Amendment

Protocol Number: 09C0195-X **Reference Number:** 365264

Principal Investigator: Ravi Madan NCI GMB 301.480.7168 madanr@mail.nih.gov

(NIH Employee Name, Institute/Branch, Telephone and e-mail)

Protocol Title: A Phase 2 trial of Bevacizumab, Lenalidomide, Docetaxel and Prednisone(ART-P) for Treatment of Metastatic Castrate-Resistant Prostate Cancer

SIGNATURES

Principal Investigator (*):
William Dahut - applied signature on 12/23/2016 1:33 PM EST
Ravi Madan - applied signature on 12/23/2016 1:25 PM EST

Accountable Investigator:
PI is the Accountable Investigator

Branch Chief/CC Department Head (**):
James L Gulley, MD PhD - applied signature on 12/25/2016 12:23 PM EST

Medical Advisory Investigator (if applicable):
N/A

Lead Associate Investigator signature:
N/A

Referral Contact signatures:
N/A

Associate Investigators signatures:
Ravi Madan - applied signature on 12/23/2016 1:24 PM EST

For Institute/Center Scientific Review Committee:
N/A

Other IC Clinical Director signatures:
N/A

APPROVALS

IRB Chair:
Michael Hamilton - applied signature on 01/12/2017 2:53 PM EST

Clinical Director:
N/A

CONCURRENCE

OPS Protocol Specialist:

Lemuel Clayborn	AM X	01/24/2017
Signature	Print Name	Date

* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** 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

DEC Clearance Date: 11/29/2016

Protocol Version Date: 11/15/2016

CTEP Protocol #: 8217
CC Protocol #: 09C0195 Amendment X

Title: A Phase 2 trial of Bevacizumab, Lenalidomide, Docetaxel, and Prednisone (ART-P) for Treatment of Metastatic Castrate-Resistant Prostate Cancer

Abbreviated Title: ART-P for mCRPC

NCI Principal Investigator: Ravi A. Madan, MD[A- F]
Genitourinary Malignancies Branch (GMB), CCR, NCI
Bldg 10, Room 13N240B
10 Center Drive, Bethesda 20892
Phone 301-480-7168, Email: madanr@mail.nih.gov

Statistician: *Seth Steinberg, PhD, BDMS, NCI [E, F]

NIH Associate Investigators: *William D. Figg, PharmD, GMB, CCR, NCI [B, E, F]
James Gulley, MD, PhD, GMB, CCR, NCI [A-F]
William L. Dahut , MD, GMB, CCR, NCI [A-F]
Howard Parnes, MD, DCP, CCR, NCI [A-F]
John Wright, MD, CTEP, NCI [A-F]
Anna Couvillon, CRNP, GMB, CCR, NCI [A-F]
*Jane Trepel, PhD, DTB, CCR, NCI [E, F]
*Douglas Price, PhD, GMB, CCR, NCI [E, F]
Andrea Apolo, MD GMB, CCR, NCI [A-F]
Guinevere Chun, RN, OCD, CCR, NCI [A, B, C, E, F]
Fatima Karzai, MD, NIMHD [A-F]

Non-NIH Associate Investigator: *Michelle Ojemuyiwa, M.D. [V], OCD, CCR, NCI [E, F]
(Special Volunteer, Walter Reed National Military Medical Center)
Philip Arlen, MD, OCD, CCR, NCI [A-F]
(Special Volunteer, Precision Biologics)

Referral Contact/ Study Coordinator: Guinevere Chun, RN, OCD/CCR/NCI/NIH[A,B,C,E,F]
10 Center Drive, Room 13N224
Phone: 240-760-6065
Email: gchun@mail.nih.gov

Drug Monitor: Helen Chen, M.D., CTEP, NCI
Howard Z. Streicher, M.D., CTEP, NCI

Drug Sponsor: CTEP, NCI
Drugs Supplied: **Lenalidomide** (CC-5013, IND 70116, NSC703813), **Bevacizumab** (IND 7921, NSC704865)

Commercial Agents: Docetaxel and Prednisone

* These investigators will not be involved in direct patient care or clinical decision-making.

Investigator Roles:

A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals
C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
G. Some/all research activities performed outside NIH

PRECIS

Background:

- The dual antiangiogenic therapy with bevacizumab and thalidomide in combination with docetaxel and prednisone (ATTP) is highly active in patients with metastatic castration resistant prostate cancer (mCRPC), associated with unprecedented results (90% patients had PSA declines of ≥50% and 64% ORR in measurable disease)
- Most patients in the ATTP trial required dose reduction due to thalidomide toxicities.
- Lenalidomide, an analogue of thalidomide, is antiangiogenic and inhibits TNF-alpha, but has a favorable toxicity profile. Lenalidomide is well tolerated in patients with solid tumors when used alone or in combination with docetaxel.
- To preserve the efficacy of ATTP and to potentially reduce toxicity, lenalidomide may be a good substitute for thalidomide.

Objectives

Primary:

- To assess if lenalidomide at its approved dosing schedule can be safely combined with docetaxel, bevacizumab, and prednisone in patients with mCRPC (<25% Grade 4 toxicity)
- To evaluate the efficacy of the combination

Eligibility:

- Patients with progressive mCRPC who have not received any chemotherapy or antiangiogenic therapy for mCRPC

Design:

- A single-stage Phase 2 study, with an early stopping rule for excessive toxicity: the goal is to enroll 45 patients at the 25 mg dose level of lenalidomide. However, if 7 in the first 18 or fewer patients receiving lenalidomide at 25 mg develop grade 4 non-hematologic toxicity at any time during study, no further patients will be enrolled. With respect to the stopping rule, a grade 4 hematologic toxicity will be considered if the episode has lasted for greater than or equal to 5 days. Grade 4 lymphopenia of any duration will not be counted. If less than 7 of the first 18 patients experience the above level of toxicity, accrual will continue until 45 patients have been enrolled at the 25 mg dose level of lenalidomide.
- A run-in phase with lenalidomide at 15 mg will be conducted in the first three patients and at 20mg for the next three patients for assessing its tolerability within the combination prior to dosing at 25 mg thereafter.
- An expansion cohort of a lower dose of lenalidomide (15 mg) in combination with docetaxel and bevacizumab will be conducted to assess if this lower dose of lenalidomide could have similar efficacy with less toxicity.

Treatment Schema of ART-P

Cycle Number: _____

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
Len	X	X	X	X	X	X	X	X	X	X	X	X	X	X								X
Doc	X																					X
Bev	X																					X
Pre	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
Peg		X																				

Dex -Dexamethasone 8 mg po 12 hours pre, 3 hours pre, and 1 hour pre infusion of docetaxel (patients who were on prior regimen which included a lower dose of decadron and did not have a reaction do not have to increase their decadron to the 8 mg dose)

Len - Lenalidomide 25 mg po, days 1-14. Lenalidomide 15 mg and 20mg for the proposed run-in phase. Lenalidomide 15 mg for the expansion cohort.

Doc - Docetaxel 75 mg/m2 IV

Bev - Bevacizumab 15 mg/kg IV

Pre - Prednisone 10 mg PO daily throughout cycle

E - Enoxaparin given SQ daily based on weight (see dosing chart in section 5.2.5)

Peg - Pegfilgrastim 6mg SQ given at least 24 hours after docetaxel administration

Baseline screening evaluations are to be conducted within 15 days prior to protocol enrollment. Baseline scans and x-rays must be performed 4 weeks prior to protocol enrollment. Patients must be evaluated at the NCI clinic each cycle for treatment continuation. For patients who have been on study for at least 2 years and are being treated with prednisone only, follow-up evaluations may be performed every 6 weeks at the physician's discretion. Staging scans will be performed after the first 2 cycles of treatment and then every three cycles. If the patient has been on study for at least two years, scans may be performed only if there is evidence of disease progression. All follow-up evaluations can be done on the last week of the prior cycle.

TABLE OF CONTENTS

1 BACKGROUND AND OBJECTIVES

1.1 OBJECTIVES

1.1.1 PRIMARY OBJECTIVES

- To evaluate if lenalidomide is able to be safely incorporated with the combination of docetaxel, bevacizumab, and prednisone, to confirm that the drug does not have an excessively high rate of toxicity in a moderately large cohort of patients, and to evaluate the efficacy of the combination of the four agents.

1.1.2 SECONDARY OBJECTIVES

- To evaluate overall survival of patients studied
- To evaluate the effects of the combination on the immune system before and after drug administration
- To analyze the patients' genotype with regard to genes involved in transport and metabolization of these agents to correlate that with efficacy
- To evaluate changes in circulating apoptotic endothelial cells before and after drug administration
- 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, lenalidomide and bevacizumab
- To evaluate the toxicity profile of the four-drug combination

1.2 BACKGROUND

1.2.1 Prostate Cancer

Metastatic prostate cancer is a leading cause of death from cancer in men. Though initially responsive to hormone therapy, metastatic prostate cancer eventually progresses in almost all patients. For this reason, there has been a search for novel agents to use in the treatment of castration resistant prostate cancer (CRPC).

Historically, chemotherapy was not considered to have significant activity in metastatic CRPC. However, this view changed within the past 15 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 CRPC [1-3]. Docetaxel, both as a single agent and in combination with estramustine has activity as well. Two regimens containing docetaxel and either prednisone or estramustine improved overall survival when compared to mitoxantrone/prednisone, leading to the FDA approval of docetaxel and prednisone in CRPC. [4,5]

1.2.2 Docetaxel

Docetaxel is a semi-synthetic 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 G2/M phase, which ultimately leads to apoptosis [6]. 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 [7,8]. 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[9].

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 CRPC. Several phase II studies used single agent docetaxel every three weeks at 75 mg/m^2 and demonstrated a PSA decrease of at least 50% in 38-46% of patients with CRPC [10,11].

Tannock et al. conducted a phase III trial of docetaxel in combination with prednisone in 1006 patients with CRPC. Patients were randomized to 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 CRPC 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 CRPC and strongly encourage further trials using these and other docetaxel combinations in this disease.

1.2.3 Prednisone

Prednisone, a glucocorticoid has been shown to have some activity in patients with CRPC. Twenty-nine patients received prednisone at a dose of 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%. However, the median progression free survival was only 2.8 months[12].

