Amendment

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** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

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A Phase II trial of Docetaxel, Thalidomide, Prednisone and Bevacizumab in Patients with Androgen-Independent Prostate Cancer

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C. Obtaining the voluntary informed consent of individuals to be subjects
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F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
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Commercial Agents: Docetaxel, Prednisone, Thalidomide, Bevacizumab

PRÉCIS

This is a Phase II study of docetaxel, bevacizumab, prednisone and thalidomide in patients with androgen independent metastatic prostate cancer who are previously untreated with chemotherapy. The primary objective of this study is to determine if the combination of docetaxel, thalidomide and bevacizumab is able to be associated with a sufficiently high proportion of patients with a PSA response to be worthy of further investigation in metastatic prostate cancer. We will also be looking at multiple secondary endpoints. These will include possible pharmacokinetic interactions among the study agents, potential correlation between patient genotype and efficacy of treatment. We will also be looking for circulating endothelial cells in blood before and after treatment. Additionally, we will be monitoring the tolerability of the regimen, time to disease progression, and survival duration as endpoints as well. We hope to use this trial to build on the promising results seen in our thalidomide/docetaxel protocol where there was a significant PSA decline and a trend toward survival benefit.

Treatment Schema:

Cycle Number: _____

Study Schedule for patients in the original protocol

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	1
Dex.	X	X																			X	X
T	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Do	X																					X
B	X																					X
P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
E	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Dex - Dexamethasone 4 mg. PO 12 and 1 hour pre and 12 hours post-docetaxel infusion
T - Thalidomide 200 mg. PO daily throughout cycle
Do - Docetaxel 75 mg/m2 IV
B - Bevacizumab 15 mg/kg IV
P - Prednisone 10 mg PO daily throughout cycle
E – Enoxaparin 1 mg/kg SQ daily

Study Schedule for patients enrolled in the expansion cohort

Day	Cycle1 Day 1	Cycle1, Day 21	Cycle 2, Day 1	Cycle 2, Day 21	>Cycle 3, Day 1	>Cycle 3, Day 2-20	>Cycle 3, Day 21
Dex.	X	X	X	X	X		X
T					X	X	X
Do	X		X		X		
B	X		X		X		
P					X	X	X
E					X	X	X

Dex - Dexamethasone 4 mg. PO 12 and 1 hour pre and 12 hours post-docetaxel infusion
T - Thalidomide 200 mg. PO daily throughout cycle
Do - Docetaxel 75 mg/m2 IV
B - Bevacizumab 15 mg/kg IV
P - Prednisone 10 mg PO daily throughout cycle
E – Enoxaparin 1 mg/kg SQ daily

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1 OBJECTIVES

1.1 PRIMARY OBJECTIVES

- The primary objective of this study is to determine if the combination of docetaxel, thalidomide, prednisone and bevacizumab is able to be associated with a sufficiently high proportion of patients with a PSA response to be worthy of further investigation in metastatic prostate cancer.
- The primary endpoint of the expansion cohort is to determine if docetaxel and bevacizumab cause immunologic changes that would not be considered to be compatible with concomitant therapeutic vaccination. The changes will be assessed through measuring regulatory T-cell (Treg) percentage and function, lymphocyte function, myeloid suppressor cells, and mixed lymphocyte reaction.

1.2 SECONDARY OBJECTIVES

- To evaluate time to disease progression and survival duration of those patients treated. Time to progression will be evaluated in two ways. First by using Bubley criteria and secondarily by clinical and radiographic criteria without the use of PSA.
- To compare the PSA-elevation only group with the patients having both PSA-elevation and clinical or radiographic progression
- To characterize the pharmacokinetics of both docetaxel and thalidomide and determine if any pharmacodynamic relationships exist between plasma concentrations of either agent and clinical activity or toxicity
- To determine the existence of and quantification of circulating endothelial cells before and after drug administration
- To analyze the patients' genotype with regard to cytochrome P450 2C19 polymorphism and correlate that with pharmacokinetics and efficacy
- To evaluate the usefulness of dynamic MRI to monitor the progression of bony and soft tissue disease in metastatic prostate cancer
- To determine whether there are changes in the molecular markers of angiogenesis (including, but not limited to serum and urine VEGF) before and after administration of docetaxel, prednisone, thalidomide and bevacizumab
- To evaluate the toxicity profile of this combination

2 BACKGROUND

2.1 STUDY DISEASE

Metastatic prostate cancer is a leading cause of death from cancer in men. Though initially responsive to hormone therapy, it eventually progresses in almost all patients. For this reason there has been a search for novel agents to use in the treatment of androgen independent prostate cancer. Antiangiogenesis is a relatively new antitumor strategy that has been employed in the treatments of many malignancies.

Historically, chemotherapy was not considered to have significant activity in metastatic androgen independent prostate cancer (AIPC). However, this view changed within the past 10 years due in part to the availability of prostate-specific antigen (PSA) measurements to monitor tumor burden. Estramustine, a tubulin-targeting drug, when combined with agents such as etoposide, vinblastine or paclitaxel, can induce responses in patients with AIPC (25-27). Docetaxel, both as a single agent and in combination with estramustine has activity as well. However, while it seems that chemotherapy, either as a single agent or in combination, may lead to clinical responses, reduction in PSA measurements, pain control, and/or improved quality of life, to date, no benefit in overall survival has been shown.

2.2 DOCETAXEL

Docetaxel is a semisynthetic taxane with potent antitumor activity in a variety of malignancies. Its mechanism in prostate cancer is thought to be two-fold. First it acts as a microtubule stabilizer by binding preferentially to Beta-tubulin, leading to assembly of microtubules without GTP and other various cofactors. This leads to static polymerization, which disrupts the normal mitotic process, causing cell arrest in G2M phase, which ultimately leads to apoptosis (1). A second mechanism involves the bcl-2 gene. Bcl-2 is an oncogene that enhances tumor activity via inhibition of apoptosis. There have been several clinical and experimental studies that have shown that overexpression of bcl-2 in prostate cancer leads to chemotherapy and androgen resistance as well as protection from apoptosis (2, 3). During the G2/M cell cycle interface, bcl-2 is normally temporarily phosphorylated to facilitate mitosis. Docetaxel has been shown to induce continuous bcl-2 phosphorylation, which leads to the loss of its normal antiapoptotic properties (4).

Based on this preclinical data, there has been much investigation in the use of docetaxel both as a single agent and as part of combination therapy in patients with androgen independent prostate cancer (AIPC). Several phase II studies used single agent docetaxel every three weeks at 75 mg/m2 and demonstrated a PSA decrease of at least 50% in 38-46% of patients with AIPC (5, 6).

Two recent phase III trials of docetaxel combination therapy in 1006 patients with AIPC were presented at the most recent meeting of the American Society of Clinical Oncology (ASCO). Eisenberger et al. conducted a three arm trial of prednisone (5 mg bid) plus either a) docetaxel (75 mg/m2 q 3 wk x 10 cycles) b) docetaxel (30 mg/m2 q wk for 5/6 weeks x 5 cycles) or c) mitoxantrone (12 mg/m2 q 3 wk x 10 cycles). Results showed that the combination of daily prednisone plus docetaxel given every 3 weeks had a statistically significant improvement in survival (18.9 vs. 16.5 mos.) and PSA response (45% vs. 32 %) over prednisone plus mitoxantrone. While the prednisone plus weekly docetaxel had comparable PSA benefit, the survival benefit was less and not statistically significant. Petrylak et al. conducted SWOG 99-16, a phase III study of 770 men with AIPC randomized to either docetaxel (60-70 mg/m2 q 3 weeks) plus estramustine (280 mg d 1-5 q 3 wk) versus mitoxantrone (12-14 mg/m2 q 3 wk) plus daily prednisone (5 mg po bid). Results showed that the docetaxel and estramustine arm was superior to the mitoxantrone and prednisone arm in median survival (18 vs. 15 mos) as well as several other meaningful endpoints.

These larger randomized studies were the first to demonstrate survival benefit in men with AIPC and strongly encourage further trials using these and other docetaxel combinations in this disease.

2.3 PREDNISONE

Prednisone, a glucocorticoid has been shown to have significant palliative activity in patients with androgen-independent prostate cancer. A previous study was done in patients with androgen-independent prostate cancer that were given prednisone alone. Patients received 10 mg orally twice a day. Of the 29 patients, 48% of patients had a $\geq$ 25% PSA decline, 34% had a PSA decline $\geq$ 50% and 14% experienced a PSA decline of $\geq$ 75%. The average PSA declined in this study population was 33%. Average progression free survival was 2.8 months (7).

2.4 THALIDOMIDE

Thalidomide, a glutamic acid derivative, is a potent teratogen that causes dysmelia (stunted limb growth) in humans (8). It was marketed in Europe as a nonbarbiturate sedative but was withdrawn 30 years ago because of its teratogenic effects. It has been postulated that thalidomide-induced limb defects were secondary to an inhibition of blood vessel growth in the developing fetal limb buds. In 1994, D'Amato et al demonstrated that thalidomide inhibited bFGF-induced angiogenesis (9). Bauer et al subsequently determined that a metabolite of thalidomide was responsible for this antiangiogenic activity (10). Thalidomide was later shown to inhibit the growth of V2 carcinoma and Lewis lung carcinoma in animal models by antiangiogenic mechanisms (11). As angiogenesis appears to play a prominent role in the development, growth and metastasis of prostate cancer (24-29), there have been considerable efforts to investigate the use of antiangiogenic agents such as thalidomide with cytotoxic chemotherapy drugs in this particular malignancy.

A recent phase II trial randomized 75 chemotherapy naïve AIPC patients to receive 30-mg/m2 weekly docetaxel for 3 consecutive weeks followed by a 1-week rest period; or docetaxel at the same dose and schedule plus thalidomide 200 mg orally each day. The patients were enrolled in a 2:1 randomization scheme with 50 patients receiving combination therapy and 25 receiving docetaxel alone. Both regimens were well tolerated with only mild toxicities. It should be noted that there was a significant amount of thromboembolism seen in the initial group of patients receiving combination therapy. However, subsequent patients in the combination group were given prophylactic anticoagulation and no further thromboembolic events occurred. Measurement of the angiogenic markers VEGF and bFGF showed no significant changes between pre and post treatment levels in either the combination or docetaxel-alone group. After a follow-up period of 26.4 months, the percentage of patients with a greater than 50% decline of PSA was higher in the combination group (51% vs. 37% in the single agent docetaxel group). Median progression-free survival was 5.9 months in the combination arm and 3.7 months in the docetaxel arm. The median survival in the docetaxel group was 14.7 months and 28.9 months in the combined group. The primary objective of the study was to determine whether the combination of thalidomide and docetaxel can produce a sufficiently high clinical response rate to warrant further investigation in patients with

androgen independent prostate cancer. It should be noted that though the study was not powered to detect a survival difference, the addition of thalidomide nearly doubled the median survival in patients with metastatic AIPC (12, 12a).

This study represented an exciting step in the movement to combine traditional cytotoxic chemotherapy and antiangiogenic therapy. Significant improvement in the major clinical endpoints (PSA decline and progression-free survival) was demonstrated, as was a strong trend toward an improvement in overall survival.

Recently there has been significant interest in combinations of cytotoxic and antiangiogenic agents. A recent multi-center Phase III trial randomized 800 patients with metastatic colorectal cancer to bevacizumab, a VEGF inhibitor, plus 5FU/ Leucovorin/CPT-11 or placebo plus 5FU/Leucovorin/CPT-11. The results showed that the arm that included bevacizumab had increased overall survival, progression-free survival, response rate and duration of response (13). As previously mentioned, prostate cancer seems to utilize angiogenesis in its growth and metastasis, it is therefore logical to include an antiangiogenic agent like thalidomide which has proven antiangiogenic effects, in the treatment of AIPC. Additionally, thalidomide has demonstrated very promising activity when combined with docetaxel alone in the treatment of AIPC.

2.5 BEVACIZUMAB (RHUMAB)

Background: Bevacizumab (rhuMAb) is a recombinant humanized anti-VEGF monoclonal antibody composed of human IgG1 framework regions and antigen-binding complementarity-determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1) which blocks the binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence, including most of the antibody framework, is derived from human IgG_1, and ~7% of the sequence is derived from the murine antibody.

Preclinical data: In cynomolgus monkeys, twice weekly IV treatments with bevacizumab (doses of 2, 10 and 50 mg/kg) for 4, 13 or 26 weeks were well tolerated, with no overt signs of acute toxicity (14, 15). Animals with open growth plates showed physeal dysplasia as well as focal to diffuse chondroid necrosis and linear fissuring of the cartilaginous growth plate. Females treated with 10-50mg/kg twice weekly had decreased ovarian and uterine weights, which were associated with absence of corpora lutea. These findings were expected, considering the known role of VEGF in formation of the corpora lutea and of the growing bone (16). A further study using a similar treatment regimen, in the recovery period the physeal dysplasia and ovarian and uterine changes induced by rhuMAb VEGF were partially reversible. No antibodies against bevacizumab were detected.

Phase I Clinical studies: Two phase I studies have been performed. Study AVF0737g was a dose escalation trial of single and multiple intravenous (IV) administration of rhuMAb in patients with advanced malignancies. Five dose levels were evaluated (0.1, 0.3, 1.0, 3.0, and 10mg/kg). rhuMAb VEGF was administered as a 90-minute infusion on days 0, 28, 35 and 42 (17). Study AVF0761g evaluated multiple doses of rhuMAb VEGF 3 mg/kg weekly for up to 8 weeks in combination with one of three cytotoxic chemotherapy regimens (5-fluorouracil/leucovorin, carboplatin/paclitaxel, or

doxorubicin) in subjects with advanced solid malignancies (18). rhuMAb VEGF was administered as eight weekly doses of 3mg/kg.

In both studies, rhuMAb VEGF appeared to be well tolerated. In study AVF0737g, 3 of 25 patients treated experienced tumor-related hemorrhagic events, possibly related to the administration of rhuMAb VEGF. In two cases the event was considered serious: an intracranial hemorrhage (at an occult cerebral metastasis) in a patient with hepatocellular carcinoma and bleeding at the tumor site in a 38-year-old woman with a slowly progressing sarcoma of the thigh. No patient in AVF0761g reported serious bleeding. No dose limiting toxicity was reached in either study. No antibodies to rhuMAb VEGF were detected after therapy in either study. Three subjects from each study subsequently enrolled in the extension study.

Pharmacokinetics: In study AVF0737g, the pharmacokinetics of rhuMAb VEGF appeared to be linear for doses $\geq$ 1mg/kg with a half-life of approximately 15 days. Comparable pharmacokinetic data was seen in study AVF0761g. Co-administration of rhuMAb and cytotoxic chemotherapy did not appear to result in a change in the systemic concentration of the cytotoxic agents.

Phase II Clinical Studies: There are 4 Phase II Clinical Trials that have been conducted or still accruing patients (see below).

Table 1: Phase II Clinical Trials

Study	Population	Study Treatment	rhuMAb VEGF Dosing Regimen
AVF0757g	Stage IIIB or IV non-small cell lung cancer	Carboplatin/paclitaxel $\pm$ rhuMAb VEGF	7.5mg or 15mg/kg every 3 weeks until disease progression
AVF0780g	Metastatic colorectal cancer	5-FU/leucovorin $\pm$ rhuMAb VEGF	5mg or 10mg/kg every other week until disease progression
AVF0776g	Relapsed metastatic breast cancer	Single-agent rhuMAb VEGF	3,10 or 20 mg/kg every other week over a 168-day treatment period or until disease progression
AVF0775g	Hormone-refractory prostate cancer	Single-agent rhuMAb VEGF	10mg/kg every other week over a 168-day treatment period or until disease progression

In Study AVF0780g, patients with metastatic colon cancer were treated with either 5-FU/leucovorin (500mg/m^2 5-FU and 500mg/m^2 leucovorin administered weekly for six

weeks, with courses repeated every eight weeks) alone or in combination with rhuMAb VEGF 5mg/kg or 10mg/kg every two weeks. Response rates were 17%, 40% (p=. 03) and 24% (p=. 23), respectively. A prolonged time to disease progression was seen in patients treated with rhuMAb VEGF 5mg/kg in combination with chemotherapy (9.0 months p=. 005) compared with those who received rhuMAb VEGF 10mg/kg (7.2 months p= .217) or chemotherapy alone (5.2 months).

