for thrombosis:

8.8.1 For grade 3 venous thrombosis or asymptomatic pulmonary thrombosis: Hold bevacizumab/placebo treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab/placebo should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab/placebo may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on stable dose of low molecular weight heparin prior to restarting bevacizumab/placebo treatment.
- The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels).
- The patient must not have had hemorrhagic events while on study

8.8.2 For grade 4 or recurrent/worsening venous thromboembolic events after resumption of bevacizumab/placebo: the patient should be removed from bevacizumab/placebo therapy. Patients may continue therapy with docetaxel/prednisone.

8.8.3 If any clinical evidence of symptomatic pulmonary embolism is seen, patients will discontinue all protocol therapy.

8.8.4 Arterial thrombotic events

- **For grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy**, remove the patient from bevacizumab/placebo therapy. Patients may continue therapy with docetaxel/prednisone.
- **For grade 3 or 4 arterial thrombotic events** including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, remove the patient from bevacizumab/placebo therapy. Patients may continue therapy with docetaxel/prednisone.

8.9 Bevacizumab/placebo dose modifications for hemorrhage/bleeding

- **For grade 3 hemorrhage/bleeding:** Discontinue bevacizumab/placebo; once hemorrhage or bleeding resolves, protocol therapy with docetaxel and prednisone may be continued at the treating physician's discretion.
- **For grade 4 hemorrhage/bleeding:** Discontinue all protocol therapy.

8.10 Dose modifications for GI perforation and wound dehiscence

- **For any grade GI perforation, GI leak, or intra-abdominal fistula:** Discontinue all protocol therapy.
- **For wound dehiscence requiring medical or surgical intervention:** Discontinue all protocol therapy.

8.11 Bevacizumab/placebo dose modifications for proteinuria: Urinalysis is to be done within 48 hours prior to each bevacizumab/placebo dose. For 2+ proteinuria, the scheduled dose of bevacizumab/placebo may be given while awaiting the results of the UPC (urine protein to creatinine) ratio or 24-hour collection. For > 2+ proteinuria, skip bevacizumab/placebo while awaiting results of the UPC ratio or 24-hour urine collection. See Appendix III for information regarding the calculation of UPC ratio.

- **For UPC Ratio < 2.0 or urine protein < 2 g/24 hours:** Bevacizumab/placebo may be given as scheduled
- **For UPC Ratio ≥ 2.0 or urine protein ≥ 2.0 g/24 hours:** Hold bevacizumab/placebo therapy until resolved to UPC < 2.0 or urine protein < 2.0 g/24 hours. If bevacizumab/placebo treatment is delayed for more than one cycle due to proteinuria, discontinue bevacizumab/placebo. Docetaxel and prednisone may be continued.
- **For UPC Ratio ≥ 4.0 or Nephrotic Syndrome:** Discontinue bevacizumab/placebo. Docetaxel and prednisone may be continued.

8.12 Docetaxel dose modifications for erythema, desquamation

- **Grade 0-2:** No change
- **Grade 3-4**: Hold both docetaxel and bevacizumab/placebo until the toxicity resolves to grade 2 or less and then resume with docetaxel at one lower dose level. If toxicity recurs, remove the patient from all protocol treatment.

8.13 Hypersensitivity and infusion reactions

In the event of any grade 3 or 4 hypersensitivity reactions, discontinue all protocol therapy.

8.13.1 Docetaxel dose modifications for hypersensitivity reactions

- **Grade 1:** Slow the rate of infusion until resolution of symptoms, then complete infusion at the initial planned rate.
- **Grade 2:** Stop infusion. Give diphenhydramine 50 mg IV with dexamethasone 10 mg IV plus an H_2 blocker, all at the physician's discretion. Resume docetaxel infusion after recovery. Pretreat with diphenhydramine and H_2 blocker for future cycles.

8.13.2 Bevacizumab/placebo dose modifications for infusion and hypersensitivity reactions

The initial bevacizumab/placebo dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated. Patients may receive premedication with diphenhydramine 25 to 50 mg intravenously 30 minutes prior to bevacizumab/placebo if they have previously experienced allergic reactions.

8.14 Dose adjustments for corticosteroid toxicity

Prednisone may be discontinued if severe or uncontrolled hyperglycemia is encountered; tapered per the treating physician's discretion. Treatment with bevacizumab/placebo and docetaxel may be continued. (Also, see Section 8.5 for instructions regarding fluid retention.)

Prednisone and dexamethasone may also cause insomnia and mental status changes. Treating physicians may modify the dose of dexamethasone and/or discontinue prednisone as clinically indicated.

8.15 For patients who require surgery while on study, it is recommended that bevacizumab/placebo be discontinued for at least 60 days prior to surgery whenever possible. Re-initiation of protocol therapy should be discussed with the CALGB Study Chair.

8.16 For persistent fatigue interfering with activities of daily living (grade 2/3), docetaxel and/or bevacizumab/placebo may be held for up to 6 weeks at the discretion of the treating physician.

8.17 Other non-hematologic toxicities

For all other ≥ grade 3 non-hematologic toxicities not described above, hold all protocol treatment and monitor toxicity at least weekly. If toxicity resolves to ≤ grade 1 within 6 weeks, treatment may be resumed, with docetaxel at one lower dose level.

8.18 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, **all dosing is to be determined solely by the patient's actual weight without any modification unless explicitly described in the protocol**. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. **Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on CALGB protocols.

9.0 CORRELATIVE SCIENCES COMPANION STUDIES

There will be three components of the correlatives studies and all patients are encouraged to participate. Part A will be to determine serum PSA values using a unified assay\laboratory to prospectively evaluate the validity of PSA as a surrogate marker and Part B will evaluate the utility of novel biomolecular markers in hormone refractory prostate cancer. Parts A and B will comprise the companion study 150411. Part C, CALGB 60404, will be a pharmacogenetic companion study evaluating germline polymorphisms in patients and correlating the clinical outcomes in patients treated with docetaxel plus prednisone with or without bevacizumab.

9.1 PSA as a surrogate marker for outcome

9.1.1 Background

A potential surrogate endpoint for survival is PSA levels. PSA has been shown to be a strong marker of progression-free survival and death in patients with hormone sensitive disease. In retrospective studies, several investigators have reported that PSA decline of greater than 50% correlated with improved survival and these findings have also been validated in independent studies. However not all investigators have been able to correlate PSA decline from baseline with improved survival. PSA decline has been considered as a potential marker in men with HRPC, but its use has not been validated.

Prentice's criteria require that for an endpoint to be surrogate for the "true" endpoint, three conditions should be satisfied. First, there is a treatment effect with respect to the surrogate endpoint. Second, the surrogate endpoint is a prognostic factor of the true endpoint, and finally that the surrogate endpoint should capture all treatment effect on the true endpoint (32).

In this study we will prospectively explore the use of PSA levels as surrogate endpoints for overall survival. We will use Prentice's criteria to determine if PSA PFS, 50% post-therapy decline in PSA at 12 weeks from from baseline, and PSA slope are potential surrogate endpoints for overall survival. If the PSA endpoints are found to satisfy Prentice's criteria, these findings will be trial-specific and will not be generalizable to other trials with different agents or patient populations. In other words, the PSA endpoints will be not established as surrogate endpoints of overall survival.

9.1.2 Objectives

9.1.2.1 To determine prospectively whether PSA progression is a surrogate endpoint for overall survival.

9.1.2.2 To determine prospectively whether a 50% post therapy decline in PSA at 12 weeks from baseline is a surrogate endpoint for overall survival.

9.1.2.3 To assess prospectively whether post-therapy PSA slope is a surrogate endpoint for overall survival.

9.1.3 Methods

Sample collection and laboratory methods: The PSA slope will be defined as the post-randomization chemotherapy PSA slope and will be calculated assuming first order kinetics and using a minimum of three PSA values. All PSA measurements will be made using a single centralized assay with the exception of the PSA data collected prior to the patient entering the study. However, the pre-randomization PSA history will be obtained dating back to the patient's last three (or four) PSA measurements used to determine PSA progression.

Blood samples will be sent to the CALGB PCO for serum collection, aliquoting, and storage. Samples will be submitted every three weeks (once per cycle) until the end of protocol treatment, then every 3 months until 5 years after registration or until progression. Aliquoted samples will be batched and sent to the clinical laboratory at Memorial Sloan Kettering Cancer Center, directed by Dr. Martin Fleisher to have PSA determination performed using the Tosoh Nexia IEA assay.

Assessing PSA slope, PSA PFS, and PSA decline at 12 weeks from baseline as surrogate endpoint of survival: Prentice's criteria will be applied to determine if PSA PFS, 50% post-therapy decline in PSA at 12 weeks from baseline, and PSA slope are potential surrogate endpoints for overall survival. The proportional hazards model will be used to test if the treatment is prognostic of overall survival and of the surrogate endpoints. Next, the proportional hazards model will be used to test if the surrogate endpoints are prognostic of overall survival. Finally, the proportional hazards model will be used to test if the treatment effect on overall survival is explained by the surrogate endpoints. That is, we will test if survival is independent of treatment given that the patient has failed biochemically (or did not experience a 50% decline in PSA at 12 weeks from baseline) and if survival is independent of the treatment given that the patient did not fail (or experience a 50% decline in PSA at 12 weeks from baseline).

9.2 Validating The Role Of Novel Bio-Markers In HRPC

9.2.1 Background

Over the past 5 years the CALGB Genitourinary Correlative Science Working Group has used plasma collected prospectively from a subset of patients who participated in a prior CALGB study (9480) to demonstrate prognostic significance of individual candidate biomarkers. This phase III study included 390 patients treated with three different doses of suramin and demonstrated no significant survival advantage for any arm (35). Nonetheless, the subset of patients with samples was invaluable in identifying the prognostic significance of RT-PCR of peripheral mononuclear cell (PMC) DNA for PSA (36), plasma vascular endothelial growth factor (VEGF) (19), chromogranin A (CgA), and interleukin-6

(IL-6). Respective cut points for each of these markers were identified and were found to be independent prognostic "host" factors. Unfortunately, the limited size of this one trial and the number of factors involved prohibited a more comprehensive analysis involving multiple biomarkers and ultimately creation of a more cancer-specific nomogram. The current trial represents an ideal opportunity to prospectively test these biomarkers and confirm their independent prognostic significance and to attempt to create a more comprehensive prognostic model of HRPC. The value of a biomarker-rich prognostic model of HRPC is two-fold. First, the clinical utility of this model would allow us to better define our patient population for both clinical trials as well as for appropriate standard care. Patients with particularly poor-risk disease might be candidates for more investigative treatments early in their course, while relatively good risk patients could benefit from more standard therapeutic approaches. ELISA assays to measure these biomarkers are routinely performed for a number of other circulating factors, including PSA, and represent a feasible wide-scale application. Second, the prognostic significance of some biomarkers would suggest a potential functional role in HRPC for the particular signaling pathway they represent. Prospectively tested cut points would help determine appropriate subsets of HRPC patients to test targeted approaches against these pathways. Combinations of biomarkers might even identify otherwise unappreciated biologic associations. Evaluation of these biomarkers might also have predictive value for response to therapy.

Hypotheses: Plasma VEGF, IL-6 and CgA levels have independent prognostic significance in men with HRPC. When combined, these biomarkers may have greater prognostic significance. In addition, changes in VEGF, IL-6 and CgA levels may predict for response to docetaxel/prednisone with or without bevacizumab chemotherapy. Finally, RT-PCR of PMC DNA has prognostic significance in men with HRPC and may correlate with elevated levels of plasma VEGF, IL-6 or CgA.

Preliminary Data

Plasma VEGF levels are significantly elevated in patients with HRPC compared to patients with localized disease and have been associated with disease progression in other cancer patient populations (17, 19, 37, 38). Therefore, we measured VEGF levels in plasma prospectively collected from patients enrolled onto CALGB 9480, an intergroup study of suramin in patients with HRPC, in order to determine if these levels had prognostic significance (19). Plasma VEGF levels in this population ranged from 4 to 885 pg/mL, with a median level of 83 pg/mL. As a continuous variable, plasma VEGF levels inversely correlated with survival time ($p = 0.002$). Using various exploratory cut points, plasma VEGF levels appeared to correlate with survival. In multivariate models in which other prognostic factors (serum PSA, alkaline phosphatase, evidence of measurable disease, hemoglobin) were included, plasma VEGF level was significant at various cut points tested, particularly at a cut point of ≥ 260 pg/mL (see Table). While these data are exploratory and need to be confirmed in an independent data set, these do suggest that VEGF may have clinical significance in patients with HRPC.

Multivariate model of plasma VEGF levels predicting survival time among 197 patients

Factor	HR (95% CI)	p-value
VEGF (> 260 vs. ≤ 260)	2.42 (1.29-4.54)	0.006
Measurable Disease (yes vs. no)	2.01 (1.36-3.00)	< 0.001
Alkaline Phosphatase (> 170 vs. ≤ 170)	1.60 (1.05-2.44)	0.030
Baseline PSA (> 150 vs. ≤ 150)	1.48 (1.0-2.20)	0.050
Hemoglobin (> 12.6 vs. ≤ 12.6)	0.95 (0.64-1.42)	0.810

Plasma CgA levels in prostate cancer patients may reflect extent of tumor neuroendocrine phenotype. The hypothesis that CgA levels are of prognostic value in patients with metastatic HRPC was therefore tested. Pretreatment plasma was collected from 390 patients with metastatic HRPC enrolled in CALGB 9480, a study of 3 different dose levels of suramin. Plasma CgA levels ranged from 7.7-19.3 U/L, with a median level of 12 U/L. In univariate analysis, plasma CgA levels inversely correlated with survival times at the median CgA level (CgA < 12 versus ≥ 12) with survival 17 months (95% CI 14-19) compared to 11 months (95% CI 8-14, p = 0.014) and at all exploratory cut points including CgA ≤ 9.5 versus > 9.5 with survival 19 months compared to 12 months (p = 0.0015). In multivariate models in which other prognostic factors (performance status, prostate specific antigen (PSA), lactate dehydrogenase (LDH)) were included, plasma CgA levels remained predictive of overall survival. These results support the hypothesis that plasma CgA levels correlate with outcome in HRPC patients.