1.2.4 Lenalidomide

Lenalidomide (Revlimid) is an immunomodulator that is an analogue of thalidomide. Thalidomide is most well known for being a potent teratogen that causes dysmelia (stunted limb growth) in humans [13]. But since that time several pre-clinical models have shown the potential for anti-tumor activity based on anti-angiogenesis [14-16]. Since angiogenesis may have a significant role in prostate cancer [17,18], several clinical trials have been conducted with thalidomide.

Clinical Trials with Thalidomide

Seventy-five chemotherapy naïve CRPC patients received 30-mg/m2 weekly docetaxel for 3 consecutive weeks followed by a 1-week rest period; or docetaxel at the same dosing 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). 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. 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 CRPC and eventually became statistically significant [19,20].

Currently ongoing is a study combining bevacizumab, docetaxel, thalidomide and prednisone (ATTP trial) in the MOB, CCR, NCI. The most recent analyses of the trial after the targeted enrollment of 60 pts has competed were reported in the 2008 ASCO annual meeting. Most patients in the trial had multiple poor prognostic factors, with a median predicted survival of 14.7 months based on the Halabi's model. As of the report, the median treatment cycles were 15 (2-51). The toxicities that have been noted are: febrile neutropenia (6/60), syncope (7/60), colon perforation or fistula (4/60), grade 3 bleeding (3/60), thrombosis (3/60). In addition, most patients experienced lower grade toxicities related to thalidomide, including neuropathy, fatigue, somnolence and constipation. Although none of the toxicities were more than grade 2 in intensity, almost all of the patients required initial intervention. In efficacy evaluation, fifty-two of 58 patients with PSA positive disease (*90*%) had PSA declines of $\geq$50%, with a median $\geq$50% PSA-duration of 14 cycles [*0~50*]. Forty-four of the 58 patients (*76*%) had >75% PSA declines. Thirty-three patients with measurable disease were evaluable: 2 CR and 19 PR, with an ORR of 64%.

The toxicities related to thalidomide in the ATTP trial appear consistent with the known side effects of thalidomide. These include but are not limited to sedation, peripheral neuropathy, rash, dizziness, constipation, tremors, mood changes and headaches [21]. The exploration of other anti-angiogenic compounds associated with thalidomide lead to further development of lenalidomide due to its increased potency and less side effects.

Lenalidomide [3-(4-amino-1-oxo 1, 3-dihydro-2*H*-isoindol-2-yl) piperidine-2, 6-dione] has already been through multiple clinical trials. The immunomodulation properties include of inhibition of TNF-α, up-regulation of IL-10 and induction of T-cell proliferation after T-cell receptor activation [22]. It is an FDA approved agent (with dexamethasone) in patients with multiple myeloma and for patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. The drug has gained interest in solid tumors not only because of the immunomodulation properties but also because of its anti-angiogenic properties, anti-neoplastic properties and favorable toxicity profile. Like thalidomide, the precise mechanism of action of lenalidomide remains to be identified.

Lenalidomide has been investigated in solid tumors, including a phase I study conducted in the MOB. In this phase 1 trial (n=45) accrued to 9 dose levels using two dosing schedules consisting of 21 days on and 7 days off (15-40 mg/day) and continuous 28 day dosing (5-20 mg/day). The patients were heavily pretreated with a median of 5 prior chemotherapeutic regimens. The majority of tumors in this study were prostate cancer (n=35). Using a modified Fibonacci design of escalation, the study demonstrated that in the continuous dosing scale at the 20 mg dose two patients had grade 3 DVT and hypotension. The toxicities observed during the 21 day dosing consisted of grade 3 (3) and 4 (3) neutropenia, grade 3 diarrhea (1) and grade 4 arrhythmia (1) and hemolysis (1). There were no responses per RECIST criteria. The study demonstrated that doses of up to 40 mg/ day were well tolerated with minimal toxicity.

Miller et al. also conducted a Phase 1 trial (n=20) at doses of 5, 10, and 25 mg/day for 28 days [23]. There were several tumor types (lung, colorectal, breast) that were evaluated. Toxicities consisted of grade 3 neuropathy (1) and thrombocytopenia (1) at the 25 mg/ day dose. One patient had a partial response and three had stable disease. The study showed that 25mg/ day continuous dosing was well tolerated with minimal toxicity.

Trials have shown the applicability of lenalidomide with cytotoxic chemotherapeutic agents. A Phase 1 trial (n= 19) assessed the tolerability of lenalidomide (10-25 mg/day for days 1-14) in combination with docetaxel (60 or 75 mg/m2 on day 1 of 21) in metastatic CRPC (less than two prior regimens). [24]. The toxicities consisted of grade 3 neutropenia (3) and grade 2 neuropathy (1) and fatigue (1)**.** Nine pts (47.4%) had a ≥50% decline in serum PSA**.** A total of 13 patients had measurable disease. 5 (38.5%) achieved a partial response (PR) and 7 pts (53.9%) had stable disease. The MTD had not been reached at the time of the publication. Although the results of the study have been not updated recently, the safety profile and tolerability of the combination at the 25 mg dose level of lenalidomide were acceptable and the responses were encouraging (per Dr. Dahut's personal communication with the investigator of the study).

It should also be noted that currently several combination trials are ongoing in multiple myeloma. This includes combinations of bevacizumab and lenalidomide with dexamethasone that is currently ongoing at the Mayo Clinic.

Toxicities

The most common grade 3 and 4 toxicities as seen in the above solid tumor trials have been thrombocytopenia and neutropenia. It appears from the initial trials that the occurrence of thrombosis is lower than in thalidomide trials.

Lenalidomide Dosing

Studies have evaluated combined angiogenesis inhibition with docetaxel in the treatment of metastatic castration resistant prostate cancer. A previous study of docetaxel, thalidomide and bevacizumab demonstrated higher response rates and longer survival than either docetaxel with thalidomide or docetaxel with bevacizumab.[25] The combination of lenalidomide, bevacizumab, docetaxel and prednisone (ART-P) is highly effective in metastatic castration-resistant prostate cancer. A PSA decline of ≥ 50% was seen in 86.4% of patients and 87.5% of the patients with measurable disease achieved either complete remission or partial response. In this trial, lenalidomide was administered at 25 mg daily for 14 days of a 21-day cycle, with the exception of the initial 6 patients enrolled during the dose-escalation phase of the study. Three patients in two cohorts were dosed at 15 mg and 20 mg to ensure tolerability. All 3 of the patients, who were treated with 15 mg, have demonstrated both PSA decline of ≥ 75% and partial responses of their measurable diseases. [26]

Among patients treated at the 25 mg, 20/47 patients (44.7%) required dose reductions of lenalidomide due to grade 3/4 adverse events, including cytopenia, febrile neutropenia, fatigue, and diarrhea. Of these 20 patients, 7 (14.9%) experienced ≥ 2 dose reductions along the course of their treatments. One patient developed repeated thrombocytopenia which necessitated the discontinuation of lenalidomide. The toxicities associated with 25 mg lenalidomide appeared higher than those of lower doses (15 and 20 mg) of lenalidomide. [26] These findings are consistent with a previous phase I/II randomized trial where patients received either 25 mg or 5 mg

lenalidomide for biochemical recurrent prostate cancer. The majority of toxicities were experienced in the 25 mg cohort. Most of the toxicity was experienced in the 25 mg cohort [27].

Several investigations demonstrate no significant alterations in immunological and clinical parameters when higher dose lenalidomide (25 mg) is compared to low dose (5 mg). Plasma concentrations of lenalidomide have not correlated with the changes in PSA slope (3). The progression rates are similar in patients with biochemically recurrent prostate cancer receiving either 5 mg or 25 mg lenalidomide [27]. Furthermore, from the experience of CLL and multiple myeloma studies, lenalidomide at 5 mg dosing may be sufficient for potentiating an immune response in vivo, by reducing regulatory T cells and production of IL-17 as well as improved clinical activity [28,29].

Although initial PSA decline is not a validated predictive or prognostic biomarker, data from TAX 327 and SWOG 99-16 showed that PSA decline of ≥ 30% within 3 months of chemotherapy has the highest degree of surrogacy for OS [30,31]. Despite a small cohort with only 3 patients treated at 15 mg daily, there is a suggestion that the clinical activity of a lower dose lenalidomide with less accompanying side effects may be comparable to those of the higher dose when used in combination with docetaxel, bevacizumab, and prednisone. [26]

In summary, the lack of significant variation in clinical parameters between lenalodimide 25 mg and lower dose levels, and the toxicity profile favoring lower doses make it reasonable to pursue further investigation of lower dose lenalidomide in metastatic castration-resistant prostate cancer. This approach could potentially allow for improved quality of life for patients on trial and sustained therapy, which could lead to improved clinical outcomes.

1.2.5 Bevacizumab (rhuMab)

Background: Bevacizumab (rhuMAb) is a recombinant humanized anti-VEGF monoclonal antibody composed of human IgG1 framework regions and antigen-binding complementarily-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.

Bevacizumab has been approved by the FDA as first line therapy in combination with chemotherapy for treatment of patients with metastatic colorectal cancer or unresectable, locally advanced, recurrent or metastatic, non-squamous non-small cell lung cancer because of improved overall survival in the patients receiving combination therapy as compared to receiving chemotherapy alone. In addition, bevacizumab has also received accelerated approval for use in patients with HER-2 negative, untreated metastatic breast cancer in combination with weekly paclitaxel because of a marked improvement in progression free survival. These lines of evidence demonstrate that bevacizumab is clinically effective when combined with chemotherapy. The important information about this agent and its use in studying prostate cancer is discussed as follows.

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 [32,33]. 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 [34]. 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 1 Clinical studies: Two phase-1 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 [35]. 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 [35]. 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 ≥ 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 2 Clinical Studies:

Study	Population	Study Treatment	rhuMAb VEGF Dosing Regimen
AVF0757g	Stage IIIB or IV non-small cell lung cancer	Carboplatin/paclitaxel ± rhuMAb VEGF	7.5mg or 15mg/kg every 3 weeks until disease progression
AVF0780g	Metastatic colorectal cancer	5-FU/leucovorin ± 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) [36].