The anti-VEGF antibody Bevacizumab (rhuMAb) was evaluated as a single agent in several malignancies including AIPC (18, 19). In a Phase II trial 15 patients with AIPC were treated with 10 mg/kg every 14 days. Results of the study showed that though the drug was tolerated well, there were no significant objective responses. Picus et al. is conducting an ongoing CALGB trial looking at the use of bevacizumab, estramustine and docetaxel in 79 patients with AIPC. Early results show that 53% of patients had a PR and 65% of patients had a >50% decrease in PSA in those patients with sufficient data to analyze. This regimen was well tolerated, though there was some increase in thrombosis (20). This trial is using 15 mg/kg of bevacizumab every 3 weeks.

Toxicities: Life threatening toxicities seen in clinical trials to date with rhuMAb VEGF have included hemorrhage and thrombosis. Less severe toxicities have included proteinuria, hypertension, fever, chills, rash, headache, infection, epistaxis and mouth ulceration.

a) Hemorrhage: Life threatening hemorrhage was seen in a Phase I trial (AVF0737g) in the form of an intracranial hemorrhage (at an occult cerebral metastasis) in a patient with hepatocellular carcinoma and in the Phase II study (AVF0757g) in the form of massive hemoptysis or hematemesis. There were 6 life-threatening hemorrhages among 66 patients receiving rhuMAb VEGF-treated patients of which four of these events were fatal. An analysis of possible risk factors for life-threatening bleeding identified squamous cell histology as a risk factor (4 of 6 bleeds occurred in patients with squamous cell histology whereas only 13 of 66 rhuMAb VEGF-treated patients had squamous histology). A number of investigations were performed on two of the patients with pulmonary hemorrhage and in eight patients in AVF0780g receiving rhuMAb VEGF including platelet count, prothrombin time, activated prothrombin time, fibrinogen, bleeding time, euglobulin clot lysis, d-dimer, alpha2-antiplasmin, PFA-100 (a platelet function assay) and these were all within normal range (Novotny,W. Genentech Inc personal communication).
b) Thrombosis: In Study AVF0780g in metastatic colorectal cancer, venous and arterial thrombosis were seen more frequently than in patients treated with rhuMAb VEGF plus 5-FU/leucovorin than in patients treated with 5-FU/leucovorin alone: 3 of 35 patients in the control arm, 9 of 35 patients in the 5mg/kg rhuMAb VEGF arm and 4 of 32 patients in the 10mg/kg rhuMAb VEGF arm. One event was fatal (a pulmonary embolism in the 10mg/kg arm) and three events required study discontinuation (a pulmonary embolism and a superior mesenteric vein occlusion in the 5mg/kg arm and a cerebrovascular event in the 10mg/kg arm). Cancer patients are known to be at high risk for thromboembolism owing to a number of factors

including intrinsic tumor pro-coagulant activity, immobilization, indwelling catheters and the pro-thrombotic effects of chemotherapy. The incidence of thrombosis among patients with breast cancer receiving chemotherapy is approximately 5-10% being higher in patients on tamoxifen and in patients with metastatic disease (22). In the first 59 patients with metastatic breast cancer treated with rhuMAb VEGF monotherapy, two patients have developed a subclavian/axillary deep venous thrombosis on the side of the indwelling central line.

c) Hypertension: Hypertension has been seen in all rhuMAb VEGF clinical trials to date. There has been one reported case of hypertensive encephalopathy in a patient receiving 3mg/kg of rhuMAb VEGF on Study AVF0776g. In addition, 12 other patients have developed either new hypertension (7 patients) or worsening existing hypertension (5 patients) for which 10 of these patients required medical therapy (3 patients in 3mg/kg rhuMAb arm [n=18] and 7 in the 10mg/kg [n=41], no data available from 20mg/kg arm).

   After 10 weeks of treatment, the mean change in blood pressure for all subjects compared with baseline was as follows (mean systolic change/mean diastolic change); 3mg/kg rhuMAb VEGF +10.5mmHg/+8.5mmHg and 10mg/kg rhuMAb VEGF +18.5mmHg/+8.2mmHg. In Study AVF0780g (colorectal cancer), using NCI-CTC Grade 3 or 4 events, there were four events in the control arm (n=35), four events between 2 patients in the 5mg/kg rhuMAb VEGF (n=35) and nine-events among 5 subjects in the 10mg/kg rhuMAb VEGF (n=32). The most commonly used therapies to treat this hypertension have been angiotensin converting enzyme inhibitors and calcium channel blockers.

   VEGF has been shown to induce nitric oxide-mediated vasodilatation and hypotension (23). In a recent study, VEGF has been shown to govern endothelial nitric oxide synthase expression via a KDR/flk-1 receptor and protein kinase C signaling pathway, which suggests a possible mechanism for rhuMAb VEGF (24).

d) Proteinuria: Proteinuria by dipstick analysis has been seen in all rhuMAb VEGF clinical trials and has ranged in severity from clinically silent trace proteinuria to nephrotic syndrome. In study AVF0776g, 8 of 59 subjects treated with 3mg/kg or 10mg/kg have developed some degree of proteinuria (detected by dipstick) during the study to date. Three of these patients have also developed hypertension. Two patients were discontinued from study because of proteinuria; one patient (10mg/kg arm) had >2.5g/24 hr which decreased to 0.7mg/24 hr within 4 weeks with a normal serum creatinine and a second patient in the 20mg/kg arm who developed >5g/24hr. Another patient (3mg/kg arm) developed hypertensive encephalopathy, which was followed by the development of nephrotic syndrome (5g/24hr). This patient died of progressive disease soon thereafter and renal biopsy was not performed.

   A recent study has shown that VEGF mediates glomerular repair, which suggested a possible mechanism for rhuMAb VEGF-associated proteinuria (24).

e) Congestive Heart Failure: Two patients with metastatic breast cancer in study AVF0776g who had been treated previously with doxorubicin developed congestive

heart failure while on rhuMAb VEGF, one patient after one year at 10 mg/kg and the second patient after two doses at 20 mg/kg.

f) Dyspnea: In study AVF2107g, an ongoing trial with bevacizumab with 5FU/leucovorin in metastatic colon cancer, one patient on this study developed dyspnea and pneumonitis requiring intubation eleven days after receiving her fifth infusion of bevacizumab with irinotecan and 5-FU. Two other patients on this study also developed grade IV respiratory failure felt to be related to end-of-life events and not directly related to the drug. In study AVF0757g, for stage IIIb and IV non-small cell lung cancer, 3 patients had grade IV dyspnea events, the etiology of which is unclear but at least partially attributable to their underlying disease. No other grade IV dyspnea events were reported in other trials.

2.6 RATIONALE FOR COMBINATORIAL THERAPY

We have shown that the combination of docetaxel and thalidomide is clinically promising in androgen independent prostate cancer (improvement in response rate and trend towards improvement in overall survival). However it is important to have a molecular rationale in adding bevacizumab to this combination. In microarray experiments using thalidomide and thalidomide analogs (the analogs are similar to the active metabolite of thalidomide) multiple angiogenesis factors are down regulated (KIF5A, TTK, etc), but not VEGF. VEGF expression was not altered in xenograft experiments using these analogs, however PDGF was significant reduced. The CALGB has published data to suggest that an elevation in VEGF is a poor prognosis factor in prostate cancer and the reduction of VEGF results in a survival advantage. We believe that by combining the anti-VEGF activity of bevacizumab with the anti-angiogenic activity of thalidomide (against multiple targets but not VEGF) we will have effectively suppressed all of the important angiogenic factors. This approach will begin to test the hypothesis that the blockade of multiple factors in angiogenic is the most effective anti-tumor strategy.

VEGF, VEGFB or VEGFC were not de-regulated by any of the analogs or thalidomide in either PC3 or 22Rv1 xenografts or HUVECs in vitro, though other genes related to angiogenesis were. Thalidomide down- regulated anti- apoptotic proteins such as the NFkB activator TNFSF11 as well as the endothelial cell- specific protein BIRC8, which protects cells from shear stress- induced apoptosis via caspase regulation. Other genes in this dataset have roles in cellular respiration (NDUFC1), detoxification of superoxides in blood vessels (SOD3) and peroxides (CAT), interleukin-2 signaling (IL2RG) and cellular vitamin A homeostasis (RBP1). These results strongly suggest that thalidomide in particular promotes endothelial cell death by reducing the levels of various transcripts that have housekeeping functions in the endothelial cell. Catalase (CAT), which is activated by IGF-1R-mediated anti-apoptotic signaling via caspase-3 inhibition in a PI-3 kinase- dependent manner, has an anti- apoptotic function. Interestingly, various proteins of significance in neurobiology were down- regulated specifically in thalidomide- treated HUVECs.

PC3 and 22Rv1 tumors differentially expressed VEGF, PDGF-AA and bFGF proteins (Fig. 1, A, B and C). Neither the analogues nor thalidomide significantly altered VEGF levels in PC3 or 22Rv1 tumors compared to the vehicle control (Fig. 1A). Interestingly,

PDGF-AA levels were significantly reduced by 82%, 67%, and 58% in PC3 tumors treated with CPS45, CPS49 (both thalidomide analogues) and thalidomide, respectively (Fig. 1B). All the analogues and thalidomide had no significant effects on 22Rv1 tumor PDGF-AA levels (Fig. 1B). PC3 and 22Rv1 tumor bFGF levels were unchanged by the analogues and thalidomide (Fig. 1C). Microvessel density was decreased by 64% in PC3 tumors treated with CPS49 (Fig. 2). In 22Rv1 tumors, CPS45 and CPS49 reduced microvessel density by 60% and 53%, respectively (Fig. 2). CPS11 and thalidomide did not affect microvessel density in PC3 and 22Rv1 tumors compared to the vehicle control (Fig. 2).

Figure 1: Concentrations of angiogenic factors in different cell lines vs. treatment with thalidomide and analogues

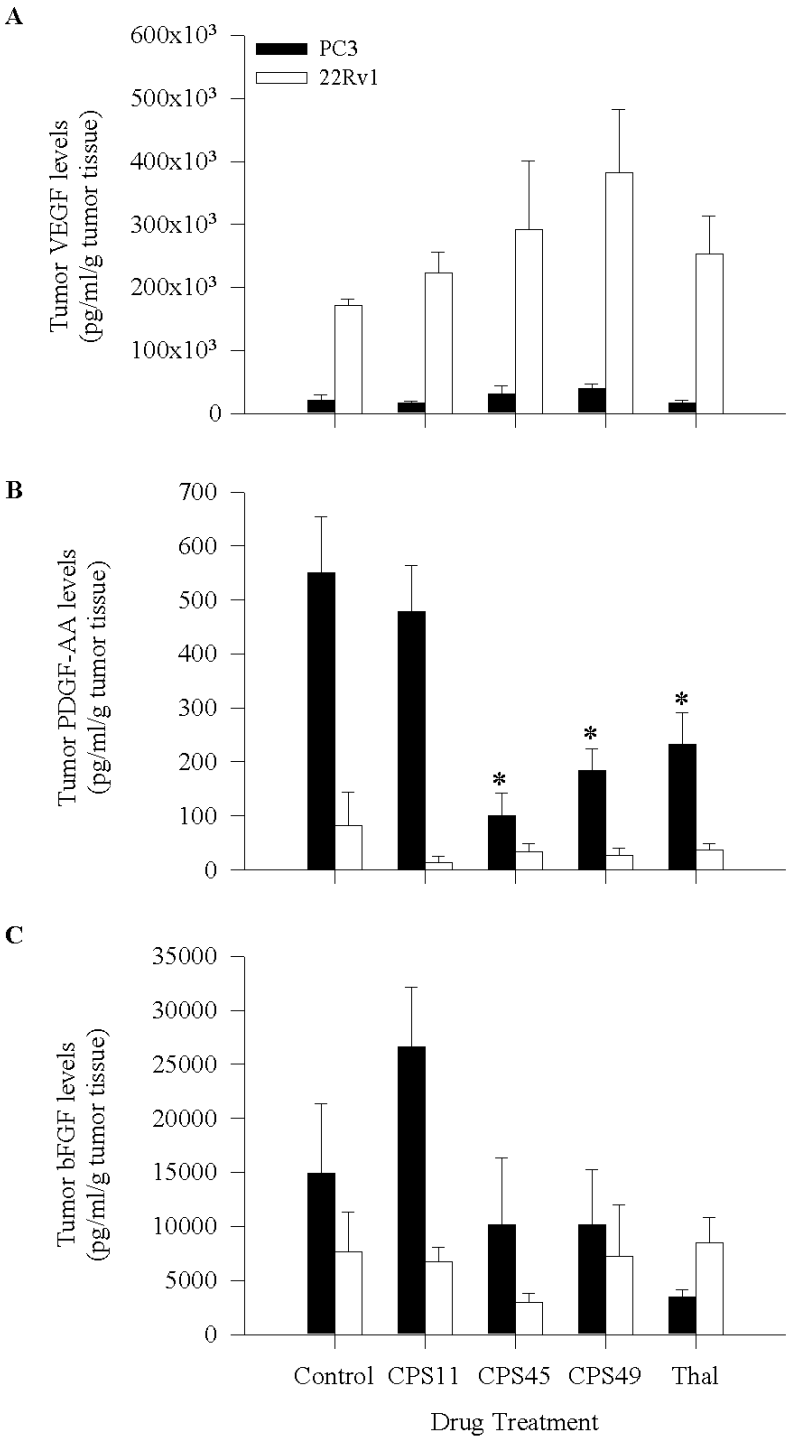
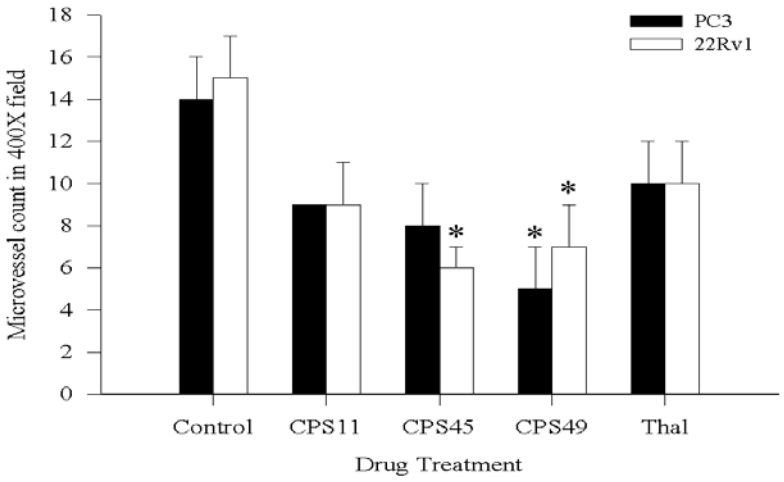


Figure 2: Microvessel count of various cell lines after treatment with thalidomide and analogues.