Plasma IL-6 level has been associated with prostate cancer progression in several small studies (39-43). In order to evaluate its prognostic significance for survival in metastatic HRPC patients, IL-6 was measured in plasma collected at baseline from patients in a large cooperative group study (CALGB 9480). Patient characteristics on the 191 samples tested were similar to the overall cohort. The median IL-6 level for the cohort of 191 patients was 4.80 pg/mL. The survival time among patients with IL-6 levels less than 4.80 pg/mL was 19 months (95% CI = 17-22) compared to 11 (95% CI = 8-14) months among patients with IL-6 levels > 4.80 pg/mL (p = 0.0004). In multivariate analysis, adjusting on performance status, LDH and PSA level, the hazard ratio was = 1.38 (95% CI = 1.01-1.89, p = 0.043) for patients with IL-6 levels above 4.80 pg/mL compared to patients whose levels are ≤ 4.80 pg/mL. By comparison, a cut point of 13.31 pg/mL (24% of the population was above this point) revealed robust prognostic significance in the same multivariate model with a hazard ratio = 2.02 (95% CI = 1.36–2.98; p = 0.0005). These findings suggest that IL-6 levels should be considered in prognostic models and support the rationale for targeted therapy against IL-6 in patients with HRPC.

RT-PCR of PMC DNA for PSA: Several reports indicate the importance of circulating prostate cancer cells as a potential marker of relapse or survival (36, 44-47). Using CALGB 9480, we first reported that patients being treated with chemotherapy who had no detectable circulating cells as measured by reverse transcriptase polymerase chain reaction (RT-PCR) for prostate-specific antigen (PSA) had a longer survival time than patients in whom circulating cells were

detected (36, 44). Further, RT-PCR for PSA was reported as an independent prognostic factor for survival in men with HRPC (36). A confirmatory study was performed using data from CALGB 9583 (48). Twenty-one percent of samples from the study were non-informative for RT-PCR. In the remaining 162 patient samples, the presence of RT-PCR for PSA-positive patients was found to be a prognostic factor predictive of poor survival. The median survival time for patients with a positive RT-PCR test was 11 months (95% CI = 8-15 months) compared with 21 months (95% CI = 18-27 months) for patients with a negative RT-PCR test (p = .001). In multivariate analysis, RT-PCR for PSA was the second most significant predictor of overall survival adjusting for age, LDH, PSA, performance status, and hemoglobin.

9.2.2 Objectives

9.2.2.1 To prospectively determine the prognostic significance of baseline plasma VEGF level > 260 pg/mL on overall survival in men with HRPC in a multivariate model adjusting on known prognostic factors.

9.2.2.2 To prospectively determine the prognostic significance of plasma CgA level > 9.5 U/L on overall survival in men with HRPC in a multivariate model with other known prognostic factors.

9.2.2.3 To prospectively determine the prognostic significance of plasma IL-6 level > 13.31 pg/mL on overall survival in men with HRPC in a multivariate model with other known prognostic factors.

9.2.2.4 To prospectively determine the prognostic significance of RT-PCR for PSA in men with HRPC in a multivariate model adjusting on known prognostic factors.

9.2.2.5 Evaluate the predictive value of plasma VEGF, IL-6 and CgA levels for response to docetaxel/prednisone +/- bevacizumab chemotherapy.

9.2.2.6 To determine the association between elevated VEGF, IL-6, CgA levels, RT-PCR for PSA status with other known prognostic markers and to develop a comprehensive predictive nomogram for survival.

9.2.3 Methods

Plasma collection and processing: Blood will be collected at baseline and with each cycle of therapy. 10 mL of blood will be collected in EDTA tubes and shipped on cool pack by overnight mail to CALGB Pathology Coordinating Office (care of Scott Jewel). Within 12 hours of receipt all samples will be centrifuged at 4° C twice to ensure no platelet contamination of supernatant; initially at 2500 rpm for 10 minutes and then at 4000 rpm for a further 10 minutes. Platelet depleted plasma will be aspirated and samples will be aliquotted into 200 μL samples and stored at -70°C for later batch analysis in the laboratory of Dr. Dan George at Duke University. In addition, the buffy coat will be removed from all samples following centrifugation and RNA isolation will be performed as detailed below. All RNA samples will be frozen at -70°C for later batch analysis in the laboratory of Dr. Phil Kantoff at Dana-Farber Cancer Institute.

Measurement of plasma VEGF level (pg/mL) will be determined in duplicate using a Quantiglo chemiluminescent ELISA kit (R&D Systems, Minneapolis, MN) following manufacturer's instructions. A MLX Luminometer (DYNEX Technologies, Chantilly, VA) will be used to measure light intensity correlating with VEGF binding.

Measurement of plasma CgA level (U/L) will be determined in duplicate using a quantitative sandwich immunoassay (DAKO Corp. Carpinteria, CA, Cat. No. K0025) following manufacturer's instructions. Normal range for CgA 10 U/L mean, with range 2-18 in healthy persons.

Measurement of plasma IL-6 level (pg/mL) will be determined in duplicate using a microplate luminescence detection system (Dynex Technologies, Chantilly, VA) and a human IL-6 immunoassay Quantiglo kit (R&D Systems, Minneapolis, MN). Quantitative levels of IL-6 can be accurately detected from 0.3-20,000 pg/ml using 300 μL of plasma.

Measurement of RT-PCR for PSA: Details regarding RNA isolation and the RT-PCR assay have been published elsewhere (36). Briefly, RNA is isolated from the mononuclear cell fraction by single-step guanadinium thiocyanate extraction. The RNA is reverse transcribed using a primer previously described and II RNase H Reverse transcriptase (Gibco BRL, Gaithersburg, MD) to synthesis cDNA for PSA and actin separately. These samples will be analyzed by Dr. Philip Kantoff's laboratory.

9.3 Pharmacogenetic Companion Study

There is increasing evidence which suggests that germline polymorphisms related to anticancer therapeutics metabolism, transport, and resistance correlate with drug response; furthermore, germline polymorphisms related to therapeutic targets and/or therapeutic pathways might also help predict therapeutic outcomes (49, 50).

This study offers an excellent opportunity to evaluate the role of genetic variants in several relevant genes responsible for metabolism, transport or toxicity of docetaxel and bevacizumab, which might influence the eventual drug response and/or toxicity of these agents.

9.3.1 Candidate Gene Approach: Drug Metabolism and Transport

Assays for genetic variants will be performed for various genes listed below: *ABCB1*, *TUBB/TUBA2*, *CYP3A4/5*, *VEGF*. These candidate genes were chosen based on their established influence on *in vivo* disposition or cytotoxicity of docetaxel or bevacizumab. Docetaxel undergoes degradation via the cytochrome P450 enzymes CYP3A (51). Recent studies have demonstrated that polymorphisms in *CYP3A5* can lead to significant interindividual and interracial differences in the CYP3A-dependent drug metabolism (52-54). These polymorphisms are common, and are due to splice variants leading to transcription of a false exon (*3A5*3, 3A5*6* and *3A5*7* alleles) with associated lack of CYP3A5 protein expression. Most individuals lack CYP3A5, but when CYP3A5 is present, it is associated with a greater total CYP3A activity. The expression of CYP3A5 requires the presence of at least one *3A5*1* allele. Such germline polymorphisms with putative functional consequence in both *CYP3A4* and *CYP3A5* (*CYP3A4*1B, CYP3A4*3, CYP3A5*3, CYP3A5*6*) are found at frequencies of 5 to 38% in the general population (52-54). Our primary hypothesis is that patients with *CYP3A5* variants will be at higher risk of severe toxicity from docetaxel therapy.

Alternatively, docetaxel can be transported out of cells via *ABCB1*, with polymorphisms such as C3435T influencing the rate of drug efflux (allele frequency 25-40%) (55). Hence, patients with a homozygous variant genotype

might be at higher risk of toxicity, but lower risk of therapy failure after docetaxel therapy. Genetic polymorphism in the cellular targets for docetaxel, alpha and beta tubulin, have also been described and are putative mediators of cytotoxicity (56). Thus, patients with variants in tubulin genes might have poorer survival after docetaxel therapy.

Bevacizumab has been shown to recognize and neutralize all VEGF isoforms. The regulatory region of *VEGF* contains many transcription factor-binding sites and its transcriptional as well as translational regulation appears to be quite complex (57, 58). *VEGF* variants in the *VEGF* promoter and UTRs have been associated with altered VEGF levels (59-61). *VEGF* polymorphisms have also been linked to altered disease risk (62). Given the fact that bevacizumab directly neutralizes VEGF, it is quite likely that *VEGF* variants, which are associated with higher VEGF levels, could influence the drug response to such a therapy. One such common variant (936 C>T) in the 3'UTR of the *VEGF* has been associated with VEGF plasma levels such that the individuals with CC genotype had significantly higher VEGF levels than individuals with CT or TT genotypes, and about 71% of a Caucasian population studied carried the CC genotype (61). We hypothesize that patients with significantly higher expression of VEGF will most likely benefit from anti-VEGF therapy. Furthermore, evaluating the role of other *VEGF* variants might also clarify any underlying influence heritable differences in altered VEGF levels might have on prostate cancer biology or treatment (62).

Finally, in addition to specific hypothesis testing for the above candidate genes, this study will also provide the framework for hypothesis generation investigations of genotype and/or haplotype in additional candidate genes of putative importance to drug response of the agents being evaluated in this study.

9.3.2 Genome-Wide Approach: SNP Scan of DNA

Most pharmacogenetic analyses have taken a candidate gene approach that utilizes biological data to guide the selection of drug response genes in a pathway. This approach is limited by our knowledge of the mechanisms underlying the phenotypes. In the case of drug response phenotypes, most candidate gene studies have focused on drug metabolizing enzymes and transporters, thus limiting the chance of discovering causal SNPs not involved in mediating drug levels [71,72]. In contrast, a genome-wide approach collects SNP data across the entire human genome and has significant power to detect common variants that confer a modest risk for a complex phenotype [73]. Genome-wide studies capitalize on the large number of SNPs (more than 10 million available in dbSNP) that have been localized and validated across the genome, a majority of which have resulted from the HapMap project [74]. This valuable collection of publicly available, validated SNPs has provided the framework for performing genome-wide association studies. Recent technological advancements in genotyping platforms have also enabled the development of genome-wide associations. Searching the whole genome in an association study requires genotyping of anywhere between 10^5 to 10^6 markers across the genome [75-78]. Until recently, this approach was fiscally prohibitive and impractical. However, new gene chip platforms from Affymetrix and Illumina have made large scale genotyping feasible and cost effective. The Illumina HumanHap550 chip that will be used in this study has the capacity to genotype over 555,000 SNPs simultaneously. In addition, there are 4,300 SNPs in regions of copy number variations (CNVs), thus allowing for the detection of CNVs as well. This new capability represents a paradigm shift in the number of genotypes that can be evaluated in any given individual with one genotyping assay and provides a platform for the identification of novel genes involved in the response to and toxicity associated with docetaxel and bevacizumab.

An increasing number of reports of significant findings from genome-wide association studies in cancer are being published. To date, these have all focused on SNPs associated with risk of developing cancer, and include studies in prostate [79-83], colorectal [84-86], lung [87] and breast cancer [88-90]. The success of these studies illustrates the power and validity of this approach for identifying genetic causes of disease. To date, there are no published reports of genome wide association analyses in cancer pharmacogenetics. The relatively large size of CALGB 90401 and robust response and toxicity phenotype data make it an ideal sample set for whole genome analysis. The identification of SNPs that contribute to response and toxicity of the two widely used drugs studied in CALGB 90401 will lead to additional studies to understand the mechanism for these associations and to investigate the application of genetic information for the optimization of prostate cancer therapy.

9.4 Objectives

9.4.1 To determine if patients with a genetic variant of *CYP3A4/5* have a higher rate of leukopenia and neutropenia from docetaxel based therapy.

9.4.2 To determine if patients with a genetic variant *ABCB1* have a higher rate of severe toxicity from docetaxel based therapy.

9.4.3 To evaluate if patients with a genetic variants of *TUBB/TUBA2* will be at a risk of lower response or survival from docetaxel based therapy.

9.4.4 To determine if *VEGF* variants are associated with differences in response to bevacizumab therapy.

9.4.5 To determine candidate genes for neutropenia and hypertension using genome-wide association studies.

9.5 Study Design/Methods

Patients have consented to the isolation of DNA for genetic investigation in this study, for the purpose of learning how genes influence the effectiveness and side effects of prostate cancer treatment, as specified in the embedded pharmacogenomic protocol 60404. The number of DNA samples that are currently available at the CALGB PCO is approximately 830. Phenotypic data will be extracted from the CALGB database by the CALGB statistical group.

Blood will be obtained from all patients enrolled in the study for pharmacogenetic evaluation. Investigation of polymorphisms will take place in germline DNA extracted from peripheral whole blood (10 mL) collected in EDTA (purple top) Vacutainer tubes prior to the start of the study. Blood will be sent to the CALGB Pathology Coordinating Office (PCO) and genomic DNA will be extracted using a commercially available kit such as Qiagen. The concentration and quality of DNA will be quantified by ultraviolet spectroscopy. All DNA samples will be stored at the PCO until they are distributed to the appropriate laboratory for analysis.

The typical yield of DNA from the CALGB 90401 samples is 12 ug (range of 5-20 ug). We will need up to 5 ug for whole genome analysis, leaving on average 7 ug for planned candidate gene analyses. A minimum of 2.5 ug of DNA from each subject will remain at the PCO for future genotyping, but typically this will be ≥ 7 ug. Considering that a typical candidate gene analysis of a single SNP requires 1-5 ng of DNA, there will be sufficient DNA remaining at the PCO to perform >500 SNP genotyping assays (and on average > 1400 assays).

9.5.1 Candidate Gene Analysis

Aliquots of DNA will be sent to the PET committee colleagues for genotype analysis. Genotyping for *VEGF* will be performed using previously published methods (63). Gentoyping for *CYP3A4/5* variants will be performed based on established and published methods (52-54). Genotyping for *ABCB1, TUBB* will be carried out using published methods (56, 69). If more efficient alternative genotyping methods become available in the future, the PET committee colleagues will change the genotyping approach to optimize the resource utilization. The genotyping information will be correlated with clinical and correlative data collected in this study.