The anti-VEGF antibody Bevacizumab (rhuMAb) was evaluated as a single agent in several malignancies including CRPC [35,37]. In a Phase II trial 15 patients with CRPC 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 conducted a CALGB trial looking at the use of bevacizumab, estramustine and docetaxel in 79 patients with CRPC using a dose of 15 mg/kg of bevacizumab every 3 weeks. Early results show that 60% of patients had a PR and 78% of patients had a >50% decrease in PSA in those patients with sufficient data to analyze. The estimated median survival was 24 months. This regimen was well tolerated, though there was some increase in thrombosis, which might be associated with estramustine or the combination of estramustine with bevacizumab [38].

1.2.5.1 Toxicities

The following are the important toxicities. The detailed information can be seen in Section **7.2**.

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).

Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Mucocutaneus Hemorrage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Thrombosis: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

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 [39]. 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.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events. Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (product insert).

VEGF has been shown to induce nitric oxide-mediated vasodilatation and hypotension [40]. 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 [18].

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab

should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria:

The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been Grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

A recent study has shown that VEGF mediates glomerular repair, which suggested a possible mechanism for rhuMAb VEGF-associated proteinuria [18].

Congestive Heart Failure (CHF):

In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials

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.

Other rare but severe toxicities, which include gastrointestinal perforation, fistula, reversible posterior leukoencephalopathy syndrome, and neutropenia. Reference should be made to the

product labeling of bevacizumab. Specific caution and clinical alertness should be exercised for patients receiving the agent.

1.2.6 Rationale for combinatorial therapy

The rationale in replacing thalidomide is based not only on the toxicity of lenalidomide but also on its molecular properties. Although lenalidomide does have less VEGF inhibition, it has more TNF inhibition. 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. (Dr. Figg's unpublished data). VEGF expression was not altered in xenograft experiments using these analogs, however PDGF was significant reduced.

During the development of thalidomide analogs such as lenalidomide (Revlimid™), chemical modifications of the thalidomide template were made in an effort to specifically optimize the anti-TNFα activity. Two discrete sub-structures of the thalidomide molecule were altered, namely the phthaloyl and glutarimide portions of the molecule. Both families of compounds were tested for TNF-α inhibition and further structural modifications were made to optimize this activity. The primary hydrolysis products of thalidomide were also used as subsidiary templates even though they showed poor potency as TNF-α modulators in their unmodified form. This strategy led to the development of two primary families of compounds showing enhanced TNF-α-inhibition properties: substituted phthaloyl analogs with intact glutarimide functionality and molecules which retain the basic phthaloyl moiety, but have substituted α-amino acid functionality in place of the glutarimide ring of thalidomide, such as lenalidomide (Revlimid™). The finding that these varied structural modifications could yield the same enhanced potency in TNF-α inhibition suggests the presence of two different pharmacophores that most likely have different pharmacological targets, but are both capable of TNF-α downregulation.

1.2.7 TNF Inhibition

Lenalidomide (Revlimid™) is a member of the Immunomodulatory (ImiD) class of thalidomide analogs. In vitro studies have shown that lenalidomide is more potent than thalidomide in inhibiting TNF-α production. Furthermore, in preliminary non-clinical and clinical studies conducted to date, lenalidomide (Revlimid™) appears to lack the sedative and teratogenic activity of thalidomide.

The pertinent pharmacologic activity of lenalidomide (Revlimid™) has been investigated in two in vitro studies. These studies suggest a pharmacological activity profile for lenalidomide (Revlimid™) that is similar to, but with a higher potency than that of thalidomide. Lenalidomide (Revlimid™) is approximately 50 to 2000 times more potent than thalidomide in these assays. In addition, these studies have demonstrated that lenalidomide (Revlimid™) has pharmacological activities that could be beneficial in the treatment of patients with MDS, i.e., inhibition of secretion of pro-inflammatory cytokines. Corral et al. examined the modulation of production of various cytokines by lenalidomide (Revlimid™) and other thalidomide analogs. Lenalidomide was approximately 50 to 100 times more potent than thalidomide in stimulation the proliferation of T-cells following primary induction provided by T-cell receptor (TCR) activation. Lenalidomide (Revlimid™) was also approximately 50 to 100 times more potent than thalidomide in augmenting the production of IL-2 and IFNα following TCR activation of PBMC (IL-2) or T-cells (IFN-α). In addition, lenalidomide (Revlimid™) exhibited dose-dependent inhibition of LPS-stimulated

production of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6 by PBMC. Finally, lenalidomide increased production of the anti-inflammatory cytokine IL-10 by LPS-stimulated PBMC.

In vitro models of anti-TNF activity have shown that lenalidomide, an analogue of thalidomide, has IC_{50}s of ~100 nM (25.9 ng/ml) and ~480 nM (103.6 ng/ml) against TNF produced by LPS-stimulated human peripheral blood mononuclear cells and LPS-LPS-stimulated human whole blood respectively (Investigator's brochure). Thalidomide, by comparison, has TNF IC_{50} in human peripheral blood mononuclear cells of ~194 μM (50.2 μM) (Investigator's brochure) (see **Table 1**). These data suggest an overlap of biologic function between thalidomide and lenalidomide.

1.2.8 Antiangiogenic Activity

Recent data suggest this overlap also includes antiangiogenic effects. In the rat aortic ring angiogenesis assay, lenalidomide demonstrated a 45% inhibitory effect on microvessel outgrowth over a range of 0.1 - 100 μM compared to the controls by Figg's laboratory, while Celgene reported over 66% inhibition.

Table 1 **compares the activity of lenalidomide to thalidomide in several preclinical models.**

Treatments	Mean MVD
Control	29
Thalidomide	19
lenalidomide	10

The combination of the four drugs is based on principles similar to that from our current ongoing trial. 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 lenalidomide (against multiple targets but not VEGF) we will have effectively suppressed all of the important angiogenic factors (preliminary data from Dr. Figg's lab). This approach will begin to test the hypothesis that the blockade of multiple factors in angiogenic is the most effective anti-tumor strategy.

Picus et al combined docetaxel and estramustine with the anti-VEGF antibody bevacizumab in a phase II study of 79 patients with CRPC. [11] The rationale for this study was in part based on the evidence that patients with CRPC 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 78% of patients had a PSA decline of ≥ 50% and that 60% 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 3 trial (CALBG 90401) is currently ongoing, though estramustine is substituted for by prednisone to improve on the toxicity profile.

As discussed earlier the combinations of docetaxel and lenalidomide and docetaxel with bevacizumab appear to be generally tolerated in CRPC with encouraging anti-tumor activity. The unprecedented antitumor activity observed with the combination of docetaxel, bevacizumab, thalidomide and prednisone, presumably through targeting different angiogenic factors, suggests that the new combination with lenalidomide's replacing thalidomide is highly worthy of being studied for development of a more effective regimen for metastatic CRPC but with less toxicity.

1.2.9 Correlative Studies

Plasma concentrations of docetaxel will be determined to assess interactions between docetaxel and the concomitant therapy. Plasma concentrations of lenalidomide will be determined to assess a possible interaction between lenalidomide 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 lenalidomide (CYP2C19) will be evaluated.

Further analysis will be performed for the following genes on blood samples: ABCB1, ABCG2, CYP1B1, NQO1, COMT, CYP17 and CYP19, OATP1B3, HIF-1alpha, VEGF, TSP1, Il-6, TNF-alpha, CYP2B6, ABCC1, ABCC6, UGT1A1, UGT1A9, CYP2A7, PPARD, SULT1C2, and CHST3.

For evaluating angiogenic markers, we will collect both serum and urine samples at baseline and monthly to measure vascular endothelial growth factor (VEGF) levels.

Circulating apoptotic endothelial cells may serve as a surrogate marker in monitoring anti-angiogenesis. The combination of thalidomide with docetaxel led to an increase in apoptotic endothelial cells in prostate cancer xenograft models, which was correlated with the observed enhanced anti-tumor activity of the combination. With those preclinical findings, circulating apoptotic endothelial cells were evaluated at baseline and again at 6 weeks in the patients enrolled in the ATTP trial. (Preliminary data from Dr. Trepel's lab) Patients with $\geq$75% PSA declines had a significant increase in the apoptotic endothelial cells as compared to those with PSA declines less than 75%, suggesting that this triple combination may be hitting tumor angiogenesis target. We will continue to evaluate circulating apoptotic endothelial cells pre- and post-treatment in this trial with lenalidomide.

1.2.10 Conclusion

Though this would be the first trial to combine docetaxel with bevacizumab, lenalidomide, and prednisone in patients with metastatic CRPC, the combination of lenalidomide with bevacizumab or with docetaxel has been found to be acceptable in safety from other studies. Most importantly, we have found from our phase 2 study that the combination of docetaxel, bevacizumab, thalidomide and prednisone, although highly active, requires dose reductions in thalidomide in the majority of patients. We believe that the new combination with docetaxel, bevacizumab, lenalidomide and prednisone has the potential to make a significant impact in the treatment of the disease. If this trial is successful, a larger randomized trial through the cooperative groups with survival as an endpoint would be warranted.

2 PATIENT SELECTION

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- Castrate-resistant metastatic adenocarcinoma of the prostate defined as progressive metastatic disease (see below) while on GnRH agonists or post surgical castration. All patients enrolled will be required to have evaluable disease on imaging studies.
- 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 outline (see below).
- Clinically progressive prostate cancer documented prior to entry. Progression must be evidenced and documented by any of the following parameters:
    i) Two consecutively rising PSA levels apart of 2 weeks
    ii) At least one new lesion on bone scans.
    iii) Progressive measurable disease.
- Patients must have undergone bilateral surgical castration or must continue on GnRH agonist.
- Those patients receiving an anti-androgen agent for at least 6 months 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.
- May not have received any chemotherapy or antiangiogenic therapy (including thalidomide, lenalidomide, bevacizumab and its target's receptor inhibitors) for metastatic prostate cancer. (Prior immunotherapy/vaccine, experimental hormonal therapy, radiation and (neo)adjuvant chemotherapy is permitted)
- Age $\geq$ 18 years
- ECOG performance status $\leq$ 2
- Must have adequate organ and marrow function as defined below:

Laboratory Test	Required value
Leukocytes	$\geq$3,000/µl
Absolute neutrophil count	$\geq$1,500/µl
Platelets	$\geq$100,000/µl

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 clearance	≥ 50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

- Recovered from any acute toxicity from surgery or radiotherapy, with minimum 4 weeks from major surgical procedures and 2 weeks from radiotherapy
- Must be willing to travel from their home to the NIH for follow-up visits
- Able and willing to follow instructions and conform to protocol.
- 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.
- No history of myocardial infarction within the past 6 months, uncontrolled CHF or uncontrolled angina pectoris
- Patients must agree to use adequate contraception (abstinence; hormonal or barrier method of birth control) prior to the study, during the study, and at least six months after completion. Males must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least six months following, even if a man has undergone a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure as indicated in the consent.
- Subjects must agree not to share study drug and not donate blood, sperm, or semen. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
- Ability to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

- Present clinical signs or symptoms of current active brain and/or leptomeningeal metastases confirmed by CT or MRI brain scan. Patients with previously treated brain metastases are allowed to participate in the study.
- Treated brain metastases are defined as having no ongoing requirement for steroids and no evidence of progression or hemorrhage after treatment for at least 3 months, as ascertained by clinical examination and brain imaging (MRI or CT). (Stable dose

of anticonvulsants are allowed). Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.