In our recent phase II trial we randomized 75 chemotherapy naïve AIPC patients to receive 30-mg/m2 weekly docetaxel for 3 consecutive weeks followed by a 1-week rest period; or docetaxel at the same dose and schedule plus thalidomide 200 mg orally each day. After a follow-up period of 26.4 months, the percentage of patients with a greater than 50% decline of PSA was higher in the combination group (51% vs. 37% in the single agent docetaxel group). The median survival in the docetaxel group was 14.7 months and 28.9 months in the combined group. Both regimens were well tolerated with only mild toxicities. Though this study was not powered to detect a survival difference, the addition of thalidomide nearly doubled the median survival in patients with metastatic AIPC (30).

Picus et al combined docetaxel and estramustine with the anti-VEGF antibody bevacizumab in a phase II study of 79 patients with AIPC (21). The rationale for this study was in part based on the evidence that patients with AIPC treated with suramin who had lower baseline VEGF levels showed an increase in overall survival compared to those with higher baseline VEGF levels (17 vs. 10 mos. p= .024). In the same study, patients who had at least a 15% reduction of VEGF levels form their baseline also had increased survival advantage (28).

In the study by Picus, patients received docetaxel (70 mg/m2 every 21 days), estramustine (280 mg on day 1-5) and bevacizumab (15 mg/kg) over a 21- day cycle. Preliminary analysis showed that 65% of patients had a PSA decline of $\geq$ 50% and that 53% of patients had a partial response in their measurable disease. While the regimen was fairly well tolerated, there was an increase in thrombotic events. Based on these promising results, a phase III trial is being planned, though estramustine will be substituted for by prednisone to improve on the toxicity profile. Thus both the docetaxel/thalidomide and the docetaxel/bevacizumab combinations have significant activity in prostate cancer, presumably through targeting different angiogenic factors.

2.7 CORRELATIVE STUDIES

Plasma concentrations of docetaxel will be determined to assess interactions between docetaxel and the concomitant therapy. Plasma concentrations of thalidomide will be determined to assess a possible interaction between thalidomide and the concomitant therapy. Single nucleotide polymorphisms (SNPs) in genes that play an important role in elimination pathways for docetaxel (in the CYP3A4 and CYP3A5 genes) and thalidomide (CYP2C19) will be evaluated.

rhuMAb VEGF has been shown to recognize all isoforms of VEGF-A and is specific for VEGF-A; it fails to recognize other peptide growth factors tested including fibroblast growth factor, epidermal growth factor and platelet-derived growth factor. Multiparametric flow cytometric analysis for identification of circulating epithelial tumor cells on the basis of forward and side scatter profiles coupled to expression of human epithelial antigen and absence of CD45 expression will be performed. These studies will be done for research purposes. We will collect both serum and urine samples at baseline and monthly to measure vascular endothelial growth factor (VEGF) levels.

Dynamic magnetic resonance imaging (MRI) with high temporal resolution permits noninvasive assessment of extravasation of extracellular paramagnetic contrast agents such as gadolinium (Gd)-chelates and thus permits an in vivo assessment of tumor vascularity and vascular permeability. Knopp et al used high temporal resolution imaging and quantification of the contrast enhancement using pharmacokinetic assessing the intensity of enhancement (amplitude), redistribution rate constant (k_{ep}) and the elimination rate constant (k_{el}) in a study comparing the vasculature of undetermined breast lesions including both benign and malignant breast tumors (33). Tissue vascular density was assessed using CD31 and expression of VEGF determined using immunohistochemistry. Using correlative analysis of histology, vascular density and expression of VEGF, the study showed significantly faster exchange rates in

malignant lesions compared to benign breast lesions, distinct differences between histologic subtypes and a significant dependence of enhancement kinetics on VEGF expression. Thus the pathophysiologic basis for the difference in contrast enhancement patterns of tumors detectable by MRI is mainly due to vascular permeability, which leads to more characteristic differences than vascular density. This same technique has been used to assess changes in tumor vasculature during primary chemotherapy for breast cancer. Response to therapy has been correlated with a deceleration of the rate of tumor contrast enhancement characteristics (33). Thus, MRI assessment of tumors may provide a suitable non-invasive way of monitoring the effects of anti-angiogenesis therapy.

Primary Functional Angiogenesis Parameter

K_{ep}, the redistribution constant of contrast between the plasma and the extracellular space is our fourth primary parameter. This pharmacokinetic parameter, K_{ep} (min-1) is directly affected by changes in the microvascular properties and is directly related to permeability. It has the highest reproducibility of the pharmacodynamic parameters and a variability of less than 10%. The other two parameters; intensity of enhancement (amplitude) and the elimination rate constant (k_{el}) will be measured in an exploratory fashion.

Microvessel density counting is a method of studying angiogenesis. Immunohistochemical staining of the tumor sample with monoclonal antibodies to the endothelial cell antigen CD31 are used. The histological sections are scanned areas of greatest vessel density “hot spots” and the individual microvessels in these areas as delineated by the stained endothelial cells are counted. The microvessel count is associated with the inherent problem that the regions of most active angiogenesis may be distributed irregularly throughout the tumor. The examination of multiple tumor sections and multiple areas within a section together with an automated counting system may help to diminish this problem. To assess microvascular density, we will obtain baseline tumor biopsies.

2.8 CONCLUSION

Though this would be the first trial to combine bevacizumab, thalidomide and docetaxel in prostate cancer, thalidomide and bevacizumab have been combined in multiple myeloma with acceptable toxicity (personal communication, unpublished data). We believe that the combination of bevacizumab, thalidomide and docetaxel has the potential to make a significant impact in the disease. We believe that if this trial is successful, a larger randomized trial through the cooperative groups with survival as an endpoint would be warranted.

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Androgen-independent metastatic adenocarcinoma of the prostate defined as progressive metastatic disease (see **3.1.3**) while on GnRH agonists or postsurgical castration

3.1.2 Histopathological documentation of prostate cancer confirmed in the NCI Laboratory of Pathology at the National Institutes of Health, the Pathology Department at Walter Reed Medical Center, or the Pathology Department at National Naval Medical Center, prior to starting this study. In addition, patients whose slides are lost or unavailable will be eligible for the study if they provide documentation of prostate cancer and if they meet criteria of clinically progressive prostate cancer as outlined in section **3.1.3**.

3.1.3 Clinically progressive prostate cancer documented prior to entry. Progression must be documented by at least one of the following parameters

3.1.3.1 Two consecutively rising PSA levels. The first rising PSA must be a minimum of one week from a reference value. It is recognized that PSA fluctuations are such that the confirmatory PSA value might be less than the previous one. In these cases, that patient would still be eligible provided the next PSA was greater than the first rising PSA value. Patients must have PSA > 5.0.

3.1.3.2 At least one new lesion on bone scans.

3.1.3.3 Progressive measurable disease.

3.1.4 Patients must have undergone bilateral surgical castration or must continue on GNRH agonist.

3.1.5 Those patients receiving an anti-androgen agent and are entering the trial due to a rise in PSA must demonstrate a continued rise in PSA 4 weeks after stopping flutamide and 6 weeks after stopping bicalutamide or nilutamide.

3.1.6 Patients may not have received any chemotherapy for metastatic prostate cancer

3.1.7 Age > 18 years

3.1.8 ECOG performance status < 2

3.1.9 Life expectancy of greater than 3 months

3.1.10 Patients must have adequate organ and marrow function as defined below:

Table 2: Adequate Organ and Marrow Function

Laboratory Test	Required value
Leukocytes	≥3,000/µl
Absolute neutrophil count	≥1,500/µl
Platelets	≥100,000/µl
Hemoglobin	≥ 8.0 g/L – transfusions acceptable
Total bilirubin	≤1.5 X institutional upper limits of normal, or ≤ 3 mg/dl in a subject with Gilbert Syndrome
AST (SGOT) and ALT (SGPT)	≤2.5 X institutional upper limit of normal
Creatinine OR Creatinine clearance	≤1.5 X institutional upper limits of normal ≥ 40 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.11 Recovered from any toxicity from surgery or radiotherapy

3.1.12 Must be willing to travel from their home to the NIH for follow-up visits

3.1.13 Able and willing to follow instructions and conform to protocol.

3.1.14 Patients may have had no other active malignancy within the past 2 years with the exception of non-melanoma skin cancer and superficial bladder carcinoma.

3.1.15 No history of myocardial infarction within the past 6 months, uncontrolled CHF or uncontrolled angina pectoris

3.1.16 Patients must agree to use adequate contraception (abstinence; hormonal or barrier method of birth control) for the study and at least 2 months after completion.

3.1.17 Ability to understand and the willingness to sign a written informed consent document.

3.2 EXCLUSION CRITERIA

3.2.1 Present clinical signs or symptoms of brain and/or leptomeningeal metastases confirmed by CT or MRI brain scan.

3.2.2 Uncontrolled, intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (AHA Class II or worse), unstable

angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.3 Persistent systolic blood pressure > 170 mmHg or diastolic blood pressure > 100 mmHg.

3.2.4 HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with docetaxel, bevacizumab, and/or the combination

3.2.5 Proteinuria, as demonstrated by a UPC ratio $\geq$ 1.0 at screening, required to be assessed if urine dipstick is $\geq$ 1+.

Urine protein should be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be <1000 mg for patient enrollment. Note: UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.2.6 Therapeutic anticoagulation with coumadin, heparins, or heparinoids.

3.2.7 Greater than Grade 2 peripheral neuropathy at baseline

3.2.8 History of transient ischemic attacks (TIA) or cerebrovascular accident (CVA) within the past 2 years.

3.2.9 History of allergic reaction to docetaxel, prednisone, thalidomide and/or bevacizumab or related products.

3.2.10 Patients who are on concurrent investigational agent(s)

3.2.11 Patients who are unable to ingest oral medication.

3.3 INCLUSION OF WOMEN AND MINORITIES

Men of all races and ethnic groups are eligible for this trial. Every effort will be made to recruit minorities in this study. Women are ineligible for this study.

3.4 ON-STUDY RESEARCH EVALUATION

3.4.1 Complete history and physical examination (including height, weight, and ECOG performance score) with documentation of 1) measurable disease, 2) narcotic use and pain assessment and 3) prior therapies (hormonal, surgical,

radiotherapeutic, and cytotoxic) will be conducted prior to starting therapy. A complete medication history will be obtained prior to starting, including over the counter medications, homeopathic remedies, vitamins, and alternative therapies.

3.4.2 Imaging Studies (baseline) – Within 4 weeks prior to enrollment

3.4.2.1 Technetium-99 Bone Scintigraphy

3.4.2.2 Chest X-ray, CT scan of chest, abdomen and pelvis

3.4.2.3 MRI* *A selected number of patients will undergo dynamic MRI as outlined in section **4.5.3.2**

3.4.3 Laboratory evaluation [baseline is to be obtained within 16 days prior to enrollment]

3.4.3.1 Hematological Profile: CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time

3.4.3.2 Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase

3.4.3.3 Urine analysis

3.4.4 Tumor Marker Profile

3.4.4.1 PSA (within 7 days prior to enrollment)

3.4.4.2 Acid phosphatase (if PSA <4ng/mL, for research purposes only)

3.4.5 Testosterone level (baseline only, should be obtained within 8 weeks prior to day 1); no required for patients with prior bilateral orchiectomy

3.5 PATIENT REGISTRATION

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

4 TREATMENT PLAN

4.1 STUDY DESIGN

This is an open label, phase II trial of up to 60 patients who will receive docetaxel 75mg/m^2 IV over 60 minutes on cycle 1 day 1, repeated every 21 days (i.e. a 3-week cycle), plus bevacizumab 15mg/kg cycle 1 day 1, repeated every 21 days, thalidomide 200 mg orally each day at bedtime plus prednisone 10 mg orally every day. All patients will receive 4 mg of oral dexamethasone, 12 hours before, 1 hour before and 12 hours after docetaxel treatment. If a patient misses a pretreatment dose of dexamethasone, he may receive dexamethasone 8 mg intravenously prior to docetaxel plus dexamethasone 4 mg orally 12 h after docetaxel administration. If a patient develops grade 3 or 4 neutropenia, pegfilgrastim will be given as described in section **4.3.1.1** to reduce risk of febrile neutropenia and facilitate full dose delivery of the chemotherapy.

After the completion of the initially planned enrollment of 60 patients, fifteen additional patients will be enrolled in an expansion cohort (Ex-Cohort) for studying the effects of docetaxel and bevacizumab on the immune system in patients with metastatic AIPC as a prelude to a possible clinical trial of the triplet of docetaxel, bevacizumab, and vaccine. These patients will receive docetaxel 75 mg/m^2 IV over 60 minutes on cycle 1 day 1, repeated every 21 days, plus bevacizumab 15 mg IV on day 1, repeated every 21 days, for a total 2 cycles. Use of dexamethasone and pegfilgrastim will be same as described above. After Cycle 2 and since cycle 3, patients will resume the original treatment regimen with the four drugs, administered as described above, plus the initiation of prophylactic enoxaparin at 1 mg/kg sq daily beginning on cycle 3, day 1. Treatment will continue until disease progression or unacceptable toxicities. If patients have disease progression or unacceptable toxicities after cycle 2, they will be taken off the study and they will not be replaced.

Patients will be evaluated by a physician and have their PSA checked every 3 weeks. PSA will be measured by the Hybritech Tandem-R (San Diego, CA) assay. This assay is used at the National Institutes of Health and the vast majority of laboratories nationally. If our patients have a PSA drawn at an outside laboratory, we will attempt to verify that this particular assay is used, if it is/was not, we will repeat the test at the NIH.

Radiographic studies (CT scans of the chest, abdomen, and pelvis, Technetium-99m bone scintigraphy) will be performed at baseline, after second cycle and then every 3 cycles. For the patients enrolled in Ex-Cohort, disease progression prior to the end of cycle 5 (after three cycles of treatment with the combination of docetaxel, bevacizumab, thalidomide, and prednisone) will not be used to remove patients from study. If patients have radiographic progression on restaging prior to Cycle 3, then these scans will serve as baseline scans for the rest of the study. If there is no significant toxicity or evidence of disease progression (as defined below) therapy will continue. For patients who simply have PSA elevations, treatment can continue till they have clinical or radiographic disease progression, unacceptable toxicities, or voluntary withdrawal from the protocol. In addition, patients who had not undergone bilateral orchiectomy will continue to receive medical castration with a LHRH agonist (leuprolide or goserelin acetate).

4.2 AGENT ADMINISTRATION

4.2.1 Docetaxel Administration

Docetaxel 75mg/m^2 will be administered intravenously over 60 minutes on cycle 1 day 1 and repeated every 21 days (i.e. a 3-week cycle). All patients will receive 4 mg of dexamethasone orally 12 hours and 1 hour prior to docetaxel, and then 12 hours after docetaxel. Patients who have excessive dexamethasone-induced toxicity (defined as Grade III toxicity in the CTCAE 3.0 felt to be caused by dexamethasone) may have their doses altered to a single 8 mg intravenously dose of dexamethasone prior to docetaxel administration.

4.2.2 Bevacizumab Administration

Bevacizumab 15 mg/kg diluted in 0.9% Sodium Chloride Injection, USP, to a total volume of 100 ml. Administration will be as an intravenous infusion over 30-90 minutes every 21 days (see below).

The initial bevacizumab dose will be delivered as an IV infusion over 90 $\pm$ 10 minutes. If the first infusion is tolerated without infusion-associated adverse events (fevers and/or chills), the second infusion maybe delivered over 60 $\pm$ 10 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions maybe delivered over 30 $\pm$ 10 minutes.

If a patient experiences an infusion-associated adverse event, subsequent infusions will be given over the shortest period that was well tolerated. The patient may be premedicated for the next bevacizumab infusion.

4.2.3 Thalidomide Administration

Patients will receive their first dose of thalidomide 200 mg orally on day 1 and will continue this dose daily throughout the cycle. For patients enrolled in Ex-cohort, thalidomide will not be started until Day 1 of cycle 3 and will continue this dose daily while patients remain in the trial.