9.5.2 Genome-Wide SNP Scan

Aliquots of DNA will be sent to the Riken Institute for the whole-genome analysis. For the whole-genome analysis, the genotyping will be performed at the laboratory of Dr. Yusuke Nakamura and Dr. Hitoshi Zembutsu at the Riken SNP Research Center and the University of Tokyo Human Genome Center, Japan. In the Nakamura/Zembutsu laboratory, the current plan is that each DNA sample will be analyzed by two platforms. The first platform is the Illumina HumanHap550 SNP chip for genome-wide screening and the analysis will be performed according to the recommended Illumina protocol. Each Illumina HumanHap550 chip requires 750 ng of DNA and additional sample will be used for repeat assays where necessary.

Illumina's HumanHap550 Genotyping BeadChip enables whole-genome genotyping of over 555,000 SNP loci efficiently and accurately on a single BeadChip. The HumanHap550 BeadChip is powered by the Infinium™ II assay, which uses a single-tube, whole-genome amplification method that does not require PCR and enables intelligent SNP selection using tagSNPs. TagSNPs are loci that can serve as proxies for many other SNPs. The use of tagSNPs greatly improves the power of association studies, as the same information and power from a larger number of SNPs can be gathered by genotyping only a subset of loci. TagSNPs on the HumanHap550 BeadChip were selected from the recently completed International HapMap Project.

The second platform that will be used by the RIKEN investigators is the combination of Invader assays with multiplex-PCR for target SNP genotyping. More than 7,000 variants in 267 possible drug-related genes can be genotyped using pre-established assays developed in Dr. Nakamura's lab [91]. The number of variants to be genotyped with the Invader assays might be less than 7,000 due to redundancy with the coverage in the Illumina platform.

10.0 DRUG FORMULATION, AVAILABILITY AND PREPARATION

10.1 Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

10.2 Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with un preserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

10.3 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

10.4 Docetaxel (Taxotere®)

Please refer to the FDA-approved package insert for docetaxel for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Availability

Docetaxel (Taxotere®) is commercially available in 20 mg and 80 mg vials. It is supplied as a concentrate containing 40 mg/mL in polysorbate 80. the accompanying diluent is 13% w/w ethanol in water for injection.

Storage and Stability

Unopened packages of docetaxel plus diluent may be stored at room temperature or under refrigeration. If stored under refrigeration, vials should be allowed to stand at room temperature prior to dilution. The initial diluted solution is reported to be stable up to 4 weeks under refrigeration or at room temperature. Infusion solutions prepared in PVC containers are reported to be stable for four days. The further diluted solutions for infusion prepared in polyolefin containers are reported to be stable for 4 weeks at room temperature (Pharm World Sci, 1999 June; 21:137-41).

Preparation

The vials of both docetaxel and diluent contain overfill. Docetaxel should be diluted with the entire volume of accompanying diluent. This results in a concentration of 10 mg/mL after dilution. The desired dose should be further diluted in 250 mL of 0.9% sodium chloride or 5% dextrose for IV infusion. Doses of docetaxel of greater than 200 mg should be further diluted in a larger volume of infusion solution in order to maintain a final concentration of 0.3 to 0.74 mg/mL.

Administration

The docetaxel infusion should be administered intravenously, as a 1 hour infusion. Docetaxel will be administered before bevacizumab/placebo.

Toxicities

Hematologic: The usual dose limiting toxicity is neutropenia, which is dose and schedule dependent and rapidly reversible. Thrombocytopenia is uncommon and rarely severe. Hematologic toxicity is greater in patients with hepatic dysfunction.

Allergic (hypersensitivity) reactions: Severe hypersensitivity reactions (hypotension and/or bronchospasm, or generalized rash/erythema) have been reported in approximately 2% of patients receiving dexamethasone pretreatment. Minor reactions do not require interruption of therapy. Patients should not be re-challenged with docetaxel if they develop a grade 4 hypersensitivity reaction.

Fluid retention: Fluid retention commonly begins in the lower extremities and may become generalized. Severe fluid retention may be characterized by peripheral edema, generalized edema, pleural effusion, dyspnea, cardiac tamponade or ascites. The likelihood of fluid retention may increase with increasing cumulative dose of docetaxel. Recommended pretreatment to prevent fluid retention consists of dexamethasone. Moderate fluid retention has been reported in 27% and severe in 6.5% of patients despite dexamethasone pretreatment.

Neurologic: Severe neurosensory symptoms (paresthesia, dysesthesia, pain) have been reported in 6% of patients. The dose of docetaxel should be modified for moderate or severe symptoms.

Cutaneous: Localized erythema of the extremities with edema followed by desquamation has been observed. In the case of severe skin toxicity, an adjustment in dosage is recommended. Nail changes, which predominantly include hypo- or hyper-pigmentation and occasionally onycholysis, have occurred in 1-2% of patients. Alopecia is seen in the majority of patients treated with docetaxel.

Gastrointestinal: Gastrointestinal reactions are generally mild to moderate. Severe reactions (nausea, vomiting, diarrhea, stomatitis) have been reported in approximately 5% of patients.

Cardiovascular: Hypotension has been reported in less than 5% of patients. Heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension have been reported rarely.

Miscellaneous: Myalgias and arthralgias have been reported in 10-20% of patients. Myalgias are severe in less than 2%. Severe asthenia has been reported in 11% of patients but has led to treatment discontinuation in only 2.6% of patients. Symptoms of fatigue and weakness may last a few days up to several weeks. Docetaxel has been associated with increased lacrimation thought to result from canalicular stenosis. Docetaxel concentrations were measured in tears in 6 patients; lacrimal concentration ranged from 14 to 70% of plasma concentration. This side effect may be more common with weekly versus three-weekly docetaxel. Artificial tears and/or ophthalmic steroids have been used with variable success. Although increased lacrimation has reportedly improved following discontinuation of docetaxel, dacryocystorhinostomy with placement of permanent tubes has been required in some patients.

Drug interactions: The metabolism of docetaxel may be modified by the concomitant administration of compounds that induce (e.g., phenobarbitol), or inhibit (e.g., ketoconazole, erythromycin, or itraconazole) cytochrome P-450 3A4. Docetaxel has also been shown to inhibit CYP3A4 in studies with human liver microsomes. Thus, docetaxel might increase the concentration of other drugs metabolized by this isoenzyme. To date, there is little documentation of such interactions in patients.

10.5 Prednisone

Please refer to the FDA-approved package insert for prednisone for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Availability

Prednisone is commercially available in 5 mg and 10 mg tablets, or as an oral solution (containing alcohol) in concentrations of 1 mg/mL or 5 mg/mL, or as an oral syrup in a concentration of 1 mg/mL.

Storage and stability

Prednisone should be stored at room temperature.

Administration

Prednisone is administered orally.

Toxicity

Short-term use of prednisone (e.g., ≤ 4 weeks) may be associated with gastrointestinal side effects (dyspepsia, ulceration); insomnia, nervousness, and occasionally, psychosis; and hyperglycemia. Immunosuppression with an increasing risk of infection is also seen.

More prolonged use may be associated with, in addition to the above, muscle weakness and muscle wasting; osteoporosis and fractures; hirsutism, acne, skin atrophy and easy bruising; sodium and water retention. Adrenal suppression can occur with long term use, necessitating tapering rather than abrupt discontinuation, and the need for steroid coverage during stress. Occasionally, a withdrawal syndrome manifest by muscle aches and pains is seen upon discontinuation.

10.6 Bevacizumab (rhuMAb VEGF, Avastin®) (NSC #704865/IND #7921)

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

Availability

Bevacizumab (NSC 704865) and matching placebo will be provided free of charge by Genentech and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Bevacizumab to be supplied for this protocol is intended for clinical trial use only and is not the commercially available Avastin®. Investigational bevacizumab and commercially available Avastin® may be produced at separate facilities and some difference may exist between the two products, although both are required to meet similar product testing criteria and are expected to be very similar in safety and activity. For further details and molecule characterization, see the bevacizumab Investigator Brochure

"Bevacizumab" and "Placebo" will be supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Vials will be labeled as "Bevacizumab or Placebo" so that the local investigators will be blinded as to the actual contents of the vials.

For “Bevacizumab”, each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

For “Placebo”, each 0 mg (0 mg/mL – 4 mL fill) glass vial contains phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal. Each box will be labeled with:

- the protocol number (i.e., “CALGB-90401”)
- the box number (i.e., “Box 1 of 2” and “Box 2 of 2”)
- the number of vials (e.g., “48 vials”)
- the patient ID number (e.g., “99999", where “99999” represents a unique patient identifier assigned at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L,FM"])
- the agent identification (i.e., “Bevacizumab 100 mg or Placebo”)
- a blank line for the pharmacist to enter the patient’s name
- storage instructions (i.e., “Store in refrigerator [2 – 8□C]. Do not freeze. Do not shake.”)
- emergency contact instructions
- a Julian date

The Julian date indicates the day the box was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2004 = 04, 2005 = 05) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2004 would have a Julian date of ‘04001’ and a box labeled and shipped on December 31, 2005 would have a Julian date of ‘05365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all vials (i.e., both Bevacizumab and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time.

Drug Ordering

No blinded starter supplies will be available for this study. Blinded, patient-specific supplies will be sent to the registering investigator at the time of randomization and should arrive within 7 to 10 days. This randomization will be performed by the CALGB Statistical Center in Durham, NC. The assigned CALGB patient ID number must be recorded by the registering institution for proper vial dispersion. Once a patient has been registered with the CALGB Statistical Center, the CALGB Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the CALGB Statistical Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day.

All shipments will be sent on blue ice by FedEx (anticipated one to two day delivery). Thus, if a patient is registered on Monday, CALGB would enter a clinical drug request for that patient on Monday and PMB would process the request on Tuesday and ship the drug on Wednesday. Both United States and Canadian sites could expect to receive their order either Thursday or Friday. Note that PMB will only send blue ice shipments on Monday through Thursday for delivery on Tuesday through Friday. Thus, if a patient is registered on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday.

The initial request will be for **48 vials** (minimum of 2 cycles/6 week supply) of bevacizumab or matching placebo. One (1) month after the initial electronic request (i.e., two weeks before the next dose is needed), sites may reorder an additional 2 cycle/6 week supply by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The assigned patient ID number (e.g., "99999"), the patient initials (e.g.,"L,FM"), **and the patient's weight (in KG)** should be entered in the "Patient or Special Code" field. All drug orders should be shipped directly to the physician responsible for treating the patient.

Drug Transfers: Vials **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved **in advance** by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-480-4612) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "99999"') and the patient initials (e.g., "L,FM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "CALGB-90401").

Drug Returns: Only intact vials should be returned to the PMB; dispose of partial vials according to local institutional destruction policies. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "99999") and the patient initials (e.g., "L,FM") should be entered in the "Lot Number" field.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "99999") on this protocol.

Storage and Stability

On receipt, bevacizumab/placebo should be stored in a refrigerator (2° to 8° C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified when lots have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry. Solutions diluted for infusion may be stored in the refrigerator for up to 8 hours.

Preparation

Vials contain no preservative and are intended for single use only. **The calculated dose should be diluted in 100 mL of 0.9% Sodium Chloride for Injection.** Once diluted in 0.9% Sodium Chloride for Injection, the bevacizumab/placebo solution must be administered within 8 hours.

Administration

Bevacizumab/placebo is administered as an intravenous infusion, after docetaxel. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

Unblinding Procedures

Unblinding can be done only in the case of an emergency. Follow the directions below to unblind patient treatment. Please note that, if a patient is unblinded, he must discontinue protocol therapy.

Emergency Unblinding Procedures: Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact a CALGB Approving Physician (i.e., Executive Officer) by calling the pager number, 773-652-0098. If an Executive Officer cannot be reached, contact the CALGB Statistical Center Help Desk at 1-877-442-2542 and the Statistical Center will contact an Approving Physician. Note that the Statistical Center cannot give permission for unblinding. Only a CALGB Approving Physician can authorize emergency unblinding.

The following information will be required when contacting the CALGB Approving Physician:

- CALGB study number (i.e., CALGB-90401)
- CALGB patient ID number (e.g., 99999)
- Patient initials (e.g., "L,FM")
- Institution name
- Name and telephone number of treating physician
- Name and telephone number of person requesting the unblinding procedure
- Name and telephone number of contact person to inform of treatment assignment
- Reason for emergency unblinding

After authorization by a designated CALGB Approving Physician, the treatment assignment will then be provided to the contact person by the CALGB Statistical Center.

Toxicities

According the Investigator Brochure for bevacizumab, the most serious adverse events associated with bevacizumab to date were gastrointestinal perforations/wound healing complications, hemorrhage, hypertensive crises, nephrotic syndrome, and congestive heart failure. The most common severe (NCI CTC Grade 3-4) adverse events among 1032 patients receiving bevacizumab in Genentech-sponsored studies to date were asthenia, pain, hypertension, diarrhea, and leukopenia. The most common adverse events of any severity among the 742 patients receiving bevacizumab in Genentech-sponsored studies to date were asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respirator infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria. Please see the most current version of the

Investigator Brochure on bevacizumab for more information on adverse events associated with the agent as well as complete prescribing information for the agent. Infusion related or allergic reactions may also occur. These include fever, chills, rigor, rash, urticaria and dyspnea. Decreasing the infusion time of bevacizumab is dependent upon the absence of infusion reactions, as described above.

Hypertension is among the most common adverse events associated with bevacizumab to date. Both new hypertension and worsening of existing hypertension have been reported. Hypertension may require treatment; ACE inhibitors, calcium channel blockers, beta blockers, and diuretics have all been reported to be effective in this setting. Although most hypertension can be controlled by medication, hypertensive crises have been reported in several studies, and the end organ consequences included CNS bleeding and ischemia, and congestive heart failure

Proteinuria, ranging from asymptomatic abnormal urinalysis to nephrotic syndrome, has been described in 10% or more of patients receiving bevacizumab. Proteinuria is managed with dose modifications as described in Section 8.0.