- Uncontrolled, intercurrent illness including, but not limited to, symptomatic congestive heart failure (AHA Class II or worse), unstable angina pectoris
- Psychiatric illness/social situations that would limit compliance with study requirements.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Proteinuria, as demonstrated by a 24 hour protein of ≥ 2000 mg. Urine protein should be screened by urine analysis. If urine dipstick is >1.0+, then a 24 hour urine collection for total protein will need to be obtained and the level should be < 2000mg for patient enrollment.
- Serious, non-healing wound, active ulcer, or untreated bone fracture, including tumor-related pathological fracture
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- 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.
- Greater than Grade 2 peripheral neuropathy at baseline
- History of allergic reaction to docetaxel, prednisone, lenalidomide and/or bevacizumab or related products.
- Patients who are unable to ingest oral medication.
- Patients on treatment for VTE.
- History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to day 1
- Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1 therapy
- Anticipation of need for major surgical procedures during the course of the study
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1
- Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair, aortic dissection or recent peripheral arterial thrombosis) within 6 months prior to Day 1
- Patients with clinically significant cardiovascular disease are excluded

- Inadequately controlled HTN (SBP > 160 mmHg and/or DBP > 90 mmHg despite antihypertensive medication)
- History of CVA within 6 months (see additional requirement for adjuvant protocols), myocardial infarction or unstable angina within 6 months (see additional requirement for adjuvant protocols)
- New York heart association grade II or greater congestive heart failure
- Serious and inadequately controlled cardiac arrhythmia
- Clinically significant vascular disease as stated above

- Patients with known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies

2.2 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 due to the nature of the disease.

3 ON-STUDY RESEARCH EVALUATION

3.1 EXAM

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. Dental evaluation will be obtained for selected patients as time allows prior to initiating protocol therapy.

3.2 IMAGING STUDIES (BASELINE)

Within 4 weeks prior to enrollment

3.2.1 *Chest X-ray, CT scan of chest, abdomen and pelvis, and Technetium-99 Bone Scintigraphy. For selected patients as time allows, CT of the mandible will be obtained.*

3.3 LABORATORY EVALUATION

Baseline is to be obtained within 16 days prior to enrollment

- Hematological Profile: CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time
- Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, TSH
- Urine analysis
- Tumor Marker Profile, PSA (within 7 days prior to enrollment)

- Testosterone level (baseline only, should be obtained within 8 weeks prior to day 1); not required for patients with prior bilateral orchiectomy.
- Thyroid stimulating hormone (TSH)

3.4 EKG

EKG within 16 days prior to enrollment.

4 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. Please note, it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

Each site must have two trained counselors available for counseling all patients receiving lenalidomide supplied by the Division of Cancer Treatment and Diagnosis. Trained counselors must complete training using the online program provided free by Celgene, the Celgene Pregnancy Prevention Counseling Program (CPPCP). Registration for CPPCP is done by completing the form found in **Appendix D** and following the directions provided in the email notification. After the training is complete, the counselors must generate a training certificate and provide it to the PMB (fax# 301-402-0429 attn. CPPCP) for documentation. Sites may not order lenalidomide until documentation for two trained counselors is provided to the appropriate office.

5 TREATMENT PLAN

5.1 STUDY DESIGN

This is an open label, phase 2 study of up to 45 patients who will receive docetaxel 75 mg/m^2 IV over 60 minutes on cycle 1 day 1, repeated every 21 days (a 3-week cycle), plus bevacizumab 15 mg/kg cycle 1 day 1, repeated every 21 days, lenalidomide once daily days 1-14 of every 21, and prednisone 10 mg orally every day. All patients will receive 8 mg of oral dexamethasone 12 hours before, 3 hours before, and 1 hour before docetaxel treatment. If a patient misses a pretreatment dose of dexamethasone, he may receive dexamethasone 8 mg intravenously prior to docetaxel. Patients who were on prior regimen which included a lower dose of decadron and did not have a reaction do not have to increase their decadron to the 8 mg dose. All patients will be given pegfilgrastim on day 2 of each cycle at least 24 hours after the administration of docetaxel to reduce the risk of febrile neutropenia.

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. In order to minimize radiation exposure, if there is no evaluable soft tissue disease on baseline CT, future CT scans will not be obtained unless clinically indicated. Patients remaining on-study after two

years will have CT and bone scans performed only if there are signs of clinical progression at physician's discretion. If there is no significant toxicity or evidence of disease progression (as defined below), therapy will continue. In addition, patients who had not undergone bilateral orchiectomy will continue to receive medical castration with a LHRH agonist (such as leuprolide or goserelin acetate).

5.2 AGENT ADMINISTRATION

Study agents may be administered within 3 days of timepoints given below in order to accommodate patient travel, hospitalizations, variations in clinical availability due to holidays, or other unpredictable personal or family situations.

5.2.1 Docetaxel Administration

Docetaxel 75 mg/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 8 mg of dexamethasone orally 12 hours, 3 hours prior and 1 hour prior to docetaxel. Patients who were on prior regimen which included a lower dose of decadron and did not have a reaction do not have to increase their decadron to the 8 mg dose. If a patient misses a pretreatment dose of dexamethasone, he may receive dexamethasone 8 mg intravenously prior to docetaxel. Patients who have excessive dexamethasone-induced toxicity (defined as Grade 3 toxicity in the CTCAE v3.0 until December 31, 2010 and in CTCAE v4.0 beginning January 1, 2011 felt to be caused by dexamethasone) may have their doses altered to a single 8 mg intravenously dose of dexamethasone prior to docetaxel administration.

In the event of a hypersensitivity reaction, infusion times may be longer. Hypersensitivity reactions may be managed clinically according to PI discretion. Please see **Appendix H** for suggested management guidelines (optional).

5.2.2 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 ± 10 minutes. If the first infusion is tolerated without infusion-associated adverse events (fevers and/or chills), the second infusion maybe delivered over 60 ± 10 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions maybe delivered over 30 ± 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 pre-medicated for the next bevacizumab infusion.

5.2.3 Lenalidomide Administration

A two dose level escalation of lenalidomide, from 15 mg to 20mg to 25 mg once daily administered for 14 days every 21 days, will be evaluated at the beginning of the study. The first 3 patients will receive lenalidomide 15 mg orally. If none of the 3 patients develops an unacceptable toxicity in the first cycle that is felt to be probably or definitely related to lenalidomide and not the other agents (≥Grade 3 non-hematologic toxicity), next three patients will receive lenalidomide at 20 mg once daily. If none of the 3 patients develops an unacceptable toxicity in the first cycle that is felt to be probably or definitely related to lenalidomide and not the other agents (≥Grade 3 non-

hematologic toxicity), next three patients will receive lenalidomide at 25 mg once daily. However, if 1 of the 3 patients at 15 mg or 20mg level of lenalidomide has an unacceptable toxicity, then 3 more patients will be treated at 15 mg or 20mg. Dose escalation to 25 mg of lenalidomide would occur only if 1 of the 6 patients has an unacceptable lenalidomide-related toxicity. Dose escalation would be halted if ≥2 of the 6 patients develop unacceptable toxicity related to lenalidomide, and the lenalidomide's dosing for continuation of the study will be evaluated at 10 mg once daily for its suitability for combination. In general, the dose selected for combination will be the maximum dose at which no more than 1/6 has unacceptable toxicity.

Patients treated with lenalidomide at 25 mg once daily will follow the same rules as discussed above. Three to six patients will be evaluated at 25 mg of lenalidomide, depending on the incidence of unacceptable toxicity in the first three patients treated. Once the 25 mg dosing of lenalidomide or other doses safe for the combination is determined, future patients will all start at that dose level and continue it while being on study. Patients will continue their initial starting dose throughout the study.

Patients in the expansion cohort will receive a lower dose of lenalidomide (15 mg) and will follow the same rules as discussed above. Up to eleven patients may be evaluated at the 15 mg dose of lenalidomide.

5.2.4 Prednisone Administration

Patients will receive their first dose of prednisone orally on day 1 (10 mg/day), administered at 5 mg twice daily, and will continue this dosing throughout the cycle.

5.2.5 Other treatments required

Enoxaparin will be administered subcutaneously once daily while on lenalidomide. If lenalidomide is discontinued, enoxaparin will be continued for 7 days after its cessation, then enoxaparin will be discontinued. Dosing of enoxaparin will be guided by the table below:

Weight (kg)	Enoxaparin Dose
<55	40mg subcut once daily
55 – 75	60mg subcut once daily
>75	80mg subcut once daily

Patients will receive pegfilgrastim at a dose of 6mg subcutaneously on day 2 of each cycle at least 24 hours after the administration of docetaxel.

5.2.6 Self-administered medications

Patients will be provided with a medication checklist (see **Appendix B**) as well as a medication instruction sheet (see **Appendix C**) to assist in keeping track of self –administered medications.

5.3 TREATMENT MODIFICATIONS

The following adjustments will only apply if the toxicities reported are attributed by the investigators to be at least possibly related to docetaxel, bevacizumab, or lenalidomide. Dose delay and dose reduction will be according to the following rules:

5.3.1 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 toxicity 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 grade 3 or higher 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. Additionally, for grade 4 neutropenia lasting greater than or equal to 5 days, docetaxel can be continued at a dosage decreased by 25% during future cycles.