4.2.4 Prednisone Administration

Patients will receive their first dose of prednisone 10 mg orally on day 1 and will continue this dose daily throughout the cycle. For patients enrolled in Ex-cohort, prednisone will not be started until Day 1 of cycle 3 and will continue this dose daily while patients remain in the trial.

4.2.5 Enoxaparin Administration

Patients will receive 1 mg/kg of enoxaparin sq daily beginning on day 1. For patients enrolled in Ex-cohort, enoxaparin will not be started until Day 1 of cycle 3 and will continue while patients remain in the trial.

4.3 TREATMENT MODIFICATIONS

4.3.1 Dose reduction will be according to the following rules

4.3.1.1 Dose modifications for docetaxel

Administration of docetaxel will be withheld on a treatment day for the occurrence of dose-limiting toxicity (DLT) defined as grade 3 or 4 hematologic toxicities or non-hematologic toxicity ≥ grade 3. Patients should have an ANC ≥1500 cells/mm^3, a platelet count ≥ 75,000 cells/mm^3 (grade 1 hematologic toxicity) and resolution of any non-hematologic toxicity to ≤ grade 1 or baseline in order to initiate another treatment cycle of docetaxel. It should be noted that no platelet transfusions would be allowed within 7 days prior to docetaxel administration.

For febrile neutropenia developed within a prior cycle and resolved before next cycle, docetaxel can be continued at a dosage decreased by 25% during future cycles and pegfilgrastim will be given to prevent future episodes. For patients who had either grade 3 or 4 neutropenia during a cycle, docetaxel treatment will continue at 100% dosages thereafter with the addition of pegfilgrastim; however, docetaxel dosage will be decreased by 25% if patients supported with pegfilgrastim continue to experience grade 4 neutropenia or febrile neutropenia.

For grade 3 constipation or fatigue, treatment can resume with a 25% dose reduction after resolution of toxicity to ≤ grade 2. The occurrence of DLT or a delay of > 2 weeks in initiating a new treatment cycle for the recovery of docetaxel-induced toxicities would result in a docetaxel dose reduction of 25%. In patients whose Grade III fatigue and/or constipation are felt to be caused by thalidomide; then docetaxel need not be held or reduced. Patients will be allowed to continue docetaxel treatment at successively reduced doses as long as they do not have progressive disease, regardless of the time required for recovery from ADEs. For dose-limiting toxicities related to docetaxel, it should be noted that thalidomide, bevacizumab and prednisone should not be interrupted.

4.3.1.2 Dose modifications for bevacizumab

Bevacizumab will be discontinued for the following toxicities: Development of proteinuria >2g /24 hr; Development of Grade 4 hypertension (hypertensive crisis); Development of Grade 4 symptomatic venous thrombosis, not including catheter related thrombi; Development of a non-healing wound; Development of ≥ Grade 3 hemorrhagic event.

Bevacizumab treatment modifications based on venous thrombosis:

Table 3: Bevacizumab and Venous Thrombosis

CTCAE Grade	Action to be Taken
Grade 3 or asymptomatic /minimally symptomatic Grade 4	• Hold Bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, Bevacizumab should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is > 2 weeks, Bevacizumab may be resumed if either: the thrombosis has resolved OR during full-dose anticoagulation **IF** all of the criteria below are met: o The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) o The subject must not have had hemorrhagic events while on study o The subject must be on stable doses of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting Bevacizumab o If thromboemboli worsen/recur upon resumption of study therapy, discontinue Bevacizumab
Grade 4 Symptomatic	Discontinue Bevacizumab

Table 4: Thalidomide and Venous Thrombosis

Thalidomide treatment modifications based on venous thrombosis:

CTCAE Grade	Action to be Taken
Grade 3 or asymptomatic /minimally symptomatic Grade 4	• Hold Thalidomide treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, Thalidomide should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is > 2 weeks, Thalidomide may be resumed during full-dose anticoagulation **IF** all of the criteria below are met:

CTCAE Grade	Action to be Taken
	○ The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) ○ The subject must not have had hemorrhagic events while on study ○ The subject must be on stable doses of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting Thalidomide ○ If thromboemboli worsen/recur upon resumption of study therapy, discontinue Thalidomide
Grade 4 Symptomatic	Discontinue Thalidomide

Bevacizumab treatment modifications based on proteinuria:

Table 5: Bevacizumab and Proteinuria

Urine Dipstick	Further evaluation	Bevacizumab dose modification
Negative	None	Continue bevacizumab
Trace	None	Continue bevacizumab
1+	None	Continue bevacizumab.
2+ or > 2+	24-hour urine	Hold bevacizumab, treatment based on 24-hour urine protein
Urine protein	Further evaluation	Bevacizumab
<2000mg	None	Resume or continue bevacizumab
> 2000mg	24-hr urine before subsequent doses	Hold bevacizumab until 24-hr urine protein < 2000 mg

In addition to the toxicities listed above, bevacizumab will be discontinued if there is persistent (≥3 weeks) NCI-CTG Grade 3 or 4 adverse events or any other significant adverse event that compromises the subjects' ability to participate in the study.

4.3.1.3 Dose modification for thalidomide

Doses may be reduced by 50 mg to 100 mg at a time, to alleviate side effects quickly, with slow escalation back to upper limit of tolerability. Patients with any grade III or IV nonhematological toxicity felt to be caused by thalidomide will have their thalidomide held. Thalidomide will be resumed with a dose reduction of 50 % when toxicity returns to the patients' baseline or is ≤ grade I. Patients who develop ≥ grade 2 peripheral neuropathy should have their thalidomide dose withheld until toxicity resolves to ≤ grade 1, at which point thalidomide may be restarted at a 50% dose reduction. Patients who develop recurrence of ≥ grade 2 peripheral neuropathy at a decreased dose or whose

toxicity fails to resolve to ≤ grade 1 will discontinue taking thalidomide. Thalidomide should be discontinued if a skin rash occurs and only resumed following appropriate clinical evaluation. If the rash is exfoliative, purpuric, bullous or if Stevens-Johnson Syndrome or toxic epidermal necrolysis is suspected, thalidomide should not be resumed. For dose-limiting toxicities related to thalidomide, it should be noted that docetaxel and bevacizumab should not be interrupted.

4.3.2 As this trial allows patients to receive treatment indefinitely, patients may have the doses of any or all drugs (docetaxel, bevacizumab, thalidomide and prednisone) temporarily withheld, and potentially resume treatment as long as they do not fulfill the off-study criteria outlined in section **4.9**.

Patients may also have those FDA-approved drugs administered at their local health care facilities other than the NIH with their own oncologists who agree to treat them under the investigational physician's guidance.

Although the treatment is planned every 21 days as a cycle, patients may have their treatments administrated about or after 21 days in order to accommodate their travel, hospitalization, variations in clinical availability due to holidays, or other unpredictable personal or family situations. Every effort will be made to minimize delay from their planned cycles and/or staging evaluations. Continuation of the treatment will be decided at the investigational physicians' discretion for the best benefits of patients with no deviations from the protocol.

4.3.3 Patients who develop deep vein thrombosis will continue on docetaxel and prednisone, receive appropriate medical care and have thalidomide and bevacizumab managed as described above." This reflects our experience from our docetaxel/thalidomide versus docetaxel alone trial in a similar patient population, where those patients in the docetaxel alone arm had no episodes of thrombosis.

4.4 PHARMACOKINETIC AND CORRELATIVE STUDIES

Research blood and urine collection described in this section are optional.

4.4.1 Pharmacokinetic Analysis

4.4.1.1 Pharmacokinetics of docetaxel

Plasma concentrations of docetaxel will be determined to assess interactions between docetaxel and the concomitant therapy. Venous blood samples will be collected in a 7-mL sodium heparin (green top) tube pre-dose on cycle 1 day 1, 5 minutes before the end of infusion, and 15, and 30 minutes, and 1, 2, 4, 8, and 24 hours after the end infusion. Sampling will also be repeated cycle 2, day 1. A heparin-lock should be placed in the opposite arm from the docetaxel infusion in order to facilitate sample collection. The samples will be analyzed by the Clinical Pharmacology Research Core, Clinical Center, Building 10, Room 5A01, Telephone: 240-760-6190. The analysis will be performed using a validated method based on liquid chromatography with mass-

spectrometric detection. Concentration-time profiles in each individual patient will be performed using non-compartmental in the software package WinNonlin.

4.4.1.2 Pharmacokinetics of thalidomide

Plasma concentrations of thalidomide will be determined to assess a possible interaction between thalidomide and the concomitant therapy. This analysis will be performed in the same samples obtained for the purpose of docetaxel pharmacokinetic analysis. The samples will be analysed by the Clinical Pharmacology Research Core, Clinical Center, Building 10, Room 5A01, Telephone: 240-760-6190. The analysis will be performed using a validated method based on liquid chromatography with ultraviolet detection. Concentration-time profiles in each individual patient will be performed using non-compartmental in the software package WinNonlin.

4.4.1.3 Pharmacokinetic collections in the expansion cohort

No pharmacokinetic sampling will be collected for patients enrolled onto the Ex-cohort.

4.4.2 Genotyping of Patients

Single nucleotide polymorphisms (SNPs) in genes that play an important role in elimination pathways for docetaxel (in the CYP3A4 and CYP3A5 genes) and thalidomide (CYP2C19) will be evaluated. For this purpose two buffy coat tubes (two 7 mL blue tiger top tubes) will be obtained, and wrapped in foil when the patient enters onto the study. DNA will be isolated only for the purpose of genotype analysis of enzymes with putative relevance for docetaxel or thalidomide disposition. The genotyping will be performed on a research basis in the Clinical Pharmacology Research Core (Bldg. 10 Room 5A01; William Figg, Pharm.D.).

4.4.3 Molecular Analysis

Patients will undergo venipuncture of approximately 25-30 cc of blood in green-top (heparinized) tubes prior to initial treatment and after cycle 2 and 5 of treatment. Selected patients will undergo bone marrow biopsy. We will collect these samples for molecular analysis and estimation of circulating endothelial cells. These samples will be sent to the laboratory of Jane Trepel located in Building 10 Room 12N218. The samples will undergo testing which will include multiparametric flow cytometric analysis for identification of circulating epithelial tumor cells on the basis of forward and side scatter profiles coupled to expression of human epithelial antigen and absence of CD45 expression. These studies will be done for research purposes.

4.4.4 Angiogenesis Markers

We will collect both serum and urine samples at baseline and monthly to measure vascular endothelial growth factor (VEGF) levels. These studies will be done by the Molecular Pharmacology Section of the Clinical Pharmacology Research Core, under the direction of Dr. Figg.

Serum and plasma research samples (2 green top, 2 blue tiger top, and 2 red top 7 mls each on ice), send to Dr. Figg, Bldg 10, Rm 5A01; tel 240-760-6190. Blood collected in the course of this research project may be banked and used in the future to investigate

new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document. If new risks are associated with the research (e.g. analysis of germ line genetic mutations), the principal investigator must amend the protocol and obtain informed consent from all research subjects.

Urine Profile

Research spot urine samples should be collected in a clean catch container (approx. 30 ml) prior to first treatment cycle and after second treatment cycle and sent to Dr. Figg, Bldg. 10, Rm 5A01; tel 240-760-6190 via messenger on ice and STAT. Twenty-four hour urine samples may be collected to assess urinary elimination of parent compound.

These tests will be done for research purposes.

4.4.5 Baseline and Follow-Up Biopsy of Accessible Tumors

A baseline biopsy of accessible tumor tissue will be obtained prior to starting treatment as well as after 2-3 cycles of treatment if it can be performed with minimal risk of complications from the procedure. The location of this tissue may be an abnormally enlarged lymph node, mass or an unresected, non-irradiated prostate or radiated prostate that has a significant abnormality on either physical exam or imaging studies. However, patients can still participate in the trial even if they refuse to have the biopsy. Punch, percutaneous core, fine needle or laparoscopic techniques will be used for tumor biopsy. Anticoagulation will be held as is clinically indicated for biopsy. The Molecular Pharmacology Section of Dr. William D. Figg will coordinate rapid acquisition and evaluation of patient samples. The samples will be processed by Dr. Mike Buck in the NCI Laboratory of Pathology according to a routine MOCRU protocol. Tissue acquisition form will be included if applicable.

4.4.6 Immune Cellular and Molecular Studies

4.4.6.1 Regulatory T-cell Assay

The PBMC of patients enrolled onto the Ex-cohort will be analyzed pre-treatment and post-cycle 2 for any changes in the function of regulatory T cells. Six green tops and 2 SST's (a total of ~56 mL blood for these collections) will be collected pre-chemotherapy and post-cycle 2 (pre the introduction of prednisone /thalidomide). These samples will be sent to the laboratory of Dr. Jeffrey Schlom, Ph.D, Head of Laboratory of Tumor Immunology and biology, for the analyses as described below.

Flow Cytometry Analysis

To determine the regulatory T-cell phenotype, three color flow cytometry analysis will be performed on PBMCs. Cells will be resuspended in staining buffer (phosphate-buffered saline containing 3% fetal bovine serum) and stained for 30 minutes at 4°C with the combination of following antibodies: PerCP-Cy5.5-conjugated anti-CD4 and phycoerythrin (PE)-conjugated anti-CD25; (all purchased from BD Pharmingen, San Diego, CA). After that, FoxP3 intra-cellular staining will be performed on the cells stained with anti-CD4 and anti-CD25. They will be fixed and permeabilyzed using a fix/perm kit (eBioscience, San Diego,

CA) according to the manufacturer's manual, and will be labeled with FITC-conjugated anti-Foxp3 antibody (PCH101 clone) or its isotype control antibody (eBioscience). Flow cytometry will be performed on a Becton Dickinson LSRII (BD Biosciences), 1 x 10^5 cells will be acquired and data will be analyzed using FlowJo software (BD Biosciences). To determine the percentage of Tregs, lymphocytes will be gated by plotting forward *vs.* side scatter followed by gating on CD4 positive population. Then, $CD25^{high}$ and Foxp3 positive population will be gated. $CD25^{high}$ population will be separated from $CD25^{low}$ on the basis of the level of CD25 expression in $CD4^-$ T cells, as previously described.

$CD4^+$ $CD25^{high}$ T-cell Enrichment

$CD4^+CD25^{high}$ T cells will be enriched using Miltenyi $CD4^+CD25^+$ regulatory T cell isolation kit (Miltenyi Biotec, Auburn, CA) with modifications to the manufacturer's instructions. In order to achieve a consistently high $CD4^+$ purity rate, the amount of CD4 antibodies, antibiotin MicroBeads, as previously described. After $CD4^+$ T cells will be negatively enriched, it will be performed a positive selection for $CD25^+$ cells. The $CD25^+$ fraction will be collected by eluting cells twice through a magnetic separation (LS) column to further enrich for $CD4^+CD25^{high}$ T cells.

Immunosuppression Assay

$CD4^+CD25^-$ T cells (5 x 10^4 cells/well) will be cultured alone or cocultured with $CD4^+CD25^{high}$ T cells (5 x 10^4 cells/well) on three different ratios with 1 µg/ml anti-CD3 antibody (OKT3; eBioscience) in the presence of irradiated (3500 Rad) T-depleted PBMCs (2.5 x 10^5 cells/well) in a 96-well flat-bottom plate at 37°C and 5% CO_2. All cells will be cultured in medium RPMI 1640 (Mediatech, Inc., Herndon, VA) supplemented with 10% heat-inactivated human AB serum (Gemini Bio-Products, Woodland, CA); 100 units/ml penicillin and 100µg/ml streptomycin (Mediatech, Inc.); 2 mM L-glutamine (Mediatech, Inc.). Proliferation will be assessed by [^{3}H]thymidine (1 µCi [0.037 MBq] per well) (Perkin-Elmer, Boston, MA) incorporation pulsed on day 4 and quantified 18 hours later using a liquid scintillation counter (Wallac, Gaithersburg, MD). All experiments will be performed in triplicate.