Bleeding, including fatal CNS hemorrhage, has been reported. Bleeding at tumor sites or at sites of other pre-existing abnormalities (e.g., diverticulosis, hemorrhoids) has also been described. In a phase III study, fatal hemoptysis occurred in 2 of 55 patients with non-small cell lung cancer, both of whom had a history of hemoptysis. The rate of fatal hemoptysis in non-squamous NSCLC is estimated at 1-2%. Epistaxis is usually short-lived and resolves without treatment, although some episodes may require medical intervention. DIC has been described in a few patients receiving bevacizumab in combination with oxaliplatin, fluorouracil and leucovorin.

Thrombosis/embolism Both arterial and venous thromboses (including pulmonary embolism, mesenteric vein thrombosis, ischemic bowel, cerebral vascular accident), and myocardial infarction have been described in patients receiving bevacizumab. Fatal pulmonary embolus has also been described.

With regard to arterial thromboses (which include myocardial infarction, transient ischemia attack, cerebrovascular accident/stroke, and angina/unstable angina), recent studies indicate that the risk with bevacizumab and chemotherapy is 2-3 times (up to 5%) that of chemotherapy alone. Furthermore, certain baseline characteristics, specifically age > 65 years and prior TE event, conferred additional risk.

Hepatic Dysfunction: Reversible and marked elevations of liver function tests (total bilirubin and/or transaminase and AP) have been rarely reported when bevacizumab is used in combination with chemotherapy or concurrently with other drugs that are potentially hepatotoxic. The mechanism of such hepatic toxicities is unclear. It is possible that in rare occasions, bevacizumab may potentiate the liver side effect of a concurrent medication, although it is unclear at this time whether bevacizumab alone can cause LFT derangement.

Bowel perforation and bowel anastomotic dehiscence have been reported in clinical trials using bevacizumab alone or in combination with chemotherapy. Although these events were also related to co-existing factors such as tumor involvement, chemotherapy, recent invasive procedures or bowel inflammation, they have occurred at an increased rate in patients receiving bevacizumab. A fatal bowel perforation has been described. **GI perforation should be included in the differential diagnosis of patients receiving bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.** Partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies and it is possible that bevacizumab may delay or compromise wound healing in patients.

Reversible posterior leukoencephalopathy syndrome (RPLS) or similar leukoencephalophathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been recently reported in association with

bevacizumab therapy. These syndromes have been seen in < 1% of patients to date. Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2) and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

Neutropenia: When combined with chemotherapy, bevacizumab is reported to increase the risk of neutropenia over that of chemotherapy alone. Grade 3-4 neutropenia, febrile neutropenia, or increased rate of infection were increased in studies in which bevacizumab with chemotherapy (IFL, paclitaxel and carboplatin) was compared to chemotherapy alone.

Other toxicities: Other reported or potential toxicities associated with bevacizumab include:

Constitutional—Headache, infection without neutropenia, asthenia;

Cardiovascular—Hypotension, pericardial effusion, congestive heart failure

Skin—Rash, urticaria;

Gastrointestinal—Nausea, vomiting, stomatitis/pharyngitis, colitis, intestinal obstruction;

Pulmonary—Pulmonary infiltration, dyspnea;

Musculoskeletal—Arthralgia, chest pain.

Note that additional toxicities may be associated with combination chemotherapy.

For a comprehensive list of adverse events and potential risks (CAEPR), see Section 15.3. Also refer to the bevacizumab Investigator's Brochure for additional information about toxicities as well as information about the production of bevacizumab for clinical trial use.

11.0 ANCILLARY THERAPY

11.1 Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the CALGB Remarks Addenda (C-260).

11.2 Treatment with hormones (including megestrol acetate) or other chemotherapeutic agents may not be administered except for steroids given for adrenal insufficiency; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic.

11.3 Palliative radiation therapy may not be administered while the patient is on study treatment. A symptomatic lesion or one which may produce disability (e.g., unstable femur) may be irradiated before study initiation, provided other measurable or evaluable disease is present and radiation therapy is completed ≥ 4 weeks before start of therapy. All eligibility criteria for progression (including PSA progression) must still be met. Any other indications for radiotherapy after protocol treatment has begun will constitute disease progression, and the patient will stop protocol treatment (see Section 12.1.3).

11.4 Bisphosphonates: If clinically indicated, patients may initiate bisphosphonate therapy after completion of Cycle 1.

Patients receiving bisphosphonate therapy prior to initiating protocol treatment must have received bisphosphonates for at least 1 month prior to starting therapy (see Section 4.5). Such patients may continue on bisphosphonate therapy while on study, if desired.

11.5 Because prednisone may predispose patients to the development of gastritis or ulcers, physicians are advised to consider the use of an H2 antagonist or PPI for prophylaxis against GI ulceration.

11.5 CALGB Policy Concerning the Use of Growth Factors

11.5.1 Epoetin (EPO): Use of epoetin (EPO) in this protocol is permitted at the discretion of the treating physician.

11.5.2 Filgrastim (G-CSF), pegfilgrastim, and sargramostim (GM-CSF) are to be used per ASCO and NCCN guidelines, and should not be routinely used to avoid dose reductions or delays.

1. Primary, prophylactic G-CSF, pegfilgrastim, or GM-CSF should be considered for patients predisposed to complications from neutropenia per the ASCO and NCCN guidelines. Predisposing factors include medical history, disease characteristics, age, and performance status.
2. The use of CSF's may be indicated for the treatment of febrile neutropenia in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome), or fungal infection.
3. Following episodes of grade 3 or 4 neutropenia, the use of G-CSF, pegfilgrastim, or GM-CSF should be considered for subsequent cycles.

If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported on the CALGB C-260 Remarks Addenda.

11.5.3 Neumega (IL-11): The use of Neumega for patients enrolled in this study is discouraged.

12.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

For the purposes of this study, patients with measurable and non-measurable lesions should be reevaluated every 9 weeks (every three cycles) with appropriate imaging studies. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

While all areas of malignant disease will be monitored, patients will be categorized into having either measurable disease or non-measurable disease. Patients will also be evaluated for changes in PSA every 3 weeks.

12.1 Measurable Disease/Target Lesions

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

All measurable lesions (up to a maximum of 10) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions, including small lesions and bone metastasis, will be identified as non-target lesions. (See Section 12.2. for response criteria for non-target lesions.)

12.1.1 Complete Response (CR): Disappearance of all target lesions. Changes in tumor measurement must be confirmed by repeat studies (see Section 12.1.5).

12.1.2 Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Moreover, performance status must be stable or improved at the time that a PR is determined. Changes in tumor measurements must be confirmed by repeat studies (see Section 12.1.5).

12.1.3 Progression (PD) is defined if **any** of the criteria below are met:

- At least a 20% increase in the sum of the LDs of target lesions (taking as a reference the smallest sum LD recorded since the treatment started) or the appearance of two or more new lesions.
- Development of an indication for radiation therapy while on treatment.

12.1.4 Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum LD since the treatment started; AND no evidence of PSA progression (see Section 12.3.2)

12.1.5 Confirmation Measurement and Duration of Response for Measurable Disease/Target Lesions

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be at least 4 weeks after the criteria for response are first met. For this study, restaging is scheduled to take place every 9 weeks (every 3 cycles).

12.1.6 Duration of Overall Response for Measurable Disease/Target lesion

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

12.2 Non-measurable Disease/Non-target Lesions:

Response for patients with non-measurable ("bone") disease will be evaluated primarily by changes in bone scan and non-target lesions.

12.2.1 Complete Response (CR)

Complete resolution of all osseous lesions and all non-target lesions as evaluated by scans.

12.2.2 Progressive Disease (PD)

Progression will be defined by any of the following:

1. Worsening bone scan as evidenced by the appearance of more than 2 new lesions not felt to be consistent with a tumor flare. Worsening of pre-existing lesions (increase in intensity or size of a lesion) may be difficult to interpret, and therefore will not be considered evidence of PD; OR
2. Appearance of new metastatic lesions outside the bone; OR
3. Unequivocal progression of existing non-target lesions. Because a clear progression of "non-target" lesions only is exceptional, such circumstances should be discussed with the study chair. (This discussion should also be documented on the C-260 CALGB Remarks Addenda.); OR
4. Development of an indication for radiation therapy while on treatment.

12.2.3 Stable Disease (SD): Stable non-measurable disease will be defined by meeting neither the criteria for CR or PD and having no evidence of PSA progression (see Section 12.3.2).

12.3 Post-therapy changes in PSA

12.3.1 PSA Decline will be reported on all patients, and will be defined as a decrease in PSA value by ≥ 50% for two successive evaluations at least 4 weeks apart. The reference PSA value for these declines should be measured within 2 weeks before starting therapy. The reference PSA will be the last pre-treatment PSA obtained, even if obtained after registration.

12.3.1.1 Beginning of PSA decline will be measured from the date of the first 50% decline in PSA.

12.3.1.2 End of PSA decline (end of response period) is defined as the date of the first PSA ≥ 50% above nadir. In addition, a minimum PSA increase of 5 ng/mL, or a return to the pre-treatment PSA value is required.

12.3.2 PSA Progression: PSA progression will be evaluated in all patients.

12.3.2.1 In patients who have achieved a ≥ 50% decline in PSA, progression is defined by:

1. An increase in PSA by 50% above the nadir, AND
2. An increase in PSA by a minimum of 5 ng/mL, or an increase in PSA to the reference PSA value (see Sec. 12.3.1), AND
3. Confirmation by a second consecutive rising PSA at least 2 weeks apart.

12.3.2.2 In patients whose PSA has not decreased by ≥ 50%, progression is defined by:

1. An increase in PSA by 25% above either the pre-treatment level, or the nadir PSA level (whichever is lowest), AND
2. An increase in PSA by a minimum of 5 ng/mL, AND
3. Confirmation by a second consecutive rising PSA at least 2 weeks apart.

12.3.3 Time to PSA progression will be measured from the first day of treatment to the time of PSA progression (see Sec. 12.3.2). The time of PSA progression is defined as the date of the first PSA increase meeting the criteria of progression (i.e., not the date of confirmation).

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

13.1 Duration of Treatment

13.1.1 Complete Response: Patients may discontinue therapy after achievement of a complete response in all response categories (i.e., PSA ≤ 1.0 ng/mL and complete resolution of any measurable disease, if present) at the discretion of the treating physician. For patients who discontinue protocol treatment, all further treatment will be at the physician's discretion.

13.1.2 PR or SD: Continue treatment at the highest tolerable dose until the appearance of disease progression or unacceptable toxicity per Section 8.0, for a maximum period of 2 years.

13.1.3 Disease Progression: Patients should receive a minimum of three cycles of therapy. Patients that have disease progression after 3 cycles of therapy based on measurable disease (see Section 12.1.3), non-measurable disease (see Section 12.2.2) or PSA progression (see Section 12.3.2) should be removed from protocol therapy. All sites of disease progression should be recorded.

If there is discordance between the post-therapy changes in PSA and other manifestations of systemic disease (e.g. normalization or decrease of PSA and worsening of the bone scan) the patient will be considered to have progressive disease.

In the case that a patient has rapid clinical disease progression at any time during protocol therapy, he may be removed from protocol treatment by the treating physician only after discussion with the study chair. Document details, including tumor measurements, on CALGB Form C-660. Patients will be followed for secondary malignancies and survival.

13.2 Extraordinary Medical Circumstances: If, at any time, the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on the C-260 CALGB Remarks Addenda.
- Follow the patient for secondary malignancies, disease response, and survival for a minimum of 2 years following registration.

13.3 There is no crossover in this study. After disease progression (or termination protocol therapy), bevacizumab/placebo will no longer be provided and further treatment is at the discretion of the patient and the treating physician.

14.0 STATISTICAL CONSIDERATIONS

14.1 Endpoints: The primary endpoint is overall survival (OS). Secondary endpoints are proportion of patients who experience a 50% post-therapy PSA decline, progression-free survival (PFS), biochemical (PSA) PFS, and toxicity. OS will be measured from the date of randomization to date of death due to any cause. PFS will be measured from the date of randomization to date of progression or death due to any cause, whichever occurs first. PSA progression-free survival will be defined per Section 12.3.3.

14.2 Stratification: Randomization will be stratified by: predicted 24 month survival using the nomogram developed by Halabi, et al (1) (< 10%, 10-29.9%, ≥ 30%), age (<65, ≥ 65) and prior history of arterial events (yes, no).

14.3 Power Considerations: This is a randomized, double-blinded phase III trial in which 1,020 men with HRPC will be randomized with equal probability to one of two possible treatment regimens: either docetaxel, prednisone, and placebo or docetaxel, prednisone and bevacizumab.

The following calculations assume a monthly accrual rate of 29 patients/month accrued over a 35-month period, and will be followed for approximately 25 months after study closure and a two-sided alpha level of 0.05. Survival time is assumed to follow an exponential distribution. The power to detect a hazard ratio (HR) of 1.26 (equivalent to an increase in median OS from 19 months to 24 months) is 86%.

14.4 Interim Analysis: Efficacy (overall survival) and PFS analyses will be conducted on semiannual basis to coincide with the semiannual meetings of the CALGB Data and Safety Monitoring Board (DSMB). Under the alternative hypothesis, 748 events (deaths) are expected at the end of the follow-up period. There will be seven interim analyses, plus the final analysis. The first interim analysis for the OS endpoint will be performed when 17% of the full information has occurred (approximately at about 18 months after study activation). Other interim analyses will be performed at 29% of the full information (at about 24 months), and at 42% (30 months), 55% (36 months), 72% (42 months), 83% (48 months), 92% (54 months), and at 100% of the full information (at about 60 months after study activation). To help insure complete data on which to base the interim analyses, progression events (clinical or biochemical) and deaths should be faxed to the CALGB Statistical Center within 24 hours of being reported to the institution.

A group sequential test design by Emerson and Fleming (1989) will be used to stop the trial early to reject the null hypothesis. Alpha levels less than 0.0001 will be truncated to 0.0001. Assuming the above percent information available at each look, the boundaries for stopping for superiority (OS) are: 3.72, 3.72, 3.22, 2.81, 2.46, 2.29, 2.18, and 2.09. The z-score boundaries for stopping for futility at a fixed alpha level = 0.005 for OS are: -1.27, -0.87, -0.53, -0.23, 0.11, 0.30, 0.46, and 2.09. Should any boundary be crossed, accrual to the study will be stopped. These rules have a negligible impact on the type I and II error rates of this trial [Freidlin, 199 #14079]. The power for the OS endpoint is at least 85% with this design.