5.3.2 Docetaxel Dose Modifications for Neutropenia without Fever:

When Neutrophils fall to	**for a Duration of**	**Recommended Course**
<1000 but ≥ 500/mcL (Grade 3)	Any length of time	No dose reduction for future cycles.
<500/mcL (Grade 4)	< 5 days	No dose reduction for future cycles.
<500/mcL (Grade 4)	≥ 5 days	Dose reduce DOCETAXEL 25% for future cycles.

For grade 3 constipation or fatigue, treatment can resume with a 25% dose reduction after resolution of toxicity to ≤ grade 2. For other grade 3 toxicities felt to be related to both lenalidomide and docetaxel consideration will be given to possibly reducing or holding both agents. 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 lenalidomide; 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 that lead to withholding docetaxel temporarily, lenalidomide and bevacizumab may be withheld along with docetaxel at the discretion of the investigators for the best interest and safety of patients. However, prednisone and Lovenox should not be interrupted.

Patients should potentially discontinue Docetaxel if a grade 3 or 4 toxicity considered probably or likely related to docetaxel persists for ≥ 21 days. The other agents may continue

5.3.3 Dose modifications for bevacizumab

5.3.3.1 Dose Modifications/Delays guidelines

Note: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below.

Note 2: If bevacizumab is interrupted for ANY reasons for > 8 weeks, the patient should discontinue bevacizumab therapy on protocol.

5.3.3.2 Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE.v3.0 Grade	Action to be Taken
Allergic reactions, **or** **Acute infusion reactions/ cytokine release syndrome**	Grade 1-3	Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) should discontinue bevacizumab. For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.
	Grade 4	Discontinue bevacizumab
Arterial Thrombosis - Cardiac ischemia/ infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Venous Thrombosis		
	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, 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 during full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: – 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 on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension*	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1	Consider increased BP monitoring
	Controlled BP	Continue bevacizumab
	Persistent or symptomatic HTN	Hold bevacizumab. If treatment is delayed for >4 weeks due to uncontrolled hypertension, discontinue bevacizumab.
	Grade 4	Discontinue bevacizumab.
Congestive Heart Failure	Grade 3 (symptomatic)	Discontinue bevacizumab

Event	CTCAE.v3.0 Grade	Action to be Taken
	Grade 4	Discontinue bevacizumab
Proteinuria	Proteinuria should be monitored by urinalysis	
	≥2+ on UA	Obtain 24 hour urine for total protein
	24 hour total protein is > 2 grams	Hold bevacizumab for one cycle.
	nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (CNS or pulmonary)	Grade 2-4	• Discontinue bevacizumab
Hemorrhage (other)	Grade 3 (non-CNS or non-pulmonary) G1 (CNS or pulmonary)	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome)		• **Discontinue bevacizumab upon diagnosis of RPLS.**
Wound dehiscence requiring medical or surgical intervention		•**Discontinue bevacizumab**
Perforation (GI, or any other organ)		Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab
Bowel obstruction	G2 requiring medical intervention	• Hold bevacizumab until complete resolution
	G3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to ≤ grade 1 and unlikely to recur with retreatment.

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

Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice.

Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

If bevacizumab is held or discontinued due to toxicity, patients should continue the rest of the regimen provided that patients have no toxicities that require dose interruption or dose modification of other agents of the regimen. For potentially overlapping toxicities between bevacizumab and lenalidomide, both agents should be discontinued or dose modified.

Patients should be assessed clinically for toxicity prior to, during, and after each infusion. If severe bevacizumab-related toxicity, such as visceral perforation, aortic dissection, or nephritic syndrome, occurs at any time during the study, treatment with bevacizumab should be discontinued.

In general, bevacizumab will be withheld or discontinued for its related toxicities, but not dose-reduced.

*5.3.4 **Dose modification for lenalidomide***

Doses may be reduced by 5 mg at a time, to alleviate adverse reactions quickly, with slow escalation back to upper limit of tolerability. Patients with CrCl <50ml/min will be dose reduced by 5mg daily. If not rapidly corrected, or lasts longer than 1 week, dose reduce by 50%. Patients with CrCl < 30ml/min, not corrected within 1 week, will be taken off treatment, and dialysis initiated. Patients with a grade 3 or 4 non-hematological toxicity felt to be caused by lenalidomide will have lenalidomide withheld. Lenalidomide can be resumed with a dose reduction of 5 mg when the toxicity returns to the patients' baseline or becomes ≤ grade 1. Lenalidomide should be discontinued if patients continue to experience the toxicity after two times of reduction. If Grade 2 or 3 rash occurs, patients should undergo appropriate clinical evaluation before resuming lenalidomide.

Dose modifications for lenalidomide that occur as a result of venous thrombosis are as follows:

CTCAE Grade	Action to be Taken
Grade 3 or asymptomatic/minimally symptomatic Grade 4	• Hold lenalidomide treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, lenalidomide should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is > 2 weeks, lenalidomide may be resumed 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)

CTCAE Grade	Action to be Taken
	○ 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 lenalidomide ○ If thromboemboli worsen/recur upon resumption of study therapy, discontinue lenalidomide • Placeholder
Grade 4 Symptomatic	Discontinue lenalidomide

For dose-limiting toxicities related to lenalidomide, it should be noted that docetaxel and bevacizumab should not be interrupted.

For patients who experience grade 4 neutropenia lasting <3 days, lenalidomide will be held until ANC ≥1000 then may be re-started without any dose reduction. For grade 4 neutropenia lasting greater than or equal to 3 days, once ANC ≥1000 lenalidomide may be re-started with a 5mg dose reduction.

For febrile neutropenia developed within a prior cycle and resolved before next cycle, lenalidomide can be continued at a dosage decreased by 5 mg during future cycles

For grade 3 toxicities felt to be related to both lenalidomide and docetaxel consideration will be given to possibly reducing or holding both agents.

Dose modification guidelines, as summarized below are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia judged to be related to lenalidomide.

Lenalidomide Dose Modifications for Thrombocytopenia:

When Platelets	**Recommended Course**
Fall to <50,000/mcL Return to ≥50,000/mcL	Interrupt LENALIDOMIDE treatment, follow CBC weekly Restart LENALIDOMIDE at 15 mg daily
For each subsequent drop <50,000/mcL Return to ≥50,000/mcL	Interrupt LENALIDOMIDE treatment Resume LENALIDOMIDE at 5 mg less than the previous dose. Do not dose below 5 mg daily

Lenalidomide Dose Modifications for Neutropenia without Fever:

When Neutrophils fall to	**for a Duration of**	**Recommended Course**
<500/mcL (Grade 4)	< 3 days	Hold LENALIDOMIDE until ANC≥1000 then restart without dose reduction.

When Neutrophils fall to	for a Duration of	Recommended Course
<500/mcL (Grade 4)	≥ 3 days	Hold LENALIDOMIDE until ANC≥1000 then restart with a 5mg dose reduction.
<1000/mcL but ≥ 500 (Grade 3)	Any length of time	Hold LENALIDOMIDE until ANC≥1000 then restart without dose reduction.

The dose of lenalidomide will not be reduced below 5mg daily.

5.3.5 Other modifications

- As this trial allows patients to receive treatment indefinitely, patients may have the doses of any or all drugs (docetaxel, bevacizumab, lenalidomide and prednisone) withheld temporarily for resolution of toxicities or taking drug holidays, and potentially resume treatment as long as they do not fulfill the off-study criteria outlined in section **5.10**.
- Although the treatment is planned every 21 days (42 days if on prednisone only after 2 years) as a cycle, patients may have their treatments administered and their clinical/radiographic evaluation about or after the end of each cycle 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 violations of the protocol. Each patient's treatment plan will be reviewed annually in order to determine continuing clinical benefit.
- Patients who develop ≥Grade 3 thrombosis will receive appropriate medical care and will continue on docetaxel and prednisone. Dose modifications for bevacizumab and lenalidomide are outlined elsewhere in this protocol. This reflects from the prior mentioned trials with docetaxel/ lenalidomide versus docetaxel alone in a similar patient population, where those patients in the docetaxel alone arm had no episodes of thrombosis
- There will be no dose modification of study medications for lymphopenia of any grade.

5.4 PROTOCOL EVALUATION

All Patients will be evaluated for toxicities and efficacy after enrollment

5.4.1 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 about every 3 weeks by a physician in the NCI outpatient clinic (weight and ECOG performance status should be included in the database). Patients remaining on-study for at least 2 years and who are being treated with prednisone only, may have follow-up evaluations performed on Day 42 (every 6 weeks) at the physician's discretion.

5.4.2 Dental Evaluations

Follow-up dental evaluations will be performed following cycle five of protocol therapy and then following every other re-staging visit. Specifically, follow-up dental evaluations will occur post cycle 5, then post cycle 11 and then post cycle 17. Additional dental examinations will be performed once per year as long as patient is on study. Tests during these evaluations might include:

5.4.2.1 Oral fluid collection

In order to study the local changes associated with the potential development of bisphosphonate related osteonecrosis of the jaws (BRONJ), saliva and other oral fluids, such as gingival crevicular fluid (GCF) and plaque samples, may be taken at an initial dental visit and at follow-up dental visits. Collection procedures are non-invasive and non-painful, without the potential for harm beyond that of a standard dental examination.

5.4.2.2 Oral Microbiome

Bacterial samples may be collected from multiple sites in the oral cavity, by scraping the gingival tissue around teeth using a dental instrument. Initial microbial profiling will be performed with the Human Oral Microbe Identification Microarray (HOMIM), which allows for the simultaneous detection of about 300 of the most prevalent oral bacterial species, including those that are uncultivable. The oral microbiome could be compared both longitudinally and across groups (those developing BRONJ and those not). Future studies may involve culturing of select species and deep sequencing of oral bacteria.

5.4.2.3 Protein Assays

Evaluation of host defense molecules and collagen and bone metabolism proteins could be performed with whole saliva or targeted salivary gland saliva or GCF. Levels of such biomarkers will be measured in the oral fluids of patients, and could be compared both longitudinally and across groups (those developing BRONJ and those not). In parallel *in vitro* assays may interrogate the changes involved in BRONJ pathology.