4.4.6.2 Phenotypic and Functional Analysis of Human Dendritic Cells Derived from Peripheral Blood Mononuclear Cells

Generation of Dendritic cells from Peripheral Blood Mononuclear Cells

PBMCs will be obtained from heparinized blood. PBMCs will be separated using lymphocyte separation medium gradient (Organon Teknika, Durham, NC). DCs will be prepared using a modification of the procedure described by Sallusto and Lanzavecchia. PBMCs (1.5 x 10^8) were resuspended in AIM-V medium containing 2 mmol/L glutamine, 50µg/mL streptomycin, and 10µg/mL gentamycin (Invitrogen Life Technologies) and allowed to adhere to a T-150 flask (Corning Costar Corp., Cambridge, MA). After 2 hours at 37°C, the nonadherent cells will be removed with a gentle rinse. The adherent cells were cultured for 6 to 7 days in AIM-V medium containing 100 ng/mL of recombinant human granulocyte macrophage colony-stimulating factor (rhGM-CSF) and

20 ng/mL of recombinant human interleukin 4 (rhIL-4). The culture medium will be replenished every 3 days

Immunophenotyping of Dendritic Cells

DC generated from PMBC will be analyzed for cell surface markers by flow cytometry using a Becton Dickinson LSR2 flow cytometer. Multiple-color flow cytometric analysis will be performed on DCs by using the following antibody combinations: anti-CD80-FITC, anti-CD83-PE, anti-MHC class II-APC, anti-CD58-Cy7, anti-MHC Class I-PerCP Antibodies will be purchased from BD Biosciences (San Jose, CA). Staining will be conducted simultaneously for 1 hour at 4°C, cells will then be washed thrice with cold Ca^{2+}- and Mg^{2+}-free PBS, resuspended in the same buffer, and immediately analyzed

Mixed Lymphocyte Responses (MLR)

The Dendritic cells (DC) generated from the patients will be analyzed for their ability to stimulate proliferation in an allo-MLR assay. Peripheral blood mononuclear cells (PMBC) will be isolated from two different normal healthy donors. The two different samples will be mixed in a 96-well flat-bottomed microtiter plate at a concentration of 1 x 10^5 cells/well with 1:1 ratio. DCs are added at a concentration of 5% and 10% of the total cell concentration. Control wells contained 10^5 of each sample alone and mixed cells with no DC added. Cells will be incubated for 5 days at 37° C in 5% CO_2. After incubation, 1 μCi of radiolabeled [^{3}H] thymidine will be added to each well, and the plate will be incubated for an additional 18 h. After the final incubation period, the cells will be harvested and counted for radioactivity.

Immunophenotyping of Myeloid Dendritic Cells and Plasmacytoid Dendritic cells

PMBC will be analyzed for cell surface markers by flow cytometry using a Becton Dickinson LSR2 flow cytometer. Multiple-color flow cytometric analysis will be performed on DCs by using the following antibody combinations: anti-CD11c, anti-CD14, anti-CD1a, anti-CD123, anti-BDCA2. Antibodies will be purchased from BD Biosciences (San Jose, CA). Staining will be conducted simultaneously for 1 hour at 4°C, cells will then be washed thrice with cold Ca^{2+}- and Mg^{2+}-free PBS, resuspended in the same buffer, and immediately analyzed

Phenotyping peripheral myeloid-derived suppressor cells

Phenotypically, Myeloid-derived suppressor cells are identified as $CD34^+CD33^+CD13^+CD15^-$ cells. PBMC will be analyzed flow cytometry. Antibodies used will be FITC-CD34, APC-CD33, PE-CD13 and PerCP-CD15. Data acquisition and analysis will be performed using LSR-2 flow cytometer (BD BioSciences) and BD FACSDiVa software (BD BioSciences).

4.4.7 Prediction of bone metastasis risk in mCRPC

A nomogram to predict which men with CRPC were at high risk for developing bone metastasis was developed using men from the Centers for Prostate Disease Research through Walter Reed National Military Medical Center who were on androgen deprivation therapy with castrate testosterone. In this population it was found that PSA

nadir on androgen deprivation therapy, PSA doubling time and a novel metric, Alkaline Phosphatase Velocity (APV) predicted bone metastasis-free survival. The patients used to develop the nomogram had not been treated with chemotherapy and had no evidence of bone metastases.

An evaluation of patient records of the subjects enrolled on this protocol through BTRIS, using the identical analysis, is planned. Subjects in this protocol differ from the original cohort used to develop the nomogram in that these patients had evidence of bone metastases upon enrollment. We plan to determine whether the APV metric is still valid in this different cohort of patients. If the APV metric proves to be valid in this independent analysis and a similar nomogram to the original can be created, we intend to validate the new nomogram on a different set of patients in order to determine whether alkaline phosphatase velocity is independent of PSADT and whether it predicts progression of bone metastasis and/or overall Survival and/or other evidence of progression of disease.

4.5 PROTOCOL EVALUATION

4.5.1 History and physical examination (including weight and ECOG performance status) each clinic visit, as well as height at the first visit. History and PE do not need to be included in the electronic database. However, weight will be included in the electronic database. Patients will be seen and examined on or about day 21, and then every 3 weeks by a physician in the NCI outpatient clinic (weight, and ECOG performance status if changed, should be included in the database). Patients will undergo imaging evaluation (CT and bone scan as discussed in section **4.5.3.1**) 2 months after start of study and every 3 months thereafter.

4.5.2 Laboratory Evaluation

4.5.2.1 Hematological profile (every cycle)

4.5.2.2 PSA (every cycle)

4.5.2.3 Acute care panel (every cycle) – to include hepatic panel and LDH

4.5.2.4 Mineral panel (calcium, phosphorus, albumin, magnesium) every cycle

4.5.2.5 Urinalysis (every cycle). A patient found to have 2+ or greater proteinuria on urinalysis must have a 24-hour urine collection

4.5.3 Radiographic evaluation

4.5.3.1 CT scan and bone scan will be performed after 2 cycles after start of trial and every 3 cycles thereafter during the first year. Patients remaining on-study after a year will have CT scans and bone scans performed when patient has signs of clinical progression at physician's discretion.

4.5.3.2 MRI

We will conduct an observational pilot study utilizing dynamic MRI to evaluate the tumor response in a cohort of patients on study. As this imaging technique has not been well studied in prostate cancer (particularly in the evaluation of bony disease), we are hopeful it will provide information about changes in tumor vascularity prior to a clinical response. We will acquire dynamic MRI scans on at least 10 study patients at baseline and at 3-month intervals. Target lesions in the bone or soft tissues will be identified from the patient's CT scan. Dynamic MRI will be performed after the intravenous administration of 0.1mmol/kg of Gadolinium chelate. If after the first ten patients dynamic MRI results do not appear to predict clinical response dynamic MRI will NOT be performed on the remaining patients in the study. If, however, dynamic MRI results correlate with clinical response in at least 5 of the first 10 patients evaluated, this examination will be extended to the remainder of the study population. Dynamic MRI will be reported in the following manner: Pharmacokinetic parameters A and k_{ep} will be generated from time signal curves. Additionally, initial slope, peak, and washout and area under the curve (AUC_{90}) will be evaluated. Data will be displayed by cluster analysis and by average value over the entire tumor Dynamic MRI will not necessarily be used as criteria for progression. If a patient chooses not to undergo MRI evaluation he may still proceed on protocol.

4.6 CONCURRENT THERAPIES

A medication history including complementary and alternative medications, herbal and nutritional products, and dietary supplements should be reviewed at the initial screening visit and at each clinic visit to assure that no agents have been introduced that may interact with experimental treatment.

All patients will be instructed to consult a member of the study team prior to commencing any other medications (including over the counter agents).

Patients who have not undergone surgical castration should be maintained on an LHRH agonist.

4.7 SURGICAL GUIDELINES

There are no surgical guidelines in this protocol.

4.8 RADIATION THERAPY GUIDELINES

There are no radiation therapy guidelines in this protocol.

4.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to documenting removal from protocol therapy, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

4.9.1 Criteria for removal from protocol therapy

- Completion of protocol therapy

- Disease progression as evidenced by radiographic progression, either in RECIST measurement or new lesions on CT or bone scans, or clinical progression
- Patient request
- Best medical judgment of the Principal Investigator or a physician in the list of Associate Investigators
- Inter-current illness that prevents further administration of treatment
- Unacceptable (intolerable) adverse event(s) defined as a grade 3 or 4 toxicity that is probably or likely related to protocol therapy that persists for ≥ 21 days.

4.9.2 Post Treatment Evaluation

Once the patient is no longer receiving treatment (as per section **4.9.1**), he may receive follow-up calls to monitor his well-being and progress. The phone calls will likely be annual though no specific guidelines shall be set.

4.9.3 Off Study Criteria

The patient will be considered off study upon either:

a) Patient's death
b) Patient's decision to no longer participate in post treatment follow-up

4.9.4 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov.

5 SUPPORTIVE CARE

Anti-emetic treatment and secondary prophylaxis may be given as needed, but should NOT include the agent aprepitant.

Agent-specific expected adverse events are listed in Section **9**. The supportive treatment plan for these adverse events is discussed in detail in Section **4**. Pegfilgrastim 6 mg will be administrated subcutaneously 24 hours post-docetaxel infusion for patients with indications as described in section **4.3.1.1**. Other supportive care will be provided in accordance with good medical care and consistent with standard care for the individual's type of cancer. Supportive care will continue until patient care can resume with primary medical doctors.

Transfusions of red blood cells (RBCs) will be allowed as clinically required.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION (PATIENTS RECORDS AND QUALITY ASSURANCE)

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Quality assurance complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (e.g.: laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

6.1.1 The patient met all eligibility criteria

6.1.2 Signed informed consent was obtained prior to treatment

6.1.3 Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes)

6.1.4 Toxicity was assessed according to protocol (laboratory report slips, etc)

6.1.5 Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate)

6.1.6 Drug Accountability

The unused thalidomide and prednisone (partial bottles, empty bottles, and full bottles) will be returned for drug accountability at each clinic visit. An oral study agent case report form will be used to document drug accountability for each patient on this study. Unused drug supplies that are not returned to the patient for the next dose cycle will be disposed of according to the Procedure of Disposal of Returned Oral Agents.

6.1.7 Patients will use a diary to document daily drug intake and adverse events

6.2 RESPONSE CRITERIA

6.2.1 Biochemical response – PSA measurements (PSA Consensus Criteria) (31)

6.2.1.1 PSA Decline > 50%

6.2.1.2 A decline of PSA of at least 50% (confirmed by a second value at least 4 weeks after the first) with no other evidence of disease progression

6.2.1.3 PSA Progression (all progression dates require to be confirmed by a second value after the first)

6.2.1.3.1 A 50% increase in PSA over nadir (confirmed by a second reading 4 weeks later) in patients whose PSA has fallen by at least 50%. PSA increase must be at least 5 ng/ml.

6.2.1.3.2 A 25% increase in PSA over nadir (confirmed by a second reading) in patients whose PSA has not fallen by at least 50%. PSA increase must be at least 5 ng/mL.

6.2.1.4 A 25% increase in PSA over baseline in patients whose PSA has not decreased. PSA increase must be at least 5 ng/mL.

6.2.2 Time to PSA Progression

6.2.2.1 The time between the first day of treatment to the day of PSA progression as described in 6.2.1.2.

6.2.3 Measuring of Soft Tissue Disease

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (32). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

6.2.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.2.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response

Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.2.3.2.1 Although a clear progression of a “non-target” lesion only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair.)

6.2.3.2.2 If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response

6.2.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation.

Table 6: Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

6.2.3.4 Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

6.2.3.5 In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesions be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

6.2.4 Confirmatory Measurement/Duration of Response

6.2.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met.

6.2.4.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met or CR or 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 time treatment started).

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

6.2.5 Measurable Disease

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).

6.2.6 Non-measurable Disease

All other lesions (or sites of disease) including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI) and cystic lesions are all non-measurable.

6.2.7 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and 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 repeated 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 characterize the objective tumor response.

6.2.8 Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.2.9 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended

6.2.10 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up

6.2.11 Methods of Measurement

Chest X-ray - Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI - CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. For this study helical Multi-detector CT will be performed with cuts of 5mm in slice thickness for chest, abdomen and pelvis lesions and 2-3mm thickness for head and neck lesions.

6.3 TOXICITY CRITERIA

The study will use the NCI Common Toxicity Criteria (CTCAE) 3.0 for grading toxicity and adverse events. A copy of the CTCAE can be downloaded from the CTEP homepage (http://ctep.cancer.gov). All treatment areas should have access to a copy of the CTCAE 3.0.

6.4 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to determine if the combination of docetaxel, bevacizumab, prednisone, and thalidomide is able to be associated with a sufficiently high proportion of patients with a PSA response and be worthy of further investigation in metastatic prostate cancer. The toxicity of this combination will also be evaluated, and if unacceptably high, will result in modification to the treatment regimen. As a secondary endpoint, survival duration will be evaluated.

Data from the recently conducted NCI trial of thalidomide and docetaxel in the same intended patient population indicated that approximately 50% of patients (25/49) were able to achieve a PSA decline of greater than 50% while undergoing treatment. An ongoing study has indicated that bevacizumab in combination with docetaxel and estramustine have resulted in a 53% PR and a 65% decrease of at least 50% in PSA. The CALGB is planning a large phase III trial based on this data. Prednisone will be substituted for estramustine due to toxicity concerns.

The trial will be conducted using a two-stage MinMax design (Simon Controlled Clinical Trials 1989 10:1-10) with the undesirably low response proportion of 65% (p0=0.65) and targeting an improvement to 80% with a PSA response (p1=0.80). With alpha=0.10 and beta=0.10, the trial will initially enroll 33 patients and evaluate until PSA decline can be definitively determined. Per section **6.2.1**, this may require several months in some patients.

If no more than 22 of 33 patients have an eventual PSA decline of >50%, then no further patients will be accrued. If 23 or more of 33 are able to have a PSA decline of >50%, then accrual to a total of 60 patients will take place as soon as this can be determined. It is quite possible that accrual may need to be halted for an extended period of time while this is being determined. If so, patients otherwise eligible for this

trial will be enrolled onto other available studies until this trial is able to resume enrollment.

Provided that enrollment to 60 is permitted, if 23 to 43 of 60 have a PSA decline of >50%, then this will not be considered sufficient for further investigation. However, if 44+/60 have this response, then this will warrant investigation in a subsequent trial. Under the null hypothesis (65% proportion with 50% PSA decline), the probability of early termination of this trial is 64%.

Toxicity is also an important parameter to evaluate in this trial. Based on previous data, it would be considered problematic, balancing the nature of the disease and the toxicity, if the true fraction of patients who received adequate anti-coagulation and developed grade III thrombosis or grade III hemorrhage could be greater than one-third. It is expected that 90-95% of patients or greater on this trial will be able to receive adequate anti-coagulation. Monitoring for this toxicity will be taking place during the initial 33 patient enrollment stage of the trial. It will be assumed that 30-33 patients will receive adequate anti-coagulation from among the first 33 on study. Should greater than 4 adequately anti-coagulated patients in the first protocol stage experience a grade III thrombosis or grade III hemorrhage, then the trial will be amended with appropriately reduced doses of agents, as soon as this occurs, in order to limit this from happening on the remaining patients. This bound of 4 patients was selected since the upper 95% confidence interval about 4/33 is 25.6%, and is 26.4% for 4/32, 27.1% for 4/31 and 28.0% for 4/30-any of which would be marginally tolerable with respect to this outcome. Higher fractions (5 or more patients with thrombosis anytime in the first stage of accrual) would not be.