		Boundaries for Interim Analysis	
Interim Analysis	**Percent Information**	**For Superiority**	**For Futility**
1	17%	3.72	-1.27
2	29%	3.72	-0.87
3	42%	3.22	-0.53
4	55%	2.81	-0.23
5	72%	2.46	0.11
6	83%	2.29	0.30
7	92%	2.18	0.46
8	100%	2.09	2.09

14.5 Toxicity Monitoring

Monthly conference calls (including study chair, committee chair, the statisticians, data coordinator and protocol coordinator) will be held to monitor for early stopping due to unacceptable arterial events. Unacceptable arterial toxicity will be defined as any grade 3 or higher cardiac ischemia/infarction (angina, acute MI), CNS cerebrovascular ischemia (TIA, CVA, stroke), peripheral arterial ischemia, or CNS hemorrhage (subarachnoid). Institutions will be asked to fax the Arterial Thromboembolic Event Report (C-1396) within 24 hours of its being reported to the institution. In addition adverse event forms must be submitted after each cycle of treatment (every 21 days). Institutions with patients enrolled on this phase III study that do not submit toxicity forms in a timely manner may be denied future registration to the study. Unacceptable arterial toxicity rates will be compared by the two treatments arms for: 1) the first 120 randomized patients who are 65 years of age and older and 2) the first 120 patients with prior history of arterial events. It is assumed that the incidence of arterial events in the control population is 10%.

Based on prior CALGB studies, we expect that 75% of patients will be ≥ 65 years of age and older. Assuming an accrual rate of 29 patients/month, we expect to accrue 120 patients that are 65 years and older in about six months. Five interim analyses of the unacceptable arterial toxicity rates will be performed when 20% (24 patients 65 years of age and older), 40% (48 patients), 60% (72 patients), 80% (96 patients), and 100% (120 patients) will be performed. Using the methodology described by Jennison and Turnbull, the repeated confidence interval will be used to monitor for excessive toxicity. If the lower boundary of the 90% confidence interval for the difference in arterial rates exceeds 10%, accrual to the trial will be immediately suspended. At each scheduled time of analysis, a 90% confidence interval for the difference in arterial rates will be computed using the Lan-Demets boundaries (-3.50, -2.36, -1.87, -1.59, -1.41).

In addition, we will monitor the toxicity on the first 120 patients with prior history of atherosclerosis. Based on previous studies, we expect that 30% of the patients will have a prior history of atherosclerosis. We expect to accrue the first 120 patients with a prior history of atherosclerosis at about 14 months after study activation. Similar to the above, five interim analyses at 20% (24 patients with prior history of AE), 40% (48 patients), 60% (72 patients), 80% (96 patients) and 100% (120 patients) will be performed at all scheduled conference calls. If at any scheduled time of analysis the lower boundary of a one-sided 90% confidence interval for the difference in arterial rates among patients with prior history of arterial events exceeds 10%, accrual to the trial will be immediately suspended. The following Lan-Demets boundaries will be used (-3.50, -2.36, -1.87, -1.59, -1.41). Results will be reported to the DSMB at all scheduled meeting and as necessary between scheduled meetings. If there is

evidence of treatment-related unacceptable toxicity, accrual to the trial will be immediately suspended. The trial will remained closed until the review of all toxicity data is completed and it is considered safe to reactivate the study.

14.6 Data Analysis: An intent-to-treat approach will be used in this phase III study to analyze OS. Patients who withdraw consent or withdraw from the study due to toxicity will continue to be followed for survival, even if they begin another therapy. The Kaplan-Meier product-limit estimator (34) will be used to estimate the OS, biochemical PFS, and PFS. The stratified log-rank test will be used to compare the two treatment arms on OS, biochemical (PSA) PFS, and PFS. In addition, the proportional hazards model (33) will be used to assess the importance of the treatment arm adjusting on baseline clinical characteristics, stratification variable and other important covariates in predicting overall survival, PFS, and biochemical PFS. The chi-square statistic will be used to compare the two arms on the proportion of patients who experience a 50% post-therapy decline in PSA from baseline. Further, the Fisher exact test will be used to compare the two treatment arms on the proportion of patients with unacceptable treatment-related grade 3 or higher toxicity for all patients, for patients who are 65 years of age and older, and for patients with prior history of arterial events.

14.7 Accrual and Follow-up: Based on previous data from patients enrolled on CALGB 90004, the projected accrual rate is 16 patients per month. However, the accrual is anticipated to be higher as the ECOG GU Committee has indicated that they would support this study, and the study would also be opened through the CTSU. Assuming an accrual rate of about 29 patients/month, accrual is expected to be completed within about 36 months of study activation. This rate is reasonable as we expect other cooperative groups and institutions to enroll patients through the CTSU. All patients will be followed for 10 years after randomization.

Statistical considerations for correlative sciences studies

14.8 PSA as a surrogate marker for outcome

Prentice's criteria will be applied to determine if PFS, PSA PFS, 50% decline in PSA at 12 weeks from baseline, and PSA slope are potential surrogate endpoints for overall survival. The PSA slope will be calculated for every patient using the least squares method. The proportional hazards model will be used to test if the treatment is prognostic of overall survival and of the surrogate endpoints. Next, the proportional hazards model will be used to test if the surrogate endpoints are prognostic of overall survival. Finally, the proportional hazards model will be used to test if the treatment effect on overall survival is explained by the surrogate endpoints. That is, we will test if survival is independent of treatment given that the patient has failed biochemically (or did not experience a 50% decline in PSA at 12 weeks from baseline) and if survival is independent of the treatment given that the patient did not fail (or experience a 50% decline in PSA at 12 weeks from baseline).

14.9 Biomolecular markers in hormone refractory prostate cancer

14.9.1 Power Computation

Because we are testing four primary hypotheses, each hypothesis will be tested with a significance level of 0.0125. Power computations are presented assuming that either 100% (n = 1,020) or 80% (n = 816) of the samples will be available.

Based on a preliminary data of 197 patients, 10% of the patients had plasma VEGF levels > 260 pg/mL. The median survival time was 17 months among patients with VEGF levels less than or equal to 260 pg/ml compared to 11 months in patients with VEGF levels > 260 pg/mL. With 1,020 patients, the power is 93% to detect a hazard ratio of 1.55. With 816 patients, the power of is 85% to detect a HR = 1.55. The power computations are based on the following assumptions: the survival time follows an exponential distribution, accrual rates of 29 patients/month or 23.2 patients/month (assuming that n = 816), about 36-months accrual period, about 24 months post-accrual follow-up, a two-sided significance level of 0.0125 and the median survival time among patients with VEGF ≤ 260 is 11 months.

In addition, based on preliminary data of 321 patients with plasma CgA 64% of patients has CgA levels > 9.5 U/L. The median survival time among patients with CgA levels > 9.5 U/L was 12 months compared to 18 months among patients with CgA levels ≤ 9.5 U/L. The power is at least 90% to detect a HR of 1.33. Further, if we assume that the sample size = 816, the power is 86% to detect a HR = 1.33. The following assumptions were made: the survival time follows an exponential distribution, an accrual rates of 29 patients/month or 23.20 patients/month (assuming n = 816), about 36-months accrual period, about 24 months post-accrual follow-up, a two-sided significance level of 0.0125, and the median survival time among patients with CgA ≤ 9.5 U/L is 18 months.

For the Il-6 data, based on preliminary data of 191 patients, 24% of patients had IL-6 data > 13.31. The median survival time among patients with IL-6 levels > 13.31 pg/ml was 7 months compared to 17 months among patients with IL-6 levels ≤ 13.31 pg/mL. The power is at least 90% to detect a HR of 1.36. If we assume that the sample size is 816, the power is 86% to detect a HR = 1.36. The following assumptions were made: the survival time follows an exponential distribution, accrual rates of 29 patients/month or 23.20 patients/month, about 36-months accrual period, 24 months post-accrual follow-up, a two-sided significance level of 0.0125, and the median survival time among patients with IL-6 ≤ 13.31 pg/mL is 17 months.

For the RT-PCR for PSA data, based on CALGB 9583, 44% of patients had positive RT-PCR for PSA. The median survival time among patients was 11 months compared to 21 months among negative patients. The power is at least 90% to detect a HR of 1.33. If we assume that the sample size is 816, the power is 86% to detect a HR = 1.33. The following assumptions were made: the survival time follows an exponential distribution, an accrual rate of 29 patients/month or 23.20 patients/month, about 36-months accrual period, about 24 months post-accrual follow-up, a two-sided significance level of 0.0125, and the median survival time among negative RT-PCR patients is 21 months.

14.9.2 Data Analysis

A sample of 52 (5%) specimens will be used to assess the reproducibility of the VEGF assays. Replicate samples will be performed among the first 52 patients that are randomized to the study. Inter-batch and intra-batch variation will be estimated by splitting the 52 specimens into two batches. Analysis of variance will be used to estimate the within and between batch variance. If the correlation coefficient between the VEGF replicates, IL-6 replicates, CgA replicates or RT-PCR data is at least 0.9, then the assay will be considered "reproducible." However, if the correlation coefficient is less than 0.90, the study team will discuss how to proceed with these assays. Recommendations may include modifying the assay, or training the laboratory personnel who are performing these assays. The reproducibility rates will be reported at the end of the study.

The Kaplan-Meier product-limit estimator will be used to estimate the survival distribution by the several markers (VEGF, IL-6, CgA, RT-PCR for PSA). In order to validate the previous results, we will use the proportional hazards model to compare: the low and high VEGF levels (using the cut-point of 260 pg/mL), low and high CgA levels (using the cut point of 9.5 U/L), the low and high IL-6 levels (using the cut point of 13.31 pg/mL) positive and negative RT-PCR for PSA adjusting for the baseline covariates such as PSA, alkaline phosphatase, LDH, hemoglobin levels and other known prognostic factors. Because of the multiplicity of analysis, we will use the Bonferroni correction to adjust on the type I error rate. A type I error rate of 0.0125 will be used for the primary analyses based on survival time by plasma VEGF level (cut-point of 260 pg/mL), CgA (cut point of 9.5 U/L), IL-6 (cut point of 13.31 pg/mL), and RT-PCR for PSA (negative, positive). However, an alpha level = 0.01 will be used as a substitute for formal tests of significance to perform exploratory analyses (VEGF levels, CgA and IL-6) in predicting response. The correlation coefficient will be calculated to test for an association between VEGF levels, IL-6, and CgA levels. Further, the chi-square statistic will be used to test for the relationships between RT-PCR for PSA (negative, positive) and VEGF levels, IL-6 and CgA levels.

14.10 Pharmacogenomic Companion Study

14.10.1 Candidate Gene Analysis

The primary objective is the assessment of discrepancy of leukopenia/neutropenia toxicity rates with respect to the *CYP3A5* genotype. We assume that occurrences of such toxicities are mainly due to docetaxel. The target genotypic populations are given in Table 1.

Table 1

Group 1	at least one *1 allele (e.g., *1/*1, *1/*3, *1/*6, etc.)
Group 2	homozygous *3 (i.e., *3/*3)

In particular, we hypothesize that due to increased clearance in patients with at least one *1 allele, group 1 will experience lower toxicity than group 2. The hypotheses of interest can be canonically presented as testing H_0: $\pi_1 = \pi_2$ versus H_1: $\pi_1 < \pi_2$, where π_1 and π_2 denote the toxicity probabilities for groups 1 and 2 respectively. It is assumed that the discrepancy in toxicity, between groups 1 and 2, is homogeneous across treatment arm (i.e., no interaction between treatment arm (A or B) and genotype (groups 1 or 2) when modeling toxicity). Furthermore, occurrences of toxicity are mainly due to docetaxel and will not be attributed to bevacizumab. As such, the primary analysis will be effectively reduced to that of a two-sample (i.e., group 1 versus group 2) problem for binomial proportions.

Kuehl et al. (52) report an allelic frequency for *CYP3A5*1* of q=0.45 for African Americans and q=0.15 for Caucasians. For the purpose of calculating the projected prevalence rates for groups 1 and 2, we will assume that relative frequencies of *CYP3A5* variants, other than *3, are negligible. As such, based on the *1 allelic relative frequency reported by Kuehl and the aforementioned simplifying assumption, the allelic relative frequency for *CYP3A5*3* are projected to be p = 0.55 for African Americans and p = 0.85 for Caucasians respectively. The corresponding projected prevalence rates for groups 1 and 2, by ethnicity, are listed in Table 2.

Table 2

	Projected Prevalence Rates	
	Group 1 (*1/*1, *1/*3, *1/*6, etc.)	**Group 2** (*3/*3)
African Americans	0.70 (=1-0.3)	0.30 (=0.552)
Caucasians	0.27 (=1-0.73)	0.73 (=0.852)

This study plans to randomize a total of N = 1020 patients, 80% of whom are expected to be available for genotyping. This corresponds to a total sample size of n = 816. We will assume that the relative frequency of African Americans and Caucasians accrued to the study will be 0.15 and 0.85 respectively. Here it assumed that the relative frequency of other ethnicities will be comparatively low. Based on this assumption and the relative frequencies reported in Table 1, we have projected the prevalence rates and frequencies of group 1 and 2 in Table 3.

Table 3

$\mathbf{p_1}$	0.33	=0.7*0.15+0.27*0.85
$\mathbf{p_2}$	0.67	=0.3*0.15+0.73*0.85
$\mathbf{n_1}$	269	$=816p_1$
$\mathbf{n_2}$	547	$=816p_2$

It will be assumed that the overall toxicity rate for this patient population is π=0.5. So we have that $0.5=\pi= \pi_1 p_1+ \pi_2 p_2 = 0.33\pi_1+ 0.67\pi_2$. Given a hypothesized prevalence rate π_1, one can obtain a hypothesized value π_2 and the corresponding odds-ratio. The power of the two-sided test, at the 0.05 level of significance, for various baseline values of $\pi_1 \varepsilon \{0.40,\ldots,0.45\}$ and effect sizes (as quantified by odds-ratios) is illustrated in Table 4.