5.4.3 Laboratory Evaluation

hematological profile (weekly) – if lenalidomide and docetaxel are held during a cycle or for continuous cycles for reasons unrelated to treatment toxicity, weekly blood work is not necessary; PSA (every cycle); acute care panel (every cycle), including hepatic panel and LDH; mineral panel (calcium, phosphorus, albumin, magnesium) every cycle; urinalysis (every cycle). For a patient found to have verified 2+ or greater proteinuria on urinalysis, a 24-hour urine collection will be collected to assess the total protein. Patients remaining on-study for at least 2 years and who are being treated with prednisone only, may have follow-up evaluations performed on Day 42 (every 6 weeks) at the physician's discretion.

5.4.4 Radiographic Evaluation

CT scan and bone scan will be performed 2 cycles after start of the study and then every 3 cycles thereafter. For patients whose initial CT scan shows no soft tissue disease, subsequent CT scans will not be required unless clinically indicated. Patients remaining on-study after two years will have CT and bone scans performed only if there are signs of clinical progression at physician's discretion.

5.5 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. No concurrent medications will be recorded in the database captured except those designated in the protocol (lovenox, prednisone, decadron, pegfilgrastim).

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

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

Patients who need or continue treatment with zoledronic acid should have a dental evaluation to ensure it is appropriate to initiate the treatment. Patients should avoid dental procedures or notify the research team as early as possible for planning.

5.6 SURGICAL GUIDELINES

There are no specific guidelines for this protocol; however, additional precautions should be exercised regarding elective surgery during treatment with bevacizumab. Warning of possible wound healing delays, and increased bleeding risk may occur in patients that must undergo surgery during the study. Bevacizumab should be held at least 4 weeks prior to surgery.

5.7 RADIATION THERAPY GUIDELINES

There are no radiation therapy guidelines in this protocol. However, patients whose disease needs radiation therapy will be taken off the study.

5.8 OFF-TREATMENT CRITERIA

- Disease progression as evidenced by radiographic (defined in section **11**) or clinical progression. Clinical disease progression is defined as
  - 1) Worsening disease requiring intervention with radiation therapy or additional chemotherapy
  - 2) Worsening performance status preventing patients from tolerating the treatment.
  - Bone lesions progression as defined in Section **11**
  - Soft tissue and visceral lesions will be measured for progression based on RECIST criteria.
- 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 the treatment regimen
- Unacceptable toxicities will be used as off-study criteria defined as a grade 3 or 4 toxicity that is probably or likely related to protocol therapy that persists for ≥ 21 days.

5.9 POST TREATMENT EVALUATION

Once the patient is no longer receiving treatment (as per section **5.8**) he may receive follow-up calls as well as medical evaluations to monitor his well-being and progress. For patients who are taken off treatment due to treatment toxicities, a follow up evaluation will be conducted within a month and if appropriate, the subject will be taken off study. The phone calls and medical evaluations will likely be annual though no specific guidelines shall be set.

5.10 OFF-STUDY CRITERIA

The patient will be considered off study upon either patient's death or patient's decision to no longer participate in the study or post treatment follow-up.

5.11 OFF-STUDY PROCEDURES

Off-Study Procedure: Authorized staff must notify Central Registration Office (CRO) when a patient 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>.

Unacceptable toxicities that have not resolved at time of "off treatment" or "off study" must be followed until stabilization or resolution.

6 SUPPORTIVE CARE

Anti-emetic treatment and secondary prophylaxis may be given as needed. Agent-specific expected adverse events are listed in Section **7.2**. The supportive treatment plan for the important adverse events is discussed in detail in Section **5**. Pegfilgrastim 6 mg will be administrated subcutaneously 24 hours post-docetaxel infusion as described in section **5.2.5**. 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) or platelets will be allowed as clinically required.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for AE reporting until December 31, 2010. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0 and CTCAE version 4.0. A copy of the CTCAE version 3.0 and CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). Dose limiting toxicity is defined in section **5.2**.

All new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment and should be referred to as second/secondary malignancies. All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and *in situ* tumors.

Using CTCAE v4.0, the event(s) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy; (2) Myelodysplastic syndrome; (3) Treatment-related secondary malignancy; or (4) Neoplasm other, malignant (grade 3 or 4).

These events should be reported for the duration of the study treatment and during any protocol-specified follow-up periods.

As specified above, CTEP-AERS reports for these events should be submitted regardless of attribution. The distinction between secondary and second or new primary malignancies is difficult to make based on a single event. Whenever possible, the CTEP-AERS report should include the following: tumor pathology; history of prior tumors; prior treatment/current treatment including duration; any associated risk factors or evidence regarding how long the tumor may have been present; when and how the tumor was detected; molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor; and tumor treatment and outcome, if available.

7.1 DEFINITIONS

7.1.1 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. Only Grade 2 AE's and higher will be recorded on the AE case report form with the exception of Grade 1 Osteonecrosis of the jaw. [Exception: Grade 1 and Grade 2 laboratory abnormalities will not be recorded as adverse events unless considered clinically significant by the investigators, e.g., Grade 2 increase in creatinine should be clinically important, whereas Grade 2 hepatic transaminase may not be.]

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 sections **7.4**, **7.6**.

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.

7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 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.

7.1.6 Disability

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

7.1.7 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.

7.1.8 Protocol Deviation (NIH Definition)

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

7.1.9 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.

7.1.10 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 g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST

The Comprehensive Adverse Events and Potential Risks (CAEPR) list provides a single, complete list of reported and/or potential adverse events associated with an agent, using a uniform presentation of events by body system.

Below is the CTEP-provided CAEPR about lenalidomide.

7.2.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4081 patients.* Below is the CAEPR for lenalidomide (CC-5013).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, December 24, 2015[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Myocardial infarction[2]	
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 3)***
GASTROINTESTINAL DISORDERS			
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 3)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
		Immune system disorders - Other (graft vs. host disease)[3]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection (Gr 3)[4]***
INVESTIGATIONS			
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
Platelet count decreased			***Platelet count decreased (Gr 3)***

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Musculoskeletal and connective tissue disorders - Other (muscle cramp/muscle spasm)		***Musculoskeletal and connective tissue disorders - Other (Muscle cramp/muscle spasm) (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy[5]	
		Myelodysplastic syndrome[5]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[6]	
		Treatment related secondary malignancy[5]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
		Stroke[2]	
		Leukoencephalopathy	
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
SURGICAL AND MEDICAL PROCEDURES			
		Surgical and medical procedures - Other (impaired stem cell mobilization)[7]	
VASCULAR DISORDERS			
	Thromboembolic event[8]		***Thromboembolic event[8] (Gr 2)***

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

[2]Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3]Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5]There has been an increased frequency of secondary malignancies (including AML/MDS) in multiple myeloma patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant.

[6]Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[7]A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[8]Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[9]Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[10]Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[11]Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Adverse events reported on Lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (eosinophilia); Blood and lymphatic system disorders - Other (monocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Spleen disorder
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Cushingoid; Hyperthyroidism
EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Flashing lights; Retinopathy
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Anal mucositis; Ascites; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[9]; Gastrointestinal obstruction[10]; Ileus; Mucositis oral; Rectal mucositis; Small intestinal mucositis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - General disorders and administration site conditions - Other (edema NOS); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis
IMMUNE SYSTEM DISORDERS - Allergic reaction; Immune system disorders - Other (angioedema)
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=grade 2 lymphopenia)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Hip fracture; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis); Neck pain; Osteonecrosis of jaw[11]; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Myelitis; Nervous system disorders - Other (hyporeflexia); Nervous system disorders - Other (spinal cord compression); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Psychosis
RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's syndrome); Urticaria
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

Note: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the

Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, May 23, 2016[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome[2]	
	Cardiac disorders - Other (supraventricular arrhythmias)[3]		***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)***
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[2]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fasciitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular[2]	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hematuria		***Hematuria (Gr 3)***
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (nephrotic syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[15]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Vascular disorders - Other (arterial thromboembolic event)[2,16]	

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

[2]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[3]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11]There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

[12]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[13]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[14]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[15]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[16]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Adverse events reported on bevacizumab (rhuMAb VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMAb VEGF) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT

increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

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

7.3 EXPEDITED ADVERSE EVENT REPORTING

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below.

7.4 EXPEDITED REPORTING GUIDELINES

CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of the Investigational Agent on Phase 2 Trials

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

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
AdEERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

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

December 15, 2004

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.
- Pregnancy
  - If a female partner of a male subject taking investigational product

becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

7.5 ROUTINE ADVERSE EVENT REPORTING

- Adverse Events that do not require expedited reporting must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

7.6 NCI-IRB AND NCI CLINICAL DIRECTOR REPORTING REQUIREMENTS

7.6.1 NCI-IRB and NCI Clinical Director 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 Violations or Deviations
- All Unanticipated Problems
- All non-compliance

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

7.6.2 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.

7.6.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

8 PHARMACEUTICAL INFORMATION

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

8.1.1 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

8.1.2 Availability

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

8.1.3 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.

8.1.4 Preparation

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

- Preparing the "INITIAL DILUTED SOLUTION" (10 mg docetaxel/mL)[41]

[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 dissipates 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"[41]

[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[41]; 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]).

8.1.5 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.[41]

8.1.6 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.

8.1.7 Dosage and Administration

Premedication

All patients will receive dexamethasone 8 mg po 12 hours, 3 hours and 1 hour prior to docetaxel administration to reduce the incidence and severity of fluid retention and the severity of hypersensitivity reactions. Patients who were on prior regimen which included a lower dose of decadron and did not have a reaction do not have to increase their decadron to the 8 mg dose.

8.1.8 Administration

Docetaxel 75 mg/m2 will be administered as an intravenous infusion over one hour on scheduled days per section **5.2.1**.

8.1.9 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.

8.1.10 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.

8.2 LENALIDOMIDE

(Celgene Corporation, Warren, NJ) CC-5013 (NSC 703813)

NOTE:

Before lenalidomide is dispensed, patients must have 1) a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form in the protocol). The counseling requirements for investigational-use lenalidomide are separate from the RevAssist program. Only a 28-day supply may be dispensed to a patient at one time.

8.2.1 Chemical Name

3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione; α-(3-aminothalamido) glucaride.