It would also be desirable if the overall toxicity profile with this combination were equivalent to that of thalidomide plus docetaxel. Provided the data are available from the other trial, for each type of toxicity which has 5 or more patients with a maximal grade of 2 or higher on either trial, we will compare the distribution of maximal toxicity grades per patient noted between this study and the thalidomide plus docetaxel study, using a Cochran-Armitage trend test, and will report the results for these comparisons. Any such individual toxicity comparisons noted with $p<0.05$, without adjustment for multiple comparisons, will be identified as being statistically significant, and will be taken into consideration when determining the role of the three drug combination in future studies.

In addition, survival will be evaluated, using Kaplan-Meier curves, as a secondary endpoint of this trial. No formal comparison will be undertaken with other results, but informal comparisons to the survival probabilities on the trial of thalidomide and docetaxel or other studies may be undertaken.

It is expected that accrual to this trial can be completed in 20 months if the current accrual rate of 3 similar patients per month or more is maintained.

Statistical considerations for patients enrolled in the expansion cohort are as follow:

The primary endpoint of this 15 patient expansion is to determine if docetaxel and bevacizumab cause immunologic changes that would not be considered to be compatible with concomitant therapeutic vaccination. Four primary immunologic evaluations will be performed for assessment, and the results from these four will be used to decide if an individual patient has immunologic changes that are not compatible with concomitant vaccine in the following manner.

Regulatory T-cell (Treg) percentage

The percent of Treg's will be analyzed comparing baseline levels with levels after 6 weeks of therapy. Based on our previous study (Yokokawa et al, Clin Ca Res 2008) the Treg percent of 5.2 is at the 95th percentile. The following will be used to suggest that the docetaxel / bevacizumab combination may not be compatible with concomitant vaccine:

For patients with a baseline Treg <5.2% an absolute increase of ≥5% to a level >8%
For patients with a baseline Treg ≥5.2% an absolute increase of ≥5%

Treg Functional Assay

If a patient has an increase in Treg identified above but a decrease in Treg function following 6 weeks of docetaxel / bevacizumab, then that data will not be used to suggest that the docetaxel / bevacizumab combination may not be compatible with concomitant vaccine.

Lymphocyte Function

The potential for CD4 and CD8 stimulation will be analyzed comparing baseline levels with levels after 6 weeks of therapy. If there is a decrease in stimulation index of >3 with both CD4 and CD8 assays, this will be used to suggest that the docetaxel / bevacizumab combination may not be compatible with concomitant vaccine.

Mixed Lymphocyte Reaction (MLR)

The ability of dendritic cells to present antigen will be analyzed comparing baseline levels with levels after 6 weeks of therapy. If there is a decrease in stimulation index of >3, this will be used to suggest that the docetaxel / bevacizumab combination may not be compatible with concomitant vaccine. Due to the time consuming nature of making DC for this assay, it will be performed in selected individuals.

Myeloid Suppressor Cells

Phenotypic analysis by flow cytometry will be used to assess levels of myeloid suppressor cells. The results will be descriptive and not used to make a decision about the primary endpoint.

Individual Scoring of Compatibility

Each patient will be scored as to concomitant vaccine compatibility or not. If data are available for Treg and lymphocyte function only, both would have to suggest that the combination may not be compatible with concomitant vaccine to rule any patient as

having immunologic changes not compatible with concomitant vaccine. If data are available for Treg, lymphocyte function and MLR then all 3 would have to suggest that the combination may not be compatible with concomitant vaccine to rule any patient as having immunologic changes not compatible with concomitant vaccine.

Statistical Analysis

With results of immunologic assays from 15 patients, if 4 or more patients are considered to have immunologic changes not compatible with concomitant vaccine, and if the true probability of any individual having such a problem were 10%, there would be a 5.6% probability of having 4 or more patients with these immune problems. On the other hand, if the true probability of any individual having such a problem were 35%, there would be an 82.7% probability of having 4 or more patients with these problems. Thus, observance of 4 or more patients out of 15 who are considered to have immunologic changes not compatible with concomitant vaccine would indicate an excessively high true probability, consistent with 35%, of having these problems, as opposed to having a rate consistent with 10% (which would be tolerable). If 3 or fewer patients are considered to have immunologic changes not compatible with concomitant vaccine, this is more consistent with a 10% rate than a 35% rate, and thus would be tolerable.

6.5 MULTI-INSTITUTIONAL GUIDELINES

This is not relevant to this protocol as it is being conducted at a single institution.

7 HUMAN SUBJECTS PROTECTIONS

7.1 RATIONALE FOR SUBJECT SELECTION

Subjects treated on this study, will be individuals with metastatic prostate cancer, which has recurred (or persisted) after appropriate standard treatment. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

7.2 PARTICIPATION OF CHILDREN

Children will not be eligible for this protocol.

7.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor and improvement in their bony lesions, which may or may not have favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects, which are listed in the Consent Document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described in Section **4.5**.

If there is no existing DPA, all patients ≥ 18 years old will be offered the opportunity to assign a substitute decision maker on the "NIH Advance Directive for Health Care and

Medical Research Participation" form, so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

7.4 RISKS/BENEFITS ANALYSIS

For patients with androgen independent prostate cancer, median survival is in the range of 12-18 months. The agents administered in this trial have shown activity against prostate cancer in vitro and in vivo. Potential risks include the possible occurrence of any of a range of side effects listed in the consent document.

7.5 CONSENT PROCESS AND DOCUMENTATION

Patients will meet with an attending physician in the Prostate Cancer Clinic, during the initial evaluation for this study. During that meeting, the attending physician will provide verbal informed consent regarding this study, as well as provide a copy of the informed consent document that is included in this protocol. The patient will be allowed to take as much time as he wishes, in deciding whether or not he wishes to participate. If a prolonged period of time expires during the decision making process (several weeks, as an example), it may be necessary to reassess the patient for protocol eligibility.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

Reconsent for this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the changes in the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.
The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.
The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

8.1 DEFINITIONS

8.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new

illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per section **8.2**.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

8.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

8.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition, including rising PSA that has progressed as defined in Section **6.2.1.2**, or potentially serious harm to research subjects or others.

8.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

8.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

8.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

8.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

8.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**

- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 NCI-IRB AND NCI CLINICAL DIRECTOR REPORTING

8.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

8.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

8.3 DATA AND SAFETY MONITORING PLAN

8.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

9 PHARMACEUTICAL INFORMATION

9.1 DOCETAXEL (DOCETAXEL®-AVENTIS PHARMACEUTICAL, INC.; BRIDGEWATER, NJ)

9.1.1 Chemical formula:

[2aR-[2aa,4b,4ab,6b,9a(aR*,bS*),11a,12a,12aa,12ba]]-12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca [3,4]benz[1,2-b]-oxet-9-yl b-[[(1,1-dimethylethoxy)carbonyl]-amino]-a-hydroxybenzenepropanoate, trihydrate.

$C_{43}H_{53}NO_{14} \cdot 3H_2O$

Molecular weight of 861.9 Daltons

Synonyms: RP56976.

9.1.2 Availability: The drug will be purchased from commercial sources by the Clinical Center pharmacy.

9.1.3 Formulation:

Docetaxel is supplied in single-dose vials as a sterile, non-pyrogenic, non-aqueous, clear yellow to brownish-yellow viscous solution and is packaged with a sterile, non-pyrogenic, diluent in single-use vials. Both the Docetaxel® for Injection Concentrate and the diluent vials contain excess volume to compensate for fluid lost during product preparation.

The commercial drug product is available in packages containing either:

[1] Docetaxel (anhydrous) 80 mg in 2 mL polysorbate 80 (2080 mg). The diluent vial contains 6 mL 13% (w/w) in Water for Injection.
OVERFILL: Docetaxel® for Injection Concentrate vial overfilled to 94.4 mg docetaxel/2.36 mL
Diluent vial overfilled to 6.96–7.70 mL. Approximate extractable volume = 7.1 mL.

[2] Docetaxel (anhydrous) 20 mg in 0.5 mL polysorbate 80 (520 mg). The diluent vial contains 1.5 mL 13% (w/w) in Water for Injection.
OVERFILL: Docetaxel® for Injection Concentrate vial is overfilled to 23.6 mg docetaxel/0.59 mL
Diluent vial overfilled to 1.88–2.08 mL. Approximate extractable volume = 1.8 mL.

9.1.4 Preparation

Docetaxel® for Injection Concentrate requires TWO dilutions prior to administration.

- Preparing the "INITIAL DILUTED SOLUTION" (10 mg docetaxel/mL)[1]

  [1] Before proceeding, inspect the vial containing Docetaxel® for Injection Concentrate solution for clarity.
  [2] After removing vials from refrigeration, allow them to stand at room temperature for approximately five minutes.
  [3] Partially invert a vial containing diluent, aseptically withdraw the ENTIRE CONTENTS (including overfill) of the vial into a syringe, and transfer the solution to a vial containing docetaxel.
  [4] The INITIAL DILUTED SOLUTION should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process. The INITIAL DILUTED SOLUTION may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

- Preparing "DOCETAXEL INFUSION SOLUTION"[1]
  [1] With a syringe, aseptically withdraw the required amount of docetaxel INITIAL DILUTED SOLUTION (10 mg/mL) and inject it into a non-polyvinylchloride bag containing an appropriate amount of 5% Dextrose, or 0.9% Sodium Chloride Injection, USP, to produce a final concentration between 0.3–0.74 mg docetaxel/mL. Do not exceed a concentration > 0.74 mg docetaxel/mL.
  [2] Thoroughly mix the INFUSION SOLUTION by repeatedly inverting the drug container.
  [3] Visually inspect the INFUSION SOLUTION for particulate matter or discoloration. If the solution is not clear or appears to have precipitation, it should be discarded.

Docetaxel must not come into contact with polyvinylchloride (PVC) equipment or devices during solution preparation or administration. Docetaxel should be prepared in polypropylene- or polyolefin-lined drug product containers and administered using polyethylene-lined administration sets[1]; e.g., ALARIS™ LOW SORBING SET #2264-0500 (non-PVC, polyethylene-lined fluid pathway, with integral 0.2 µm polysulfone filter [Alaris Medical Systems; San Diego, CA]).

9.1.5 Stability

DOCETAXEL INFUSION SOLUTION (in either 0.9% NS or D5%W), if stored between 2°–25°C (36°–77°F) is stable for four hours and should be used within four hours after preparation.[1]

9.1.6 Storage

Store between 2°–25°C (36°–77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.[1]

9.1.7 Dosage and Administration

9.1.7.1 Premedication

All patients will receive dexamethasone 4 mg 12 and 1 h prior to docetaxel administration and 12 hours post-docetaxel to reduce the incidence and severity of fluid retention and the severity of hypersensitivity reactions.

9.1.7.2 Administration

Docetaxel 75 mg/m2 will be administered as an intravenous infusion over one hour on scheduled days per section **4.2.1**.

9.1.8 Drug Interaction

Docetaxel and dexamethasone are metabolized by the cytochrome P450 (CYP) enzyme, CYP3A4. Many other drugs and herbal and nutritional supplements are similarly metabolized, and may in addition, perturb docetaxel and dexamethasone metabolism by inhibiting or inducing the enzyme. Whenever possible we will take efforts to limit patients from being on such medications while receiving treatment on protocol Enzyme induction may hasten docetaxel and dexamethasone clearance; CYP3A4 inhibition may delay clearance. Both enzyme induction and inhibition alter the pharmacokinetic behavior of drugs that are substrates for CYP enzymes, and consequently, their pharmacodynamic effects, potentially compromising the benefit of treatment and exacerbating toxicity.

Docetaxel and dexamethasone likewise may alter the pharmacokinetics and pharmacodynamic effects of other drugs metabolized by CYP3A4. Caregivers may circumspectly permit continuation of treatment with CYP3A4 substrate drugs for patients on this study after gaining the approval of a medically responsible investigator.

Contact a medically-responsible study investigator about patient volunteers who are receiving treatment before study enrollment and to discuss using any of the drugs listed in Appendix A for patients on study.

9.1.9 Toxicities

COMMON
- Leukopenia
- Neutropenia
- Anemia
- Alopecia
- Asthenia
- Neurosensory deficits

- Fluid retention
- Nausea
- Vomiting

SERIOUS
- Myelosuppression
- Thrombocytopenia
- Neutropenia
- Hypersensitivity reaction
- Skin toxicity

Please see package insert for additional toxicities.

9.2 THALIDOMIDE (THALOMID – CELGENE CORPORATION, WARREN, NJ)

The drug will be purchased from commercial sources by the Clinical Center pharmacy. The S.T.E.P.S program will be adhered to in dispensing this agent.

Briefly, the S.T.E.P.S program requires that the patient be adequately counseled regarding the potential risks of thalidomide prior to the start of drug administration (either via consent form or in-person counseling. It also requires that the physician, patient and pharmacy register with a central agency and that all three contact this agency each month prior to when drug is dispensed to monitor effects of the agent.

9.2.1 Treatment Regimen

Thalidomide will be given orally to patients at a dose of 200 mg every evening throughout the cycle.

9.2.2 Other names: Thalomid

9.2.3 Molecular Formula C_{13} O_4 N_2 H_9

9.2.4 Molecular weight: 243 Daltons

9.2.5 Formulation: Supplied as 50 mg or 200 mg hard gelatin capsules

9.2.6 Storage: Store at room temperature.

9.2.7 Stability: Shelf life surveillance studies are ongoing.

9.2.8 Route of Administration: Oral

9.2.9 Toxicities

COMMON

Sedation
Headache
Constipation

Diarrhea
Nausea
Mucosal dryness,
Photosensitivity
Rash
Weight gain
Mood changes (including depression-like symptoms)

SERIOUS

Birth defects
Neuropathy
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Seizures
Hypertension
Neutropenia
Renal toxicity (particularly in patients receiving bisphosphonate therapy)
Hypocalcemia (particularly in patients receiving bisphosphonate therapy)

Please refer to package insert for additional toxicities.

9.3 PREDNISONE

9.3.1 Chemical formula: 17a, 32-Dihydroxy-1,4-pregnadiene- 3,11,20-trione
Chemical Formula: $C_{21}H_{26}O_5$ Molecular weight of 358.4

9.3.2 Classification: Glucocoticorticoids

9.3.3 Mechanism of Action: Multiple mechanisms leading to anti-inflammatory and immune suppression outcomes

9.3.4 How supplied: Prednisone is supplied as a tablet or suspension. We will use commercially available 5 mg tablets for this study.

9.3.5 Storage: Prednisone should be stored in original containers at room temperature, out of direct sunlight.

Stability: Prednisone tablets are stable for three years from date of manufacture

9.3.6 Route of administration: Oral

9.3.7 Toxicities: Anemia, eosinopenia, leukocytosis, lymphopenia, thrombocytopenia, leukocytosis, hypertensive crisis, hypertension, psychosis, schizophrenic psychosis, extrapyramidal effects, pseudotumor cerebri, hyperglycemia, hyperuricemia, hypercalcemia, adrenal suppression, Cushing's syndrome, porphyria, lipid abnormalities, hypokalemia, peptic ulcers, pancreatitis, abdominal

pain, nephrotoxicity, proteinuria, cataracts, papilledema, acne, osteonecrosis, osteoporosis, myopathy, and superinfections.