Table 4

π	π_1	p_1	p_2	π_2	odds-ratio	Power
0.50	0.40	0.33	0.67	0.549	1.828	0.97
0.50	0.41	0.33	0.67	0.544	1.719	0.94
0.50	0.42	0.33	0.67	0.539	1.617	0.88
0.50	0.43	0.33	0.67	0.534	1.522	0.78
0.50	0.44	0.33	0.67	0.530	1.433	0.65
0.50	0.45	0.33	0.67	0.525	1.349	0.49

Secondary Objectives

The results from this analysis will complement the existing literature on allelic relative frequencies for *CYP3A5* and other genotypes for a general North American population.

An exploratory analysis of gene-toxicity, gene-response, and gene-survival relationships will be conducted for the various other relevant polymorphisms described in the genes implicated in docetaxel pharmacology.

Finally, in this study, we would also like to investigate potential associations between *VEGF* variants associated with altered VEGF levels and treatment outcomes in the bevacizumab treatment arm.

14.10.2 Genome-wide SNP Analysis

Objectives

To identify specific SNPs and/or copy number variations that are associated with the prevalence of grade 3-4 neutropenia.

To identify potential SNPs by bevacizumab interactions with respect to outcome.

To assess other relative clinical endpoints such as adverse events (e.g., proteinuria and hypertension).

To validate results found in other CALGB studies (e.g., 80303) and perform a risk analysis by comparing the 90401 SNP data to SNP data from controls (patients thought not to have cancer) obtained from public databases.

14.10.3 Pre-processing

For pre-processing (QC and genotype calls) the Illumina chips, we will use the commercial program Bead Studio developed by Illumina. Although, Illumina does not provide a Linux port of Bead Studio, the software can be used on VMWARE running on a Linux host. A two CPU dual core (four cores) AMD Opteron Socket F workstation with 16GB of RAM will be available for this purpose (the statistical analyses will be carried out on a Linux server with 8 dual core Opteron Socket F CPUs (16 cores) with 64GB of RAM [expandable to 128GB if needed]).

14.10.4 Analyses to Assess Genotyping Quality and Population Stratification

Initial quality studies will be conducted to identify SNPs that have generated sufficiently poor quality genotype data and should be removed from analyses. Call rate, patterns of missing data, and departures from Hardy-Weinberg equilibrium (HWE) assessed using an exact test will be examined to identify markers that will not be used in analysis. In general, SNPs with call rates <95% and those with highly significant departures from HWE ($p<10^{-7}$) will not be included in the analyses. Non-random patterns of missing data are sometimes encountered in data generated on high-throughput genotyping platforms; the most common non-random missing data problem is that heterozygous genotypes are more likely to be assigned as missing than either homozygous genotype. We will perform analyses using blind duplicates as well as analyses assessing the relationship between heterozygous call rates and missing data to identify any SNPs in which data are clearly not missing at random. Depending on the number and degree of difficulty observed, we will either remove problematic SNPs from analysis, or assign quality scores to reflect the extent of the non-random missing data.

Additional preliminary quality control analyses will be conducted to ensure that the sample does not include duplicated samples or closely related individuals. These analyses can be rapidly conducted using PLINK [92]. Duplicated samples (or unrecognized identical twins) will be reduced to a single sample for further analyses. Although we do not expect to have closely related individuals included in this sample, only one member of any set of first-degree relatives will be included in subsequent analyses. For each sample, we will also generate a gender call based on the SNPs on the X chromosome and study the missingness patterns for the SNP on the Y and XY chromosomes in order to convincingly determine that all samples are from female patients.

Population structure that is not appropriately recognized and accommodated can lead to both false positive and false negative results in association studies. We will conduct studies using structure [93] to estimate ancestry proportions using 10,000 SNPs chosen for having no pairwise LD with unrelated individuals from the HapMap CEU, YRI and CHB+JPT samples used to model the ancestral populations. Substantial previous research has shown this to be a rapid and effective approach to defining historical geographic ancestry. Although self-identified race/ethnicity is usually highly correlated with estimated historical geographic ancestry, there are often a few individuals who appear to be misclassified with self-defined labels, and it is the genetically defined ancestry that is critical to ensure robust results from association studies. Each individual will then have estimates of European, African and Asian ancestry. For individuals with high ancestry proportion for a single group (>98%), we will conduct further analyses with eigenstrat [94] using all SNPs to determine whether there are additional important sources of variation among individuals leading to detectable stratification by allele frequencies (reflecting, for example, differences in ethnic make-up within individuals of European descent from different U.S. cities from which subjects for the trial were obtained). Primary analyses, described below, will be conducted within groups defined by historical geographic ancestry. Secondary analyses will be conducted using logistic regression with ancestry proportions (and any additional stratification identified using eigenstrat) as covariates.

14.10.5 Feature Discovery

The association between the genotype call (say AA, AB or BB) for each autosomal SNP and the clinical outcome [for example, adverse event (AE) or no AE] will be investigated within the framework of 2 by 3 contingency table stratified by ancestry. Fisher's exact test (i.e., randomized conditional counterpart to Fisher's test for 2x3 tables) [95] will be used for carrying out inference on these tables. A feature (SNP) will be considered significant if the corresponding nominal unadjusted two-sided P-value is less than 0.05/K, where K is number of features which pass the pre-processing step. This approach may be conservative, but it guarantees strict type I error control.

As an example, let B denote the risk allele with an assumed relative allelic frequency of q. Under the Hardy-Weinberg equilibrium assumption, the genotypes AA, AB or BB will have relative genotypic frequencies of $(1-q^2)$, $2q(1-q)$ and q^2, respectively. Let Z denote the binary clinical outcome (Z=1 if the AE event occurs or =0 otherwise) and define the probability of an AE occurrence given the copies of the risk allele on the genotype, to be denoted by T, as

$$p_j=P[Z=1 \mid T=j], \qquad (1)$$

for j=0,1,2. The relationship between the event probability p=P[Z=1] in the general population is then expressible as

$$p=(1-q)^2p_0+2q(1-q)p_1+q^2p_2 \qquad (2)$$

The effect size in the context of genome-wide association (GWA) studies is typically quantified using the genotype relative risk (GRR) whose definition depends on the disease model. Under the recessive disease model $p_0=p_1$ and so

$$p=(1-q^2)p_0+q^2p_2, \quad (3)$$

and

$$GRR=\frac{p_2}{p_1}=\frac{p_2}{p_0} \quad (4)$$

while under the dominant disease model $p_1=p_2$ and so

$$p=(1-q)^2p_0+(2-q^2)p1, \quad (5)$$

and

$$GRR=\frac{p_2}{p_0}=\frac{p_1}{p_0}. \quad (6)$$

Finally, under the multiplicative disease mode, GRR=1/p0=p2/p1 and so

$$p=(1-q)^2GRR^{-1}+2q(1-q)+q^2GRR.$$

Grade 3-4 neutropenia has a prevalence of about 27%. There are currently 790 samples from with consent banked at the CALGB Pathology Coordinating Office.

The power, at the two-sided 0.05/500000 level (i.e., assume K=500,000 autosomal SNP markers pass through the pre-processing step), is illustrated in Table 5.

Table 5

recessive	q	0.10	0.22	0.34	0.46	0.58	0.70
	GRR	**3.40**	**2.40**	**2.20**	**2.30**	**2.60**	**3.30**
dominant	q	0.40	0.50	0.60	0.70	0.80	0.90
	GRR	**3.90**	**2.90**	**2.50**	**2.30**	**2.30**	**2.60**
multiplicative	q	0.10	0.24	0.38	0.52	0.66	0.80
	GRR	**3.20**	**2.10**	**1.80**	**1.80**	**1.80**	**2.00**

Table 5. Power illustration for Objective 1: The minimum Genotype Relative Risk (GRR) detectable with a power of 0.9, at the two-sided level of 0.05/500,000 for a range of relative allele frequencies (q) assuming the event (grade 3-4 neutropenia) probability is P[D=1]=0.27 under recessive, dominant and multiplicative models assuming HWE. The sample size used in the illustration is based on N0=573 (controls) and N1=217 (cases) for a total of N=790 patients.

14.10.6 Submission of Molecular Data

The laboratory of Dr. Yusuke Nakamura will submit the Illumina *.idat image files using secure means to the CALGB Statistical Center. The lab will also submit a table along with this transmission, which at the minimum will provide the following information for each sample received from the repository:

- The lab ID number provided by the repository.
- The experimental ID, a concatenation of the plate, well and replicate information, generated by the lab.
- The idat file names (the file string name will contain the Lab ID).
- The md5sum signature of the idat files to ensure data integrity.
- The date the specimen was received from the repository.
- The date the sample was analyzed by the RIKEN laboratory.

Additionally, the lab will also provide the complete results from any quality control measures performed. If a sample had to be redone (e.g., defective or poor quality array), the lab will provide all replicate idat files and add an appropriate column to the supplementary table. The molecular data generated for this aim may not be shared with other investigators or used for any analysis not specified in the protocol until a formal approval from the CALGB Statistical Center is obtained.

14.10.7 Secondary Objectives

Logistic regression models and conditional inference trees (or more generally conditional random forests) will be used to construct multi-variable models based on the SNPs identified as interesting. These models also allow for inclusion of other potentially relevant clinical and demographic variables.

The Illumina HumanHap550 contains 4,300 SNPs in regions with common copy number variants (CNVs). Given the complex structure of CNVs, it is not always clear how to define the genotype of a CNV. Instead of categorizing copy numbers into genotypes, we will estimate relative genomic abundance probe intensities. This approach allows for the consideration of other CNVs beyond deletions, including duplications and combinations of both. For notational brevity, we shall refer to these as CNV markers.

For each objective, the association between each CNV marker and the clinical AE endpoint will be assessed using the Wilcoxon two-sample test. The family-wise error rate will be controlled at the 0.05 level using permutation resampling (based on B=10,000 replicates).

Regression methods, as in the case of the SNP markers, will be employed to construct multivariable models based on the CNV markers.

Secondary relevant clinical endpoints include other adverse events (e.g., proteinuria and hypertension), progression-free and overall survival. For censored time-to-event outcomes, the stratified log-rank test will be primarily used for assessment of significance.

A risk analysis will be carried out by comparing the genotypic distributions of the SNPs from CALGB 90401 data to those from controls. The SNP data from the controls will be obtained from public databases.

In addition to conducting analyses on all features directly assessed on the high-throughput platform used in these studies, we will also interrogate all additional HapMap SNPs that are not in strong pairwise LD with any genotyped SNP but for which there is sufficient multi-locus LD to SNPs on the high-throughput platform. TUNA (Testing UNtyped Alleles) is a robust approach for conducting such analyses that provides inexpensive in silico follow up to the initial analysis

and allows us to more efficiently design any follow up genotyping studies [96,97]. For example, use of Illumina HumanHap300 enables direct testing of 270K-450K SNPs and indirect testing of 750K-1.5M additional SNPs (i.e., these SNPs are so highly correlated with SNPs that are directly tested for association that testing them would provide little additional information). The ranges given above bracket the expectations for different human populations, with European populations at the high end of the range and populations of recent African descent at the lower end. Use of TUNA enables interrogation of additional 100K-250K SNPs that are neither on the platform nor highly correlated with any individual SNP on the platform. Note that use of TUNA will facilitate comparisons to genome-wide association studies on potentially related phenotypes (e.g., clinical trials of the same or related drugs) conducted using other high-throughput platforms or candidate gene studies utilizing SNPs not directly genotyped on the high-throughput platform chosen for our studies.

Finally, we note that the methodology field for the analysis of genome-wide SNP data is in its infancy. We will consider the employment of "newer" methods if they are deemed to be statistically sound and enable us to better interrogate, and more importantly, understand the data.

14.10.8 Statistical Software

The R statistical environment [98] and Bioconductor [99] packages will be used for all of the primary statistical analyses relating features to phenotypes. Specialized statistical genetics software, including PLINK [92], structure [93], eigenstrat [94], and TUNA [96,97] will be used for some of the quality or secondary analyses and R will be used for logistic regression analyses allowing for ancestry covariates.

15.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the Investigational Drug Branch, the CALGB Central Office, the Study Chair, and their Institutional Review Board if a patient has a reportable adverse event. This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 to determine the severity of the reaction for expedited reporting. All reactions determined to be "reportable" in an expedited manner must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS).

CALGB requires investigators to route all AdEERS reports through the Central Office for CALGB-coordinated studies.

15.1 CALGB 90401 Reporting Requirements:

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hrs; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

15.2 Additional Instructions or Exclusions from AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- All adverse events reported via AdEERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- For the purposes of expedited adverse event reporting, the CAEPR (which includes expected adverse events) for bevacizumab may be found in Section 15.3, below. Expected adverse events for docetaxel may be found in Section 10.4 and the package insert.
- A discussion of the adverse events associated with the agents used in this trial can be found in Section 10.0 (Drug Formulation, Availability and Preparation).
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require AdEERS, but should be submitted as part of study results.
- AdEERS reports should be submitted electronically to the CALGB Central Office (calgb@uchicago.edu). Faxed copies of the AdEERS paper template, available at the AdEERS web page, will be accepted (312-345-0117), but electronic submission is preferred.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (see Section 5.5 for required CALGB forms).
- Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using study form C-1305.

15.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for bevacizumab (NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/reporting/adeers.html for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Bevacizumab.