Other Names: Lenalidomide, Revlimid™ (formerly known as Revlimid™), CDC-501

Classification: Immunomodulatory Agent

CAS Registry Number: 191732-72-6

Molecular Formula: $C_{13}H_{13}N_3O_3$ M.W.: 259.26

Mode of Action: CC-5013, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is not fully characterized. In vitro, it inhibits secretion of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 and increases secretion of the anti-inflammatory cytokine IL-10. It also induces T-cell proliferation, IL-2 and IFN-γ production in vitro.

8.2.2 How Supplied

Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 5 mg (size 2) and 25 mg (size 0) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles contain 100 capsules per container.

The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

8.2.3 Storage

The capsules should be stored at room temperature (15-30°C) away from moisture and direct sunlight.

8.2.4 Stability

Refer to the package labeling for expiration date. Lenalidomide stability is adequate for at least 28 days after transferring to a pharmacy vial.

8.2.5 Route of Administration

Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

8.2.6 Potential Drug Interactions

Periodic monitoring of digoxin levels is recommended during co administration with CC-5013. Digoxin levels were slightly higher when digoxin was administered with CC-5013 in a clinical study. There was no effect on CC-5013 pharmacokinetics. Warfarin and CC-5013 may be co-administered without additional monitoring. No pharmacokinetic or pharmacodynamic interactions were observed between CC-5013 and warfarin.

Nonclinical in vitro metabolism studies suggest that CC-5013 is not likely to result in metabolic drug interactions in humans. In vitro, CC-5013 did not significantly inhibit marker enzyme activities for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. In rats, no induction of any CYP450 enzymes was observed. Administration of CC-5013 in monkeys showed no effects on the activities of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A, or CYP4A.

8.2.7 Agent Ordering

Lenalidomide (CC-5013, NSC 703813) may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of

Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of "active" account status and a "current" password. For questions about drug orders, transfers, returns or accountability, call 240 276 6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.2.8 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

8.2.9 Dispensing

Only a 28-day supply may be dispensed at one time. Sites may not mail lenalidomide to patients.

8.2.10 Patient Care Implications and Counseling

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Before starting study drug:

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Counseling

- In investigational studies where lenalidomide is supplied by the NCI, patients will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of subjects (investigators cannot counsel patients as part of this requirement). Refer to specific protocol sections for more information about training requirements.

Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Lenalidomide Education and Counseling Guidance Document (**Appendix F**) and no drug will be dispensed until this step occurs. Counseling includes verification with the female patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (**Appendix G**) will be supplied with each medication dispense.

8.3 PREDNISONE

8.3.1 Chemical formula

17a, 32-Dihydroxy-1,4-pregnadiene- 3,11,20-trione

$C_{21}H_{26}O_5$, Molecular weight of 358.4

Classification: Glucocoticorticoids

8.3.2 Mechanism of Action

Multiple mechanisms leading to anti-inflammatory and immune suppression outcomes

8.3.3 How supplied

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

8.3.4 Storage

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

8.3.5 Stability

Prednisone tablets are stable for three years from date of manufacture

8.3.6 Route of administration

Oral

8.3.7 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.

8.3.8 Availability

Prednisone will be obtained from commercial stock purchased by the NIH CC Pharmacy Department. See package insert for further information.

8.4 BEVACIZUMAB

(Avastin – Genentech BioOncology, South San Francisco, CA)

8.4.1 Chemical name and identification

Recombinant humanized monoclonal anti-VEGF antibody (rhuMAB VEGF)

Classification: Recombinant humanized monoclonal antibody

8.4.2 Mechanism of Action

Inhibition of vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis.

8.4.3 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.

8.4.4 How Supplied

Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid for parenteral administration. Each 400 mg (25mg/ml – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

8.4.5 Agent Ordering

Bevacizumab (NSC 704865) may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of "active" account status and a "current" password. For questions about drug orders, transfers, returns or accountability, call 240 276 6575 Monday

through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.4.6 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

8.4.7 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.

8.4.8 Storage

Bevacizumab must be stored under refrigeration at 2°–8°C (36°–46°F) upon receipt and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

8.4.9 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]

8.4.10 Route of Administration

Intravenous

8.4.11 Reported Adverse Events and Potential Risks

See Section 7.2

8.4.12 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.

8.5 PEGFILGRASTIM

(Neulasta™, Amgen Inc., Thousand Oaks, CA)

8.5.1 Chemical Name and Identification

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

Average molecular weight: ~ 39 kiloDaltons

8.5.2 Classification

Colony stimulating factors acting on hematopoietic cells

8.5.3 Mechanism of Action

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

8.5.4 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

8.5.5 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.

8.5.6 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.

8.5.7 Route of Administration

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

8.5.8 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 CORRELATIVE STUDIES (MANDATORY FOR STUDY PARTICIPANTS)

Proposed correlative studies follow. Other studies may be performed as further data is developed both within the study and from other investigators.

As stipulated in the informed protocol consent, the following correlative studies are mandatory and include:

9.1 GENOTYPING OF PATIENTS

Single nucleotide polymorphisms (SNPs) in genes that play an important role in elimination pathways for docetaxel and lenalidomide will be evaluated. For this purpose, one 10ml EDTA lavender top tube (BD366643) will be obtained when the patient enters onto the study. In addition, urine samples will be collected. DNA will be isolated only for the purpose of genotype analysis of enzymes with putative relevance for docetaxel or lenalidomide disposition. The genotyping will be performed on a research basis in the Molecular Pharmacology Program (Bldg. 10 Room 5A01; William Figg, Pharm D.). (See Sample Processing and Storage under Section **9.3** Angiogenesis Markers for labeling and storage of samples in Dr. Figg's lab.)

Based on the findings of this analysis of docetaxel/lenalidomide metabolism it may be possible to identify certain patients as likely responder or unlikely responders. This may have ramifications in the treatment of future patients.

9.2 CELLULAR ANALYSIS

9.2.1 Analysis of circulating endothelial cells (CEC) and circulating endothelial progenitor cells (CEP)

For this analysis, peripheral blood is drawn into 3 CPT citrate (blue/black tiger top) tubes. Mononuclear cells are isolated by centrifugation. Approximately 2 cc of plasma is removed and stored (see Immune Correlates below). Mononuclear cells are washed with PBS, and FcR solution (Miltenyi) is added to block non-specific binding. following centrifugation and stored at For identification of CECs and CEPs, cells are stained with FITC- conjugated anti-CD31 (BD), PerCP-conjugated anti-CD45 (BD), APC-conjugated anti-CD133 (Miltenyi) and PE-conjugated CD146 (Chemicon) for 30 min on ice. For isotype controls, cells are incubated with FITC-conjugated IgG1, PerCP-conjugated IgG1, APC-conjugated IgG1 and PE-conjugated IgG1. After washing

with 0.1% BSA in PBS, the cells are incubated with Hoechst 33258 dye as an indicator of cell viability and analyzed by multiparametric flow cytometry on an LSR II flow cytometer (BD Biosciences), using LSR II-equipped digital data acquisition and FlowJo cytometric data analysis software. The CEC and CEP cell concentrations are calculated as a percentage of the total number of mononuclear cells or as the number of cells/microliter of whole blood after an evaluation of a minimum of 10^5 cellular events, and preferable 10^6 cellular events. CEC cells are defined by the co-expression, or absence of expression on a single cell of the following parameters: CD45-, CD31+, CD133- and CD146+, Hoechst 33258- (viable CEC) or CD45-, CD31+, CD133- and CD146+, Hoechst 33258+ (nonviable CEC). CEP cells are defined by the co-expression, or absence of expression on a single cell of the following parameters: CD45- or dim, CD31+, CD133+ and CD146-, Hoechst 33258- (viable CEP) or CD45- or dim, CD31+, CD133+ and CD146-, Hoechst 33258+ (nonviable CEP). CEC and CEP markers may be modified or expanded in response to new studies in this rapidly developing field.

The assays will be performed by Dr. Min-Jung Lee and Dr. Yeong Sang Kim in Jane Trepel's laboratory in the Medical Oncology Branch, Building 10, Room 12N218.

Samples will be obtained prior to the initiation of treatment (C1D1 pre), prior to administration of the cycle two dose (C2D1 pre-dose), prior to administration of the cycle three dose (C3D1 pre-dose) and prior to administration of the cycle six dose (C6D1 pre-dose). If a pre-treatment (C1D1 pre) sample was unable to be collected, cycle 2, 3 and 6 samples will not be drawn. The outcome measures will be the number of CEC and CEP per 10^6 mononuclear cells or per microliter of peripheral blood, analyzed in samples taken before and after treatment. These numbers will then be examined for correlations with various parameters to assess their potential utility as surrogate biomarkers for drug activity, for establishing the optimal biologic dose, for patient stratification, and monitoring of therapy-related side effects.

Modulation of immune parameters will be explored using the samples above. Immune cell subsets including NK and NKTlevel will be determined by multiparameter flow cytometry. Approximately 1 cc of plasma is removed and stored. Depending on cell-based assay results cytokine and angiogenic factor modulation, including the Th1 cytokine interferon-gamma and IL-2 may be examined by technology appropriate to the sample such as Luminex or Molecular Diagnostics chips...

Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers. Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate protocol number, order in which the patient enrolled on the trial, type of sample, collection time, and total cell number/volume, as appropriate.

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, date of birth, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB. If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB.

9.3 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 Program, under the direction of Dr. Figg.

A Serum research sample (one 7ml red top (BD 366431) is to be drawn and kept at room temperature (RT) for 30 minutes and then placed in a 4 degree C refrigerator.

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044. 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) at baseline and at monthly clinic visit.

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

The inclusion of bevacizumab in this treatment regimen allows for the measurement of changes in VEGF levels. Such changes can then be evaluated in the context of the clinical response that is seen.

Sample Processing and Storage

Upon arrival in the Clinical Pharmacology Program (CPP), blood samples will be centrifuged for 5 minutes at 1200 x *g*, at 4°C. The serum will be transferred into two cryovials and immediately frozen. Serum samples will be stored at -80°C until the time of analysis. Urine samples will be transferred to 50ml conical tubes and stored at -20°C.