9.3.8 Availability: Prednisone will be obtained from commercial stock purchased by the NIH CC Pharmacy Department.

9.4 BEVACIZUMAB (AVASTIN – GENENTECH BIOONCOLOGY, SOUTH SAN FRANCISCO, CA)

9.4.1 Chemical name and identification:

Recombinant humanized monoclonal anti-VEGF antibody

(rhuMAB VEGF)

9.4.2 Classification: Recombinant humanized monoclonal antibody

9.4.3 Mechanism of Action: Inhibition of vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis.

Approximate Solubility: 0.19 mg/100 mL in 0.1 N HCl, 453 mg/100 mL in Ethanol, and 2971 mg/100 mL in PEG 400.

9.4.4 How Supplied: Bevacizumab will be provided by Genentech, BioOncology under the Umbrella CRADA 2407. (Copy of CRADA attached)

9.4.4.1 **Information and Supply.** NCI will provide updated quarterly forecasts of amounts of Bevacizumab anticipated to be required for ongoing and pending mutually agreeable studies, as well as quarterly study accrual updates to enable Genentech BioOncology to adequately plan for timely delivery of Bevacizumab

9.4.4.2 **Registration of Clinical Trials**. NCI represents that all applicable clinical research conducted under this CRADA will be registered, and the results of such clinical research will also be posted on the www.ClinicalTrials.gov web site in accordance with the requirements set forth in 42 U.S.C. § 282(j).

9.4.4.3 **Access, review and receipt of Identifiable Private Information.** Genentech BioOncology's access to and review of Identifiable Private Information shall be only for on-site quality auditing. Genentech BioOncology will receive Identifiable Private Information only if necessary for purposes of satisfying its or its Affiliates FDA or other health authorities' reporting requirements, and for Genentech BioOncology and Affiliates' internal research purposes directly related to regulatory filings related to Bevacizumab. Genentech BioOncology and Affiliate(s) are prohibited from access, review, receipt, or use of such information for other purposes. All IRB approved Protocols and informed consent documents related to this CRADA will clearly describe this practice. NCI will ensure that the Protocol and the informed consent clearly state (i) the existence of the Genentech BioOncology; (ii) the Genentech

BioOncology's and its Affiliate(s)' access to Identifiable Private Information; and (iii) the extent to which confidentiality will be maintained. For clinical Protocol(s) involving a Third Party, the other party's access, review, receipt, or use of Identifiable Private Information shall be subject to the same limitations as described in this section **9.4.4.3**.

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion. The commercial product is supplied in preservative-free, single-use vials containing 100 mg/4 mL and 400 mg/16 mL of bevacizumab at a uniform concentration of 25 mg/mL.

The commercial products also contain the following excipients:

Table 7: Bevacizumab Excipients

Excipients Content	Avastin® Formulations	
	100-mg	400-mg
α,α-trehalose dihydrate	240 mg	960 mg
sodium phosphate (monobasic, monohydrate)	23.2 mg	92.8 mg
sodium phosphate (dibasic, anhydrous)	4.8 mg	19.2 mg
polysorbate 20	1.6 mg	6.4 mg
Water for Injection, USP		

Preparation: Bevacizumab must be stored under refrigeration at 2°–8°C (36°–46°F) and protected from light. Store in the original overwrap carton until the product is used. Do not freeze the product. Do not shake bevacizumab during handling or preparation for clinical use.

An amount of bevacizumab needed to prepare a dose of 15 mg/kg (patient's body weight) should be withdrawn from one or more vials and diluted in a total volume of 0.9% Sodium Chloride Injection, USP, (qs.) 100 mL.

9.4.5 Storage: Bevacizumab must be stored under refrigeration at 2°–8°C (36°–46°F) and protected from light. Store in the original overwrap carton until the product is used. Do not freeze the product. Do not shake bevacizumab during handling or preparation for clinical use.

9.4.6 Stability: Intact vials bear the manufacturer's expiration dating and are stable until that date if stored at 2°–8°C. Partially used vials should be discarded because the product does not contain an antimicrobial preservative.

Bevacizumab should be diluted ONLY with 0.9% Sodium Chloride Injection, USP (0.9%NS). Diluted bevacizumab solutions are stable in both polyvinylchloride (PVC) and polyolefin containers.

No significant changes were observed in protein concentration, pH, turbidity, or potency after bevacizumab dilution with 0.9%NS to concentrations of 0.9, 2.25, 3, 6.6, 7.5, and 16.5 mg/mL and storage for 24 hours in commercial PVC and polyolefin containers at 30°C. No changes were observed with respect to protein concentration, turbidity, or potency for the undiluted drug product

(25 mg/mL) and after bevacizumab dilution with 0.9%NS to 1 mg/mL and 12.5 mg/mL and storage for 24 hours in non-PVC, polyolefin bags at 5°C (41°F) and 30°C (86°F). [DRKohler personal communication with Genentech Medical Communications; 04/13/04]

9.4.7 Route of Administration: Intravenous

9.4.8 Reported Adverse Events and Potential Risks:

Serious Adverse Events

Hypertension

Thrombosis/embolism

Fever (in the absence of neutropenia, where neutropenia is defined as absolute granulocyte count <1.0x10e9/L)

Rigors, chills

Rash/desquamation

Stomatitis/pharyngitis (oral/pharyngeal mucositis)

CNS hemorrhage/bleeding

Epistaxis

Hematemesis

Hemoptysis

Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia

Infection without neutropenia

Headache

Proteinuria

Dyspnea

Delayed wound healing – although wound healing was delayed in animal studies, this effect has not been seen in humans

Rare

Reversible and marked elevations of liver function tests (total bilirubin and/or transaminase and alkaline phosphatase) 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 likely related to co-existing factors such as tumor involvement, chemotherapy, recent invasive procedures or bowel inflammation, contribution of bevacizumab to these events cannot be excluded at this time. 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.

9.4.9 Method of Administration: bevacizumab will be administered intravenously through a secondary IV set piggybacked above the infusion control device (pump) into a primary IV set containing 0.9% NS. When the bevacizumab drug product container is empty, 0.9% NS from the primary line should be used to flush the secondary set to complete bevacizumab delivery. 0.9% NS infusion should be continued to flush the primary IV set with a volume of fluid at least equal to the tubing priming volume, thus insuring complete drug delivery. Note that this flush is not included in the infusion times below.

The initial 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 was well tolerated.

9.5 OTHER AGENTS

9.5.1 **Pegfilgrastim** (Neulasta™, Amgen Inc., Thousand Oaks, CA)

9.5.1.1 Chemical Name and Identification:

A covalent conjugate of recombinant methionyl human granulocyte colony stimulating factor (Filgrastim) and monomethoxypolyethylene glycol

Average molecular weight: ~ 39 kilo-Daltons

9.5.1.2 Classification:

Colony stimulating factors acting on hematopoietic cells

9.5.1.3 Mechanism of Action:

Binding to a specific cell surface receptor thereby stimulating myeloid proliferation, differentiation, commitment, and end cell functional activation

9.5.1.4 How Supplied:

In 0.6 mL prefilled syringes for subcutaneous (SC) injection containing 6 mg pegfilgrastim in a sterile, clear, colorless, preservative-free solution (pH 4.0). The manufacturer's product (Neulasta®; Amgen) is intended

for a single use and comes with a fixed 27 Gauge 1/2-inch needle and an UltraSafe® Needle Guard

9.5.1.5 Storage:

Stored refrigerated at 2° to 8°C (36° to 46°F) and kept in carton to protect from light until time of use. Shaking should be avoided.

9.5.1.6 Stability:

Intact syringes bear the manufacturer's expiration dating and are stable until that date if stored at 2°–8°C. The syringes may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. If left at room temperature for more than 48 hours or discoloration or particulates are observed in the product, it should be discarded.

9.5.1.7 Route of Administration:

Subcutaneous (SC) injection of 6 mg/0.6 mL administered once per chemotherapy cycle approximately 24 hours after docetaxel administration.

9.5.1.8 Reported Adverse Events and Potential Risks

COMMON

Bone pain

Reversible elevations in LDH, alkaline phosphatase, and uric acid

SERIOUS, but very rare: (with filgrastim, the parent compound of pegfilgrastim)

Adult respiratory distress syndrome (ARDS)

Allergic-type reactions (anaphylaxis, skin rash, and urticaria)

Splenic rupture

9.5.2 For any agents not specifically mentioned above, please refer to the commercial product's package insert for information on all commercial pharmaceutical agents used in this trial.

10 COLLABORATIVE AGREEMENTS

10.1 AGREEMENT TYPE

Avastin is supplied to NCI under a CRADA with Genentech.

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12 APPENDIX **A**: AGENTS METABOLISED THROUGH **C**YP450 **SUBSTRATES**

Acetaminophen	Dapsone	Levobupivicaine	Risperidone
Alfentanil	Dehydroepiandrosterone	Lidocaine	Ritonavir**
Alosetron	Delavirdine	Loratadine	Salmeterol
Alprazolam**	Desmethyldiazepam	Losartan	Saquinavir
Amiodarone	Dexamethasone	Lovastatin	Sertindole
Amitriptyline (minor)	Dextromethorphan (minor)	Methadone	Sertraline
Amlodipine	Diazepam (minor)	Mibefradil	Sibutramine
Anastrozole	Digitoxin	Miconazole	Sildenafil citrate
Androsterone	Diltiazem	Midazolam	Simvastatin
Antipyrine	Disopyramide	Mifepristone	Sirolimus
Astemizole**	Docetaxel	Mirtazapine	Sufentanil
Atorvastatin	Dofetilide (minor)	Montelukast	Tacrolimus
Benzphetamine	Dolasteron	Navelbine	Tamoxifen
Bepridil	Donepezil	Nefazodone	Temazepam
Bexarotene	Doxorubicin	Nelfinavir	Teniposide
Bromazepam	Doxycycline	Nevirapine	Terfenadine**
Bromocriptine	Dronabinol	Nicardipine	Testosterone
Budesonide	Enalapril	Nifedipine	Tetrahydrocannabinol
Bupropion (weak)	Erythromycin	Niludipine	Theophylline
Buspirone	Estradiol	Nimodipine	Tiagabine
Busulfan	Ethenyl estradiol	Nisoldipine	Tolterodine
Caffeine	Ethosuximide	Nitrendipine	Toremifene
Cannabinoids	Etoposide	Omeprazole (sulfonation)	Trazodone
Carbamazepine	Exemestane	Ondasetron	Tertinoin
Cerivastatin	Felodipine	Oral contraceptives	Triazolam**
Cevimeline	Fentanyl	Orphenadrine	Troglitazone
Chlorpromazine	Fexofenadine	Paclitaxel	Troleandomycin
Cimetidine	Finasteride	Pantoprazole	Venlafaxine
Cisapride**	Fluoxetine	Pimozide**	Verapamil
Citalopram	Flutamide	Pioglitazone	Vinblastine
Clarithromycin	Glyburide	Pravastatin	Vincristine
Clindamycin	Granisetron	Prednisone	Warfarin
Clomipramine	Halofantrine	Progesterone	Yohimbine
Clonazepam	Hydrocortisone	Proguanil	Zaleplon (minor)
Clozapine	Hydroxyarginine	Propafenone	Zatoestron
Cocaine	Ifosfamide	Quercetin	Zileuton
Codeine	Imipramine	Quetiapine	Ziprasidone
Cortisol	Indinavir	Quinidine	Zolpidem**
Cortisone	Isradipine	Quinine	Zonisamide

Cyclobenzaprine	Itraconazole	Repaglinide	
Cyclophosphamide	Ketoconazole	Retinoic acid	
Cyclosporine	Lansoprazole (minor)	Rifampin	

Inducers

Carbamazepine	Nelfinavir	Primidone	Sulfadimidine
Dexamethasone	Nevirapine	Progesterone	Sulfinpyrazone
Ethosuximide	Oxcarbazepine	Rifabutin	Troglitazone
Glucocorticoids	Phenobarbital	Rifampin	
Griseofulvin	Phenylbutazone	Rofecoxib (minor)	
Nafcillin	Phenytoin	St. John's Wort	

Inhibitors

Amiodarone	Disulfiram	Mibefradil**	Ranitidine
Anastrozole	Entacapone	Miconazole (moderate)	Ritonavir**
Azithromycin	Erythromycin	Nefazodone**	Saquinavir
Cannabinoids	Ethenyl estradiol	Nelfinavir	Sertindole
Cimetidine	Fluconazole (weak)	Nevirapine	Sertraline
Clarithromycin	Fluoxetine	Norfloxacin	Troglitazone
Clotrimazole	Fluvoxamine**	Norfluoxetine	Troleandomycin
Cyclosporine	Gestodene	Omeprazole (weak)	Valproic acid (weak)
Danazole	Grapefruit Juice	Oxiconazole	Verapamil
Delavirdine	Indinavir	Paroxetine (weak)	Zarfirlukast
Dexamethasone	Isoniazid	Propoxyphene	Zileuton
Dimethyldithiocarbamate	Itraconazole**	Quinidine	
Diltiazem	Ketoconazole**	Quinine**	
Dirithromycin	Metronidazole	Quinupristin and dalfopristin	

INSTITUTE: National Cancer Institute

STUDY NUMBER: 04-C-0257 PRINCIPAL INVESTIGATOR: Ravi Madan, M.D.

STUDY TITLE: A Phase II Trial of Docetaxel, Thalidomide, Prednisone and Bevacizumab in Patients with Androgen-Independent Prostate Cancer

Continuing Review Approved by the IRB on 02/06/17
Amendment Approved by the IRB on 03/07/17 (Q) Date posted to web: 03/18/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This study involves your voluntary participation in a research protocol. The purpose of this research is to determine if a specific treatment regimen is effective for prostate cancer patients. Each treatment will be given in a 21-day cycle. Your treatment regimen will consist of 4 anticancer agents. The first is docetaxel (a type of chemotherapy), which will be given through a vein over 60 minutes on the first day of each cycle. The second will be prednisone (a steroid

agent), which will be taken by mouth on every day of the cycle. The third is thalidomide (an agent that may inhibit new blood vessel growth) is a tablet that will be taken by mouth every evening throughout the cycle. The fourth is bevacizumab (another agent thought to inhibit new blood vessel growth will be given through a vein on the first day of each 21day cycle. We know that all of these agents have been used successfully in treating patients with prostate cancer (when used alone or in together with other agents), and we have reason to believe that these anticancer effects can be increased by giving them in this specific combination.

We are also attempting to understand how these drugs work and what side effects commonly occur when they are combined. All four drugs are approved by the U.S. Food and Drug Administration (FDA). Docetaxel is an anti-cancer drug used in the treatment of many types of cancer. Prednisone is a steroid that has been used safely in the treatment of many cancerous and noncancerous diseases. Thalidomide was initially developed as a sedative, but was found to cause birth defects in the children born to women who received the drug during pregnancy. Thalidomide is FDA-approved to treat a form of leprosy, but recently has shown an ability to block the development of new blood vessels (technically, this is called inhibiting angiogenesis). In prior clinical trials in patients with prostate cancer at the NCI, some patients had a clinical benefit (improvement in pain and a lowering of their PSA) after taking thalidomide, either by itself or together with docetaxel. Bevacizumab is a man-made antibody that blocks the development and growth of new blood vessels and has been shown to be effective and safe in the treatment of many types of cancer including colorectal, breast and prostate. Bevacizumab will be provided to the study by the company Genentech, Incorporated. There have also been studies that demonstrate that the combination of docetaxel and prednisone increases survival for patients with prostate cancer. We hope that the combination of these four drugs will provide even greater benefit than that provided by taking any of the drugs individually or as part of a two or three-drug combination. The experimental treatment in this clinical trial will be done on an outpatient basis whenever possible.

It is possible that some of the prostate cancer cells in your body may still grow if exposed to the male hormone testosterone. Thus your testosterone must be suppressed either surgically (removal of the testicles) or medically with injections (shot) of an LHRH agonist drug (leuprolide or goserelin) that are repeated approximately every three months.

Why are you being asked to take part in this study?