Version 1.1, March 28, 2006[1]

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
ALLERGY/IMMUNOLOGY		
	Allergic reaction/hypersensitivity (including drug fever)	***Allergic reaction/hypersensitivity (including drug fever)***
	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	
BLOOD/BONE MARROW		
	Leukocytes (total WBC)	
	Neutrophils/granulocytes (ANC/AGC)	
CARDIAC ARRHYTHMIA		
	Supraventricular arrhythmia NOS	
	Ventricular fibrillation	
CARDIAC GENERAL		
	Cardiac ischemia/infarction	***Cardiac ischemia/infarction***
	Cardiac troponin I (cTnI)	
	Hypertension	***Hypertension***
	Hypotension	
	Left ventricular diastolic dysfunction	
	Left ventricular systolic dysfunction	
CONSTITUTIONAL SYMPTOMS		
	Fatigue (asthenia, lethargy, malaise)	
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	***Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)***
	Rigors/chills	***Rigors/chills***
	Weight loss	
DERMATOLOGY/SKIN		
	Pruritus/itching	
	Rash/desquamation	***Rash/desquamation***
	Ulceration	
	Urticaria (hives, welts, wheals)	***Urticaria (hives, welts, wheals)***
	Wound complication, non-infectious	

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
GASTROINTESTINAL		
	Anorexia	***Anorexia***
	Colitis	
	Constipation	***Constipation***
	Diarrhea	
	Fistula, GI - Select	
	Heartburn/dyspepsia	***Heartburn/dyspepsia***
	Leak (including anastomotic), GI: large bowel	
	Mucositis/stomatitis (functional/symptomatic) - Select	***Mucositis/stomatitis (functional/symptomatic) - Select***
	Nausea	***Nausea***
	Perforation, GI - Select	
	Vomiting	***Vomiting***
HEMORRHAGE/BLEEDING		
	Hemorrhage GI - Select	***Hemorrhage GI - Select***
	Hemorrhage, CNS	***Hemorrhage, CNS***
	Hemorrhage, GU: vagina	
	Hemorrhage, pulmonary/upper respiratory: lung	***Hemorrhage, pulmonary/upper respiratory: lung***
	Hemorrhage, pulmonary/upper respiratory: nose	***Hemorrhage, pulmonary/upper respiratory: nose***
	Hemorrhage/Bleeding - Other (varices-gastric/esophagus)	
INFECTION		
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select	***Infection with normal ANC or Grade 1 or 2 neutrophils - Select***
METABOLIC/LABORATORY		
	Alkaline phosphatase	
	ALT, SGPT (serum glutamic pyruvic transaminase)	
	AST, SGOT (serum glutamic oxaloacetic transaminase)	
	Bilirubin (hyperbilirubinemia)	
	Creatinine	
	Proteinuria	***Proteinuria***
NEUROLOGY		
	CNS cerebrovascular ischemia	***CNS cerebrovascular ischemia***
	Dizziness	
	Neurology – Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome (RPLS))	
PAIN		
	Pain - abdomen NOS	
	Pain - chest/thorax NOS	***Pain - chest/thorax NOS***
	Pain - head/headache	***Pain - head/headache***
	Pain - joint	***Pain - joint***
	Pain - muscle	

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
PULMONARY/UPPER RESPIRATORY		
	Bronchospasm, wheezing	
	Cough	***Cough***
	Dyspnea (shortness of breath)	
	Nasal cavity/paranasal sinus reactions	
	Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	***Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)***
RENAL/GENITOURINARY		
	Renal/Genitourinary - Other (nephrotic syndrome)	
SYNDROMES		
	Cytokine release syndrome/acute infusion reaction	***Cytokine release syndrome/acute infusion reaction***
VASCULAR		
	Thrombosis/thrombus/embolism	***Thrombosis/thrombus/embolism***
	Visceral arterial ischemia (non-myocardial)	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on Bevacizumab trials but with the relationship to Bevacizumab still undetermined:
BLOOD/BONE MARROW - Hemoglobin; idiopathic thrombocytopenia purpura; platelets
CARDIAC GENERAL - Cardiac arrest; pericardial effusion
COAGULATION - DIC
DEATH - Sudden death (cause unknown)
DERMATOLOGY/SKIN - Hypopigmentation
GASTROINTESTINAL - Rectal abscess/necrosis; small bowel obstruction; taste alteration
METABOLIC/LABORATORY - Hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia
MUSCULOSKELETAL/SOFT TISSUE - Aseptic necrotic bone; gait/walking; myasthenia gravis
NEUROLOGY - Aseptic meningitis; confusion; encephalopathy; peripheral neuropathy; seizure; syncope
OCULAR/VISUAL - Cataract; watery eye
PULMONARY/UPPER RESPIRATORY - ARDS; pneumonitis/pulmonary infiltrates; pneumothorax
RENAL/GENITOURINARY - Urinary frequency

Note: Bevacizumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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17.0 MODEL CONSENT FORM

A RANDOMIZED DOUBLE-BLINDED PLACEBO CONTROLLED PHASE III TRIAL COMPARING DOCETAXEL AND PREDNISONE WITH AND WITHOUT BEVACIZUMAB (IND #7921, NSC #704865) IN MEN WITH HORMONE REFRACTORY PROSTATE CANCER

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have advanced hormone refractory, prostate cancer, which means that the cancer is no longer responding to treatment with hormones.

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of the combination of the chemotherapy drug docetaxel (chemotherapy) and prednisone (steroid), with the combination of docetaxel, prednisone and the experimental drug bevacizumab on you and your prostate cancer to find out which is better. Bevacizumab is an antibody that we think can block the VEGF protein and inhibit the growth of new blood vessels. Bevacizumab has been approved by the FDA for the treatment of colorectal cancer, but for prostate cancer, it is not FDA-approved and should be considered experimental.

Docetaxel and prednisone is one commonly used treatment that has been shown to make some patients with prostate cancer live longer. This research is being done to see if adding bevacizumab to the docetaxel and prednisone will delay the growth of your cancer and allow you to live longer.

How Many People Will Take Part in the Study

About 1020 men will take part in this study.

What will happen if I take part in the research study?

Before you begin the study . . .

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical examination;
- Blood tests, liver function tests, urinalysis, and PSA test;
- EKG, CAT or MRI scan, bone scan and chest X-ray.

If the exams, tests and procedures show that you can be in the study and you choose to take part, then you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor will choose or know the group you will be in. You will have an equal chance of being placed in either group. The two treatment groups are:

Arm A: Docetaxel, placebo (sugar water or salt water), plus prednisone

Arm B: Docetaxel, bevacizumab (an experimental drug), plus prednisone

The placebo is given in Arm A so that patients in both groups receive similar-looking treatments. That means all patients get docetaxel by vein (IV), prednisone tablets by mouth, and another IV that will contain either bevacizumab or placebo. This way, neither you nor your doctor can tell which group or arm you are in, and that makes the study more objective.

In case of an emergency, your doctor will be able to find out whether you are getting the bevacizumab or the placebo. If this happens, you will be required to drop out of the study.

During the study . . .

Each treatment group will receive treatment over 21 days. This 21 day period is called “a cycle.” Regardless of which treatment group you are in, you will receive treatment on the following days:

Study Schedule

Day	-1	1	2	3	4	5–21
Dexamethasone	**X**	**X**				**Rest**
Docetaxel		**X**				**Rest**
Bevacizumab/Placebo		**X**				**Rest**
Prednisone		**X**	**X**	**X**	**X**	**Daily**

Before each cycle, you will be given a steroid called dexamethasone in pill form to help decrease the side effects of the treatment. On Day 1 of every cycle, you will receive docetaxel as an infusion (through a vein in your arm) over one hour. You will always receive the docetaxel before the bevacizumab/placebo.

Your first dose of bevacizumab/placebo will be given on Day 1 of the first cycle over 90 minutes. Later infusions of bevacizumab/placebo may be given over a shorter time interval, depending on how you tolerate the infusions.

In addition, you will be asked to take the steroid prednisone by mouth every day.

You may be asked to take a low dose of aspirin every day to try to prevent some bevacizumab complications (such as stroke or heart attack).

If you have not had an orchiectomy (an operation to remove your testicles), you will also continue hormone therapy (with, for example, Lupron or Zoladex).

Tests and Procedures:

During the time that you are receiving the study treatment, you will need the following tests and procedures. They are part of regular cancer care.

- physical examinations (every 3 weeks)
- blood tests, including chemistries and PSA levels (every 3 weeks)
- liver function tests (every 3 weeks)
- CAT or MRI scans, and/or bone scans to monitor your disease

You will also have urine tests every 3 weeks. These are often part of standard cancer care, but it is possible that these tests might be done more frequently since you are in this study.

Your doctor may decide to continue your treatment for up to two years, as long as the tumor does not grow and you are able to tolerate the treatment.

When I am finished taking the study treatment:

After you have finished receiving the study treatment, you will be asked to have physical examinations every 3 months for up to 2 years after you started the study. In addition, you will have PSA tests every 3 months and periodic scans to monitor your disease for up to 5 years after you started the study.

How Long Will I be in the Study?

The study treatment will be continued for up to 2 years as long as your prostate cancer is responding to or is stabilized by the drugs and you do not have any severe side effects from the drugs. If your cancer is not growing but you develop severe side effects from the chemotherapy, your doctor may ask you to continue the bevacizumab/placebo without the docetaxel. If your

cancer worsens, you will be removed from the study. Whether or not you remain in the study, the study doctor will continue to follow your progress for up to ten years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the therapy we are studying include:

Arm A (Docetaxel, prednisone, and placebo)

LIKELY:

- Hair loss
- Fluid retention/edema
- Fatigue (feeling tired)
- Upset stomach
- Soreness and/or weakness of muscles and/or joints
- Increases in blood sugar levels, which may cause increased thirst, urination, and fatigue
- Lowered white blood cell count that may lead to an increased risk of infection
- Lowered platelet count that may lead to increased bruising or bleeding
- Lowered red blood cell count that may cause tiredness or shortness of breath (if the counts get too low, you may need a transfusion)

LESS LIKELY:

- Diarrhea
- Nausea and vomiting
- Mouth and throat sores
- Loss of appetite
- Loss of reflexes
- Darkening or lightening of fingernail beds
- Peeling skin on hands and feet
- Insomnia (difficulty falling asleep)
- Numbness and/or tingling of the fingers and toes

RARE BUT SERIOUS:

- Stomach ulcers and/or bleeding
- Severe allergic reaction (life-threatening breathing problems)
- Abnormal function of the adrenal gland which can cause weakness and fatigue, low blood pressure, nausea, vomiting, diarrhea, irritability and/or restlessness, loss of bone density
- Low blood pressure
- Abnormal changes in personality

Arm B (Docetaxel, prednisone, and bevacizumab)

LIKELY:

- Hair loss
- Fluid retention/edema
- Fatigue (feeling tired)
- Upset stomach
- Minor nosebleed
- Soreness and/or weakness of muscles and/or joints
- Increases in blood sugar levels, which may cause increased thirst, urination, and fatigue
- High blood pressure
- Headache
- Infusion reactions, which may cause fever, chills, and/or rigor
- Lowered white blood cell count that may lead to an increased risk of infection (see the additional information below)
- Lowered platelet count that may lead to increased bruising or bleeding
- Lowered red blood cell count that may cause tiredness or shortness of breath (if the counts get too low, you may need a transfusion)

LESS LIKELY:

- Diarrhea
- Nausea and vomiting
- Mouth and throat sores
- Loss of appetite
- Loss of reflexes
- Liver irritation
- Rash/hives
- Stroke (serious)
- Heart attack (serious)
- Darkening or lightening of fingernail beds
- Peeling skin on hands and feet
- Insomnia (difficulty falling asleep)
- Numbness and/or tingling of the fingers and toes
- Lower blood pressure
- Bleeding
- TIA (mini-stroke) (serious)
- Chest pain (angina) (serious)
- Protein in urine, which may be a sign of kidney damage
- High blood pressure causing serious neurological side effects or headaches

RARE BUT SERIOUS:

- Stomach ulcers and/or bleeding

- Delayed wound healing
- Bowel perforation and bowel anastomotic dehiscence have been seen with bevacizumab (see the additional information below).
- Severe or life-threatening internal or external uncontrolled bleeding
- Blood clots in the legs, lungs, brain, or in your abdomen
- Severe allergic reaction (life-threatening breathing problems)
- Abnormal function of the adrenal gland which can cause weakness and fatigue, low blood pressure, nausea, vomiting, diarrhea, irritability and/or restlessness, loss of bone density
- Low blood pressure
- Abnormal changes in personality
- Decrease in heart function
- Inflammation of the lungs, which would result in shortness of breath or cough
- Leaking from blood vessels in the brain (see the additional information below)

Neutropenia (**lowered white blood cell count**) is a common side effect of chemotherapy drugs. This may happen more often when bevacizumab is added to chemotherapy. In some studies of bevacizumab plus chemotherapy, there was also an increase in fever with neutropenia and infections. Rarely, these infections resulted in death.

Bowel perforation and bowel anastomotic dehiscence: A few patients taking bevacizumab have experienced bowel perforation and bowel anastomotic dehiscence. Bowel perforation occurs when an opening exists in the bowel wall allowing bowel contents to spill into the abdomen. Bowel anastomotic dehiscence is a breakdown in the surgical connection between two pieces of bowel. These events can be life-threatening. In addition, there have been a few reports of surgical wounds healing slowly or poorly. You should inform your doctors if you experience symptoms suggestive of bowel perforation, such as worsening or new pain in the abdomen or the rectum.

The use of bevacizumab is associated with an increased risk of conditions related to **clots in the arteries**, including stroke or heart attack; these conditions can be life-threatening or fatal. When several studies were looked at together, problems due to clots in arteries were increased about double (up to 4 to 5%) in patients receiving chemotherapy plus bevacizumab compared to chemotherapy alone (about 2%). Patients who were elderly and with past history of clots in the arteries seemed to be at a greater risk for these problems.

Reversible Posterior Leukoencephaolpathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS is a medical condition related to **leakiness of blood vessels in the brain** and can cause confusion, blindness or vision changes, seizure, and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening or fatal and may have long-term effects on brain function.

Bevacizumab is the common name for the commercial drug Avastin. The bevacizumab used in this trial, however, is for use in research studies only and may be made at *locations different* from those where Avastin is made. Although some differences may exist, bevacizumab for research use and the commercial drug, Avastin, are manufactured by a similar process, meet similar standards for final product testing and are expected to be very similar in safety and effectiveness.

Unanticipated side effects may occur which have not been reported. If you have any unusual symptoms, report them immediately to your doctor.

Reproductive risks: You should not father a baby while on this study and for at least three months after you stop taking the study drugs, because the drugs may affect an unborn baby. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask the study doctor or contact _____.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope adding bevacizumab to docetaxel and prednisone will be more useful against cancer compared to docetaxel and prednisone alone, there is no proof of this yet. We do know that the information from this study will help doctors learn more about these drugs as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study, which may involve using some or the same or different drugs
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.
Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Cancer and Leukemia Group B (CALGB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Genetech pharmaceutical company, the makers of bevacizumab (Avastin®).

The Cancer Trials Support Unit (CTSU) may also view your records if you are participating in this trial through one of their institutions.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The NCI is supplying the bevacizumab/placebo at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the bevacizumab/placebo.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person:
(name) _____ (title)_____
(address)_____ (phone number) _____.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number).

[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

* You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

RELATED STUDIES

Please note: The following section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies.

The results of these research studies will not be provided to you or your doctor, nor will the results have any effect on your treatment. It is unlikely that what we learn from these studies will have a direct benefit to you. However, the information learned from these studies may benefit other patients in the future.

The results from these studies may be published, but individual patients will not be identified in these publications.

There will be no charge to you for participating in these research studies. Your sample will only be used for research and will not be sold. The research done with your sample may help to develop new products in the future.

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone is very small.

If you decide now to participate and then change your mind at any time about participating in these studies for any reason, you should contact your institution and let them know that you do not want the researchers to use your sample. The sample will then no longer be used for research. It will either be destroyed or returned to your institution for storage. The sample will also be returned to your institution upon request if needed for any other medical or legal reasons.
You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Studies on blood:

In addition to the treatment study, the researchers would also like to collect additional samples of your blood. We would like to collect a sample of blood to verify how well changes in your prostate specific antigen (PSA) will predict which patients will do better or worse. The researchers would also like to learn more about the effects of bevacizumab on angiogenesis and VEGF levels and other markers of your cancer (for example, interleukin-6, chromogranin, and circulating prostate cancer cells). Smaller studies of these tests have shown that they may help predict which patients will do better or worse. We will try to further study these test to see if they do predict how long patients will live. In the future, this information could be used to help doctors decide how well a new drug might work for prostate cancer.

Approximately 3 tablespoons of additional blood at the beginning of the study and two tablespoons of blood when you get chemotherapy every three weeks would be collected. The plasma (the fluid portion of the blood in which the different blood cells are suspended) will be separated from the sample, and sent to a central laboratory for analysis.

1) I agree that my blood specimen may be used for research studies to learn about the effects that the experimental treatment may be having.

_____ Yes _____ No Initials _____

Genetic studies on blood cells:

The researchers would like to investigate whether substances in your blood are related to the way that your body responds (or doesn't respond) to the chemotherapy you receive in this trial. These tumor markers are inherited through your family, and could be passed to your children. These are also called genetic studies.

Blood taken before treatment will be used to learn how certain genes influence the effectiveness and side effects of docetaxel and bevacizumab. In order to study the genes the DNA must be removed from your blood sample. DNA is the substance that makes up your genes. Genes are the units of inheritance that are passed down from generation to generation. They are responsible for eye color, hair color, blood type, and hundreds of other traits.

There are specific risks associated with genetic studies. To help you make your decision, additional information about participation in genetic studies is included at the end of this consent form. This information identifies how your personal information will be protected by the CALGB and its researchers.

Blood taken for these studies will be done only once at the time you enter the study. About 1 tablespoon of blood would be taken.

2) I agree that my blood may be used for the genetic research studies described above.

_____ Yes _____ No Initials _____

Storage of your blood:

The researchers would also like to store any portion of the blood that is not used up by the related study described above. These samples may be stored indefinitely. You can still take part in the treatment study, and the research study described above without giving your consent for your samples to be stored.

It is not possible for you or the CALGB to know what studies of cancer may be appropriate in the future. We ask that you give permission in advance for other studies to be performed using the blood without being re-contacted to give permission for each test.

3) My blood may be kept for future unknown use in research to learn about, prevent, treat, or cure cancer.

_____ Yes _____ No Participant _____ Date _____

4) My blood may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease and heart disease.

_____ Yes _____ No Participant _____ Date _____

5) My doctor or someone from CALGB may contact me in the future to ask me to take part in more research.

_____ Yes _____ No Participant _____ Date _____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Safeguards of Confidentiality in Studies Involving Genes (genetic studies):

It is possible to use blood samples to study many different kinds of genes. The CALGB recognizes this possibility and will take the following steps to protect your privacy and to protect you from having your sample tested for any genetic changes not directly related to cancer:

- Blood samples will be stored at a CALGB laboratory. The CALGB Statistical Center will perform all analyses of data and store all study results. Your blood sample will not be stored with your name on it. Instead, it will be labeled with a special CALGB identification number. The only location where your name and special identification number will be stored together is at the CALGB Statistical Center. The greatest effort will be made to see that all personal information that can identify you is kept under conditions that protect your privacy.
- Information about your participation in this study and results of any tests performed on your sample will be kept only at the CALGB Statistical Center at Duke University. This information will not be made available to your doctors or to individual researchers at CALGB. Test results from this study will not be put in your medical records. All study information, including test results, is stored under conditions that limit access in order to protect the privacy of the people participating in this study.
- Your blood will be used only for the study of genes involved in cancer.
- There are no absolute legal protections against discrimination on the basis of genetic information. Instances are known in which a patient has been required to provide genetic information before applying for health insurance and/or a job. Since neither you nor your physician will be notified of the results of this test, it is unlikely that any discrimination could take place.

The same precautions to protect your privacy will be in place for such future studies. Future investigators will receive blood samples with the special CALGB identification number only, and your blood sample will not be identified with your name. These future investigators must apply to the CALGB and have their research project reviewed and approved by the CALGB.

If you decide now to give a sample of blood and then change your mind at any time about participating in the study, just contact your institution and let them know that you do not want the researchers to use your sample. The results from these studies may be published, but individual patients will not be identified in the publications.

APPENDIX I

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

To submit site registration documents:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-888-823-5923
Fax: 215-569-0206

For patient enrollments:

CTSU Patient Registration
Phone: 1-888-462-3009
Fax: 1-888-691-8039
Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)

[Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 AM and 5:30 PM.]

Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:

CALGB Statistical Center
Hock Plaza
2424 Erwin Road, Suite 802
Durham, NC 27705
Tel: 919-668-9350
Data Operations Fax: 919-668-9348
Teleform Fax: 919-416-4990

Sites should submit Teleforms via Fax or Mail. See Section 5.5 Data Submission Section for details on forms submission.

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility or treatment related questions: Contact the CALGB Study Chair.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org

The CTSU Registered Member Web site is located at http://members.ctsu.org

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://members.ctsu.org.

All forms and documents associated with this study can be downloaded from the CALGB 90401 Web page on the CTSU registered member Web site (https://members.ctsu.org).

Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for CALGB 90401 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Prestudy requirements for patient enrollment on CALGB 90401:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms, and the patient decision whether to permit use of tissue for related studies and future studies has been documented.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.

CTSU PROCEDURES FOR PATIENT ENROLLMENT

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Monday-Friday. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - CALGB 90401 Eligibility Checklist
   - CALGB Registration Worksheet (the Nomogram Group Assignment number can be obtained by accessing the 90401 nomogram calculator)
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. Registration is limited to the operating hours of the CALGB Registration Office (9 AM – 5 PM ET). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the CALGB, **within the confines of CALGB's registration hours.** The CTSU registrar will access the CALGB's on-line registration system, to obtain assignment of treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

- Protocol treatment should begin within 14 days of randomization.
- Registration to the correlative sciences study (serum sample study) for those patients who have agreed to participate will be performed at the same time as registration to the treatment study.

Procedures for late enrollment onto CALGB 60404 (pharmacogenomic companion):

- Submit CTSU Patient Enrollment transmittal form (with note indicating delayed registration to the pharmacogenomic companion study).
- Submit revised CALGB 90401 Registration Worksheet (indicating patient consent for CALGB 60404).

Note: Although it is preferable that patients are registered to 60404at the same time they are registered to 90401, registration to 60404 may occur up to 60 days following registration to the treatment trial.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the CALGB-90401 Web page located on the CTSU registered member Web site (https://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the CALGB Statistical Center, [see contact table and Section 5.5 of protocol] unless an alternate location is specified in the protocol. Do not send study data to the CTSU. A completed CTSU-CALGB coversheet should accompany all data submissions.
3. The CALGB Statistical Center will send (generally via email but may be sent via postal mail or fax) query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the CALGB Statistical Center (via postal mail or fax) and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

SPECIAL MATERIALS OR SUBSTUDIES

1. Specimen Submission for Correlative Studies (Protocol Section 5.6)
    - There are two substudies embedded within CALGB 90401. Both require patient consent.
    - PSA as a surrogate marker for survival and validation of novel biomarkers in HRPC: CALGB 150411
    - Pharmacogenomic studies: CALGB 60404
    - Collect, prepare, and submit specimens as outlined in the protocol.
    - Do not send specimens, supporting clinical reports, or transmittals to the CTSU.

SERIOUS ADVERSE EVENT (AE) REPORTING (SECTION 15.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (https://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the protocol number Web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT (SECTION 10.0):

Investigational agents: Bevacizumab/placebo (NSC 704865/IND #7921)

Commercial agents: Docetaxel, prednisone

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 10.0 of the protocol.

2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the CALGB-90401 Web page.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting

and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDS) Monitoring

This study will be monitored by the Clinical Data System (CDS-web). Cumulative CDS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDS data collected from the study-specific case report forms.

APPENDIX II

Clinical Trials Agreement

The agent (hereinafter referred to as Agent), bevacizumab, used in this protocol is provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between Genentech, Inc. (hereinafter referred to as Collaborator) and the NCI DCTD. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and should be maintained as such by the investigators.
2. For a clinical protocol where there is an investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):

    a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator for review at the appropriate time (see #5). The NCI expects that clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator, and not to other parties.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair) of Collaborator's wish to contact them.
5. Any data provided to Collaborator must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator for courtesy review following submission, but prior to presentation

at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 7111
Bethesda, Maryland 20892
FAX 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator.

Appendix III

UPC (Urine Protein to Creatinine) Ratio

The UPC (urine protein to creatinine) ratio directly correlates with the grams of protein found in a 24 hr urine. The UPC ratio can be used in the place of a 24-hour urine.

Procedure for Obtaining a Urine Protein/Creatinine Ratio:

1. Obtain at least 4 mL of a random urine sample in a sterile container (does not have to be a 24-hour urine sample).
2. Determine protein concentration (mg/dL).
3. Determine creatinine concentration (mg/dL).
4. Divide #2 by #3 above:

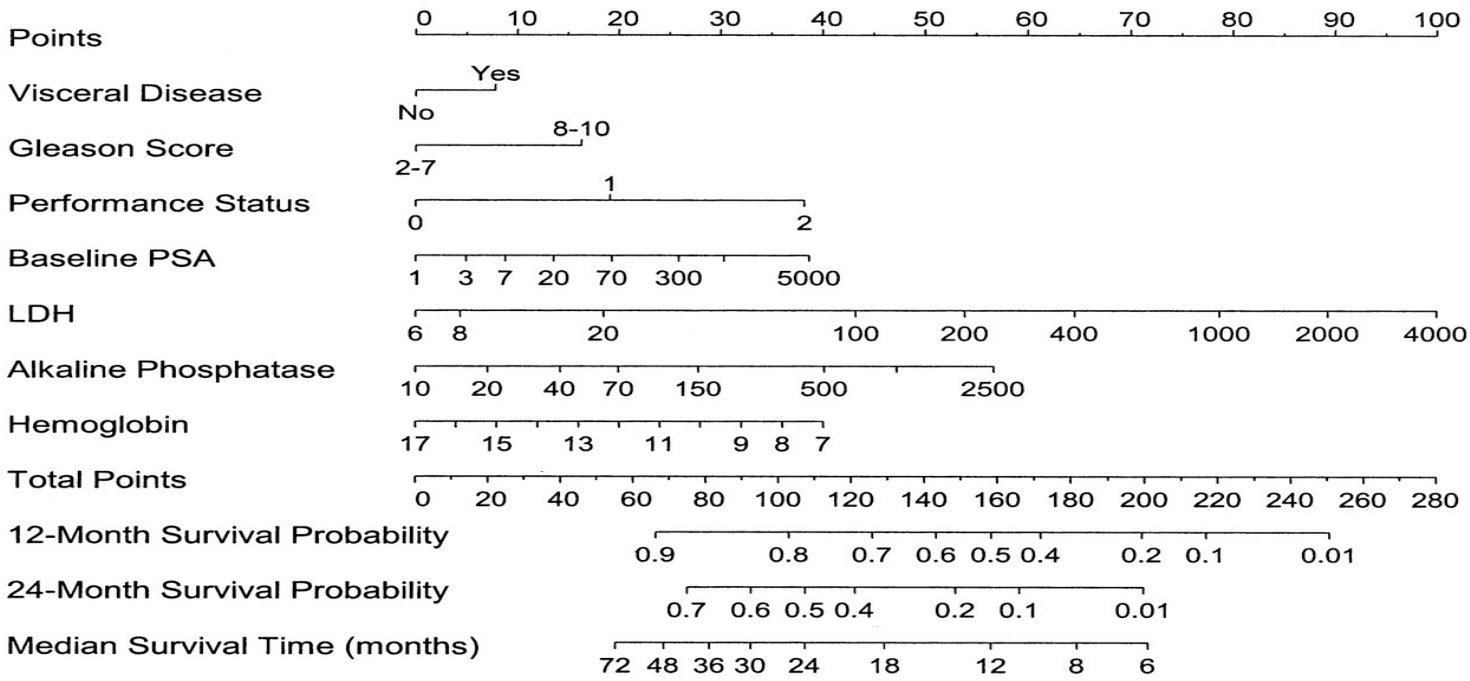
UPC Ratio =

$$\frac{\text{Protein Concentration (mg/dL)}}{\text{Creatinine Concentration (mg/dL)}}$$

Appendix IV

CALGB 90401 Nomogram for advanced HRPC (1)

For the purposes of determining the stratification factor of 24-month predicted survival probability, institutions may either use the nomogram below or access an web-based calculator available at the CALGB 90401 Web page. Please refer to the CALGB 90401 Registration Worksheet for further instructions regarding the calculation of the survival probability.



Instructions to Physicians:
Please start from the second top axis by identifying the disease measurability. Draw a vertical line to the Points axis (top line) to represent the number of prognostic points the patients will receive for measurable disease. Do the same for the other prognostic variables. Once all prognostic points for the predictors have been determined, add up the prognostic points for each prognostic variable. You can determine the 12-month survival probability by drawing a vertical line down from the "total points axis" (fourth from the bottom) to the 12-month survival probability axis (third line from the bottom). The same process can be done to estimate the 24- month survival probability.