All samples will be bar-coded, with data entered and stored in the Patient Sample Data Management System (PSDMS) (a.k.a. Labrador) utilized by the CPP. This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. The program creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number; time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Bar-coded samples are stored in bar-coded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the PSDMS. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

9.4 TIME EFFICIENT AUTOMATIC LESION IDENTIFICATION AND MEASUREMENT ON CT

Metastatic tumor burden and treatment response is commonly evaluated on serial CT scans with subjective target lesion selection and measurement on baseline and post-treatment exams (RECIST). Subjective measurement error has been studied showing false categorization of partial response based on two measurements of the same lesion[42]. Semi-automated RECIST measurements of malignant lymph nodes produce reliable results when compared to manual measurements[43]. It is generally believed that assessment on thin section data on the most tumors possible[44] would be the optimal approach to assessing response to therapy. However, with manual protocols, the detection and measurement of additional lesions compounds the total time investment in the evaluation that has been rarely feasible. Various software programs have recently been developed to address this deficiency.

We aim to assess time savings of semi-automated lesion localization and measurement on serial images of metastatic cancer patients as compared to the current manual process. The automated software that will be used is available in the PACS (Picture Archiving and Communications System) at NIH provided by Carestream Health (Rochester, NY) and called the Lesion Management Application (LMA). The application has advanced serial image co-registration as well as refined registration for lesion identification (based on original exam). The program semi-automatically segments and measures the lesion targeted by the radiologist on baseline CT, then automatically localizes and measures the lesion on the subsequent exam. Preliminary results demonstrate that target lesions can be identified, segmented, and measured (including RECIST *and* volume) in most cases. Routine inclusion of tumor measurements should greatly assist providers in quickly evaluating the efficacy of cancer therapies. Tumor evaluation by volume determination on serial CT studies can be enhanced and made more effective by semi-automated detection of previously identified and measured target lesions.

We will retrospectively assess CT scans acquired for tumor response evaluations via automated volumetric measurements obtained using LMA. We will also assess the accuracy and consistency of target lesion localization, segmentation, and resultant measurements, to include volumes, on serial CT studies.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 15 days prior to administration of protocol therapy. Scans and x-rays must be performed ≤4 weeks prior to the first treatment. On study evaluations may be performed within ± 3 days of day indicated on calendar. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. For detailed dosing information including dose modifications and use of supportive treatments, please refer to Section **5**. All follow-up evaluations can be done on the last week of the prior cycle. Long term monitoring and evaluating of secondary primary malignancies will be done at least an annual basis until the study is complete.

	PreStudy	**Cycle 1**			**Cycle 2**			**Cycles ≥3**		**Study Drug Discontinuation**
Day	-15 to 0	1	2	3-21	1	2	3-21	1[j]	2-21	3-4 weeks from the last day of last cycle
Informed consent	X									
Medical history	X									
Concurrent meds	X	X			X			X		
Physical exam	X	X			X			X		
Vital signs	X	X			X			X		
Height	X									
Weight	X	X			X			X		
Perform. Status	X	X			X			X		
CBC w/diff, plts[a]	X	X		X[a]	X		X[a]	X	X[a]	
Serum chemistries [b]	X	X			X			X		
TSH	X									
Testosterone	X									
PSA	X	X			X			X		
Coagulation (PT/PTT)	X	X			X			X		
Urinalysis[c]	X	X			X			X		
EKG (as indicated)	X									
BP monitoring[d]	X	X			X			X		

	PreStudy	**Cycle 1**			**Cycle 2**			**Cycles ≥3**		**Study Drug Discontinuation**
Day	-15 to 0	1	2	3-21	1	2	3-21	1[j]	2-21	3-4 weeks from the last day of last cycle
Adverse event evaluation	X	X	X	X	X	X	X	X	X	
Education and counseling[i]		X			X			X		X
Correlative Studies [e]	X	X	X		X	X		X		
Radiologic Studiesf	X						X[e]		X[f,]	
Dental Exams[g]	X									
NIH Advanced Directives Form[k]	X									
Docetaxel (75 mg/m^2)		X			X			X		
*Bevacizumab(*15 mg/Kg)		X			X			X		
Lenalidomide(25 mg QD) [h])		X	X	Days 3-14	X	X	days 3-14	X	days 2-14	
Prednisone (5 mg BID)		X	X	X	X	X	X	X	X	
Enoxaparin (1 mg/kg QD)		X	X	X	X	X	X	X	X	
Pegfilgrastim (6mg SQ once)			X			X			X (day 2)	

	PreStudy	Cycle 1			Cycle 2			Cycles ≥3		Study Drug Discontinuation
Day	-15 to 0	1	2	3-21	1	2	3-21	1[j]	2-21	3-4 weeks from the last day of last cycle

a. Weekly except if lenalidomide and docetaxel have been held during a cycle or for continuous cycles for reasons unrelated to treatment toxicity. For weeks 2-3, results from other medical laboratories are accepted for monitoring.
b. Electrolytes including sodium, potassium, bicarbonate, chloride, magnesium, calcium, phosphate, BUN, creatinine, glucose, uric acid, LDH, total protein/albumin, hepatic transaminases, bilirubin, alkaline phosphatase.
c. If UA/dipstick protein ≥2, then obtain a 24 hour urine for total protein to assess (see Section **5.3**).
d. BP monitoring will be done weekly during cycle one and recorded onto study diary.
e. Refer to Section **9** for specific timings for different assays.
f. Staging scans will be performed after the first 2 cycles of treatment and then every three cycles. Patients that have been on study for at least 2 years may have scans performed only at the time of clinical progression at the physician's discretion.
g. Dental evaluations will be obtained for selected patients as time allows. Follow-up dental evaluations will occur post cycle 5, post cycle 11 and post cycle 17. Additional dental examinations will be performed once per year as long as the patient remains on study.
h. Lenalidomide will administered on days 1-14 during each cycle to the 3-6 patients at dose level of 15 to 20mg for run in phase then max dose of 25mg. Only enough lenalidomide for 28 days or one cycle of study treatment (whichever is shorter) may be provided to the patient each cycle. For the expansion cohort, lenalidomide will be administered 15 mg po for 14 days.
i. The Lenalidomide Education and Counseling Guidance Document (**Appendix F**) must be completed and signed by a trained counselor at the participating site prior to each dispensing of lenalidomide treatment. A copy of this document must be maintained in the patient records. The Lenalidomide Information Sheet (**Appendix G**) will be given to each patient receiving lenalidomide treatment. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.
j. Patients who have been on study for at least 2 years and who are being treated with prednisone only, may have clinical evaluations performed every 6 weeks at the physician's discretion.
k. As indicated in section **16.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

11 MEASUREMENT OF EFFECT

Patients will be evaluated as described in Section 5. For exploratory purpose, changes in PSA and measurable lesions will be analyzed for efficacy according to the PCWG2 recommendations [JCO 26: 1148-1159, 2008]. The recommended PSA progressions criteria will not be applied to the study as the criteria are arbitrarily proposed and do not necessarily reflect overall disease status. PSA values will be captured at each visit and PSA declines and progression will be follow. As documented in the previous ATTP trial, PSA is not sufficient in the evaluation of disease progression in this patient population. This is consistent with the recent recommendations by the Prostate Cancer Clinical Trials Working Group 2. (ref: Scher, HI et al. J Clin Onc. 26(7), 2008.) Progression will be determined by radiographic evidence as discussed below or by clinical symptoms (symptomatic clinical progression).

11.1 RESPONSE CRITERIA FOR RADIOGRAPHIC STUDIES

11.1.1 Measuring of Soft Tissue Disease

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions)

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

11.1.1.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

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

Non-CR/Non-PD (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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.1.3 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 criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

b. 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.

11.1.2 Confirmatory Measurement/Duration of Response

11.1.2.1 Confirmation

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

11.1.2.2 Duration of Overall Response

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

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

11.1.3 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 by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm

with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

11.1.4 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

11.1.5 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

11.1.6 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

11.1.7 Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.8 Metastatic Bone Lesions

Disease progression is considered if a minimum of two new lesions is observed on bone scan. New lesions seen by the end of cycle 2 or before cycle 3 (after the first staging bone scan) may represent

disease that was not detected on the pre-study scan, and a confirmatory scan will be required in next scheduled staging bone scan unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected. If new lesions are seen after cycle 2, but no additional lesions are seen on confirmatory scans, the scans from after cycle 2 would serve as the baseline scan to evaluate for disease progression, (ref: Scher, HI et al. J Clin Onc, 26 (7), 2008)

11.1.9 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.2 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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

11.3 METHODS OF MEASUREMENT

11.3.1 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.

11.3.2 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 5 mm in slice thickness for chest, abdomen and pelvis lesions and 2-3 mm thickness for head and neck lesions.

12 DATA REPORTING AND REGULATORY CONSIDERATIONS

12.1 RECORD KEEPING

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:

- The patient met all eligibility criteria
- Signed informed consent was obtained prior to treatment
- Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes)

- Toxicity was assessed according to protocol (laboratory report slips, etc)
- Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate)

Symptoms will be reviewed with the patient by the nurse or physician during each clinic visit for patient education and verification of medication administration, but the principal investigator toxicity documentation supersedes all other source documentation regarding adverse event reporting.

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.

12.2 DRUG ACCOUNTABILITY

The unused lenalidomide (partial bottles, empty bottles, and full bottles) will be returned for drug accountability at each clinic visit. 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. (http://home.ccr.cancer.gov/intra/clin_ops/policies/)

12.3 DATA REPORTING

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.

Reporting guidelines as delineated by CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) will be used for reporting adverse reactions and events. The C3D data management system will be used to capture data and report to the clinical data update system (CDUS). Cumulative CDUS data will be submitted electronically to CTEP, quarterly by January 31, April 30, July 31 and October 31. The instructions for such submission can also be found at the site http://ctep.info.nih.gov/reporting/cdus.html).

12.4 DATA AND SAFETY MONITORING PLAN

All adverse events including unexpected and/or SAE will be reviewed by the research team monthly. If trends of intolerance to the combination therapy and/or risks warrant it, accrual will be interrupted and/or the protocol and consent will be modified accordingly for study

subject's safety. For adverse events related to the non-IND agents that have not been reported previously, MedWatch reporting will be performed.

12.5 CTEP MULTICENTER GUIDELINES

The trial is a single center study.

13 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)/CLINICAL TRIALS AGREEMENT (CTA)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry http://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations) contained within the terms of award, apply to the use of the Agent(