Your doctors have told you that you have advanced prostate cancer that is not responding to hormonal therapy. Your doctors have told you that although "standard" treatment can be administered to you, there is no known curative option for your cancer. For this reason, we are offering you experimental treatment on this research study. Although we hope that this experimental therapy may be of benefit to you and that your tumor will shrink, there is no guarantee that your tumor will respond. Benefit cannot be promised, nor can the chance of benefit be accurately predicted.

How many people will take part in this study?

75 people will take part in this trial at NIH.

Description of Research Study

What will happen if you take part in this research study?

You should understand that this study involves research. Eligibility criteria are routinely used to assure that it is medically appropriate for patient candidates to participate and that they have the carefully defined medical condition as outlined by the study protocol. For your own well being, as well as to ensure that the results of this study can be useful to making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Before you begin the study

Before receiving any form of treatment, you will be evaluated in the outpatient clinic to see if you are eligible for this experimental therapy. This evaluation may take up to 2 weeks and will be done on an outpatient basis. Some studies for determining the extent of spread of your cancer may be done for the first time or repeated if necessary (e.g., CT scans). In addition, blood and urine studies will be needed to determine if the experimental treatment can be safely administered to you. We will collect approximately 170 milliliters of blood (11 tablespoonfuls) from you during the first month of treatment, and then approximately 90 milliliters (6 tablespoonfuls) after 2 months of treatment and 60 milliliters (4 tablespoons) during all other months. We will also collect approximately 30 milliliters of urine at the initiation of your treatment. The collected blood and urine will be used to monitor the effects of the treatment on your body, study the concentration of drug in your body and look for other experimental factors associated with your cancer.

There is also a possibility that you will be asked to undergo a dynamic magnetic resonance imaging (MRI) test as part of this study. This is a radiological test that requires you to lie in an imaging machine for approximately one hour. This will help us determine how useful this test is for following the progress of disease and response to treatment in patients with prostate cancer.

We will ask patients to undergo a tumor biopsy before the initial treatment and after 2-3 cycles of treatment. Examples of potential sites of biopsies are an abnormally enlarged lymph node or an unresected, nonirradiated prostate or radiated prostate with a significant abnormality on either physical exam or imaging studies. The purpose of the biopsies will be to evaluate the effect of these drugs on blood vessel growth and development and markers of cell death in the tumor. This will only be done in participants who can safely undergo the procedure. The biopsy will be performed at the NIH. A separate consent form will be provided to you that describes the biopsy procedure. Please note, your decision to refuse this biopsy will not prevent you from joining the study.

Selected patients will be asked to undergo biopsy of their bone marrow to look for the presence of cancer. Once again, your decision to refuse this biopsy will not prevent you from joining the study

The research treatment that you will receive will consist of docetaxel, bevacizumab, thalidomide, and prednisone.

During the study

On this regimen, treatment cycles are 3 weeks in duration. You will take one dose of thalidomide every day throughout the cycle. You will receive an intravenous infusion of Docetaxel at a dose of 75 mg/m2 on the first day of each cycle. In association with receiving docetaxel, we will ask you to take 3 doses of dexamethasone (a steroid agent), one at 12 hours before docetaxel, a second dose just 1 hour before docetaxel, and a third dose 12 hours after you receive docetaxel. Docetaxel may cause fluid retention (edema) in some patients and dexamethasone helps to prevent this. On the first day of each cycle you will also receive an intravenous infusion of bevacizumab at a dose of 15 mg/kg. You will also begin taking prednisone by mouth at a dose of 10 mg on the first day of each cycle but you will continue to take it daily throughout the cycle. You will also start taking thalidomide by mouth at a dose of 200 mg on the first evening of each cycle and it too will be taken daily throughout each cycle. So while the docetaxel and bevacizumab will be given every 21 days by intravenous infusion, the prednisone and thalidomide will be taken every day by mouth. You will also be asked to give yourself or have a caregiver give you, a daily injection of enoxaparin, a blood –thinning drug, because both bevacizumab and thalidomide have been shown to increase the risk of blood clot formation.

If you are enrolled in the expansion cohort of the trial, you will only receive docetaxel at a dose 75 mg/m2 and an intravenous infusion of bevacizumab at a dose of 15 mg/kg one the first day of a 21-day cycle for a total of 2 cycles. The other three medicines as mentioned above, including thalidomide, prednisone, and enoxaparin will not be started until the beginning of cycle 3. In other words, your treatment will be same as that described in the paragraph above and the treatment will continue until your disease has shown evidence of progression or you could not tolerate the treatment due to considerable unwanted side effects. It is important that you begin to use the blood-thinning drug enoxaparin daily from the day that you receive thalidomide.

Throughout your treatment it will be very important to keep us informed about any new symptoms from either your disease or any of the drugs. You will come to the NIH clinical center to be seen one day of each three week cycle. We will repeat some of the studies approximately every 3 months (e.g., bone scan and/or CT scan) to determine if your cancer has responded. If there are no severe signs of toxicity or if your cancer has not progressed, we will continue to give you treatment. This is especially important for possibly maximizing potential benefits from the treatment. Although a significant PSA rise from the lowest value after your treatment is traditionally thought to be an early sign of disease progression, there has not had clear evidence showing that the PSA progression is well correlated with clinical progression of your disease.

Therefore, the therapy regimen will continue till you have clear evidence of progression in those scans, develop clinical progression signs, or unable to tolerate the therapy. Your experimental treatment is designed to be given in an outpatient setting (with the exception of the very start of treatment where you may spend two nights in the Clinical Center Hospital). The experimental therapy could last for longer than 6 months, depending on whether you are gaining benefit and not experiencing side effects. After 6 cycles of therapy (approximately 6 months) you will receive a monthly chest x-ray in conjunction with your follow-up visit. The purpose for doing so is to monitor whether there is any evidence of fluid collecting around the lining of your lungs, a side effect that has been found in some persons who received docetaxel for periods of 6 months or greater which may or may not be associated with symptoms.

Birth Control

Birth control measures must be used by all participants or their sexual partners who have child-bearing potential for at least one month before beginning thalidomide therapy, during thalidomide therapy, and for at least 1 month after stopping thalidomide therapy. Thalidomide causes severe birth defects in unborn babies if females who are pregnant take it. The risk of thalidomide causing damage to the embryo is as great as 50% for females taking thalidomide during a time that is estimated to range from 35-50 days after their last menstrual period. It is not known whether thalidomide may cause birth defects if it is taken after the sensitive period, however, even a single dose of thalidomide may cause birth defects.

Birth defects observed in babies who were exposed to thalidomide before birth include absent or abnormal legs and arms; spinal cord defects; cleft lip or palate; absent or abnormal external ear; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system, including blockage of necessary openings. Thalidomide has also been associated with autism in the children born to females who received it during pregnancy.

Because of the severity of these abnormalities, and the fact that it is not known if thalidomide is present in male ejaculate (semen), it is extremely important that pregnancies do not occur in your sexual partner while you are taking thalidomide.

Therefore, you must be counseled about the possibility that thalidomide may be present in semen. You must use a latex condom every time you have sexual intercourse with a woman during therapy and for 4 weeks after discontinuing thalidomide, even if you have had a vasectomy. You should recognize that no method of birth control besides abstinence provides 100% protection from pregnancy.

Risks or Discomforts of Participation

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

We are asking you to participate in this study. All of the drugs previously have been safely given to human patients. Although we have considerable information about potential side effects you may develop, the combination of docetaxel bevacizumab, thalidomide and prednisone have not been administered together. Thus, we cannot accurately predict the side effects that you may experience. For that reason, you will be monitored closely while you are receiving the experimental treatment for any evidence of the earliest stages of toxicity so that appropriate intervention can be done.

It is extremely important after starting to take the experimental treatment that you notify us before starting to take any new medications that your local doctors may have prescribed, or that you can purchase without a prescription. Docetaxel can have a very negative interaction with several other drugs. Thus, you should notify us before you start any new medical treatments and before beginning to use any herbal or nutritional supplements.

The side effects that have been associated with docetaxel include: Bone marrow depression, the result of which is anemia (low red cell count) that occasionally may cause you to require a blood transfusion; a decrease in the number of your white blood cells resulting in an increased risk of infection; a low platelet count, which may cause you to be at increased risk of bleeding; nausea and vomiting; changes in finger and toe nail growth; diarrhea; hair loss; and sterility.

Pegfilgrastim (neulasta), a medication which can increase the number of neutrophils (white cells that fight infection), will be given to you approximately 24 hours after docetaxel administration in every future cycle if your total neutrophils within a cycle are less than 1000. Pegfilgrastim is given as an injection (shot) under the skin. This is done to reduce the increased risk of infection which may occur with decreased neutrophils. The common side effects of pegfilgrastim include bone pain, reversible elevations in some laboratory testes such as LDH, alkaline phosphatase, and uric acid. Rare but serious side effects have also been reported with filgrastim, the parent compound of pegfilgrastim, which are adult respiratory distress syndrome (ARDS), allergic-type reactions such as anaphylaxis, skin rash, and urticaria, or splenic rupture.

Shortness of breath and eye tearing have been reported with docetaxel. In addition, docetaxel may cause fluid retention, numbness and tingling of hands and feet, and hypersensitivity reactions consisting of skin rash, wheezing, and occasionally a decrease in blood pressure. To minimize the chances of such a reaction, you will receive dexamethasone pills to take orally before and after treatment with docetaxel.

Rarely, a group of symptoms may occur with docetaxel therapy which include a blister-like rash, which may be severe; fever; inflammation of the eyes; redness, swelling, and painful sores on the lips and in the mouth. If you have this group of symptoms, it is likely you will need intravenous

(IV) fluids and medicines, and you may need to be hospitalized. If you have ever had radiation treatments, redness and soreness may develop in the treated areas.

The most common complications associated with thalidomide include: fatigue, sleepiness, constipation, damage to nerves, swelling and/or redness in the face, legs and arms, hair loss, fever, reduced function of the thyroid gland, mood changes, dry mouth, itching, depression, hypersensitivity reactions, decreased white blood cell counts, decreased platelet counts, increased blood sugar, high or low blood pressure, abnormal heart rhythm, abnormal heart rate, inflammation of the pancreas, blurry vision and nausea. Most of these side effects resolve on their own or after thalidomide has been discontinued. Damage to the nerves may cause numbness, ataxia, fainting, tingling or shooting pains. Rarely, weakness to the extremities has been observed. In most cases the nerve damage has lessened or gone away after thalidomide is discontinued; however there is a chance of permanent nerve damage.

Thalidomide may cause decreased function of the thyroid gland through an effect of the drug on a portion of the brain called the hypothalamus, which helps to regulate thyroid gland function. You may be required to take medication to treat this condition and it may be permanent.

Thalidomide may also increase your risk of developing blood clots. Blood clots are potentially serious because they may interfere with blood circulation or may dislodge and cause problems elsewhere. For this reason you will be required to inject under the skin a medication called enoxaparin that will prevent blood clots from forming by 'thinning' your blood. Though the use of enoxaparin may increase your risk of bleeding complications such as bleeding from your digestive tract, gums, nose, urinary tract or even life-threatening bleeding (because of the medications blood-thinning properties), we believe this medication is necessary and provides overall benefit to you.

Bevacizumab is a relatively new agent that has been investigated in all phases of clinical study. The common side effects seen with this agent are high blood pressure, weakness, nose bleeds, a mild increase of blood or protein in urine and fatigue. Uncommon side effects seen include fever, diarrhea, nausea, pain, blood clot formation, decreased white blood cell count and bleeding from mouth and gums. Rare side effects seen are chest pain, formation of a hole in your intestinal wall, bleeding into the lungs or brain and life threatening blood clots (including clots to the lungs).

Since bevacizumab and thalidomide together may also increase your risk for developing blood clots, enoxaparin will be injected daily as previously discussed. Though the use of enoxaparin will increase your risk of bleeding complications as well as the fact that we are combining it with bevacizumab, we believe this medication is necessary and provides overall benefit to you. If any of the following symptoms occur: sudden onset of swelling to one leg that may or may not be accompanied by leg pain (calf or thigh), chest pain, or shortness of breath, if you experience these symptoms seek immediate medical attention.

There may be changes in your blood chemistries and other blood values related to this treatment, many of these changes are mild and you will not experience symptoms. Rarely patients may experience elevated liver function tests. Any significant changes in your blood values will be discussed with you.

There is a possibility that the combination of bevacizumab and thalidomide may increase the risk of developing osteonecrosis of the jaw in patients who have received past treatment or continue to receive treatment with intravenous bisphosphanates. Zoledronic acid (Zometa) is a bisphosphonate commonly used for the prevention of fractures in prostate cancer patients with bone involvement. Osteonecrosis of the jaw occurs when the jaw fails to heal after minor trauma, such as a tooth extraction; this can be a debilitating condition if not recognized and treated early. For this reason we recommend you have a dental exam before beginning treatment and periodically throughout the study.

In the previous study with bevacizumab (Avastin) two study patients experienced aortic dissection. There is a possibility that Bevacizumab may possibly increase the likelihood of the development of an aortic dissection.

Aortic dissection is a medical emergency. The aorta is the major artery that carries blood from the heart to the rest of the body; aortic dissection occurs when the inner layer of the aorta's artery wall splits open (dissects). Aortic dissection may cause sudden chest pain often described as very severe and tearing. The pain may be localized to the front or back of the chest. Typically the pain moves as the dissection gets worse. If you experience these symptoms seek immediate medical attention.

High blood pressure is the most common factor predisposing the aorta to dissection. Bevacizumab can cause an increase in blood pressure. We will aggressively monitor your blood pressure at clinic visits and also ask you to continue management of your blood pressure with your regular physician. Additionally, we review a CT scan of your chest every nine weeks as part of your cancer restaging; this scan may also help us detect aortic dissection. Aortic dissection can be treatable with either surgery or medical management when found in the early stages.

It is not possible to accurately predict all of the side effects of docetaxel, bevacizumab, thalidomide and prednisone when given together. We will be watching your physical condition and laboratory tests very closely while you are on this study. Any significant new findings that relate to your treatment will be discussed with you.

Alternative Approaches or Treatments

It has been explained to you that you have prostate cancer that has come back despite hormonal treatment and that Docetaxel and prednisone is the standard treatment for your cancer at this time. Other treatment alternatives which can be considered for you now include: 1) other forms of commercially available drugs, chemotherapy or additional hormone-based treatments, 2) other forms of experimental drugs or hormonal treatments, 3) radiation therapy to the tumor that is

limited to certain areas to relieve symptoms, and 4) you may also elect to receive no treatment for your cancer now, but to wait until symptoms or complications develop and receive supportive care or other therapies at that time in order to lessen or eliminate symptoms.

Please talk to your doctor about these and other options.

Potential Benefits of Participation

Are there benefits to taking part in this study?

This is a phase 2 study, which means we are trying to determine if the experimental drug combination is effective for the treatment of prostate cancer.

Individual benefit cannot be promised, nor can the chance of benefit be accurately predicted. It is possible that you may experience some, all, or none of the side effects described above. It is also possible that the combination of drugs may produce some unanticipated side effects. For that reason, you will be monitored closely while you are receiving the experimental treatment for any signs which might signal the earliest stages of toxicity so that appropriate intervention can be done.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your 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. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- Qualified representatives from Genentech, the pharmaceutical company who produces Bevacizumab.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Genentech or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research

team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using Bevacizumab developed by Genentech through a joint study with your researchers and the company. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of Bevacizumab.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Ravi Madan, M. D.; Building 10 CRC, Room 13N240B, Telephone: 301-480-7168. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative | Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian | Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian | Date | Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 06, 2017 THROUGH FEBRUARY 05, 2018.

Signature of Investigator | Date | Signature of Witness | Date

Print Name | Print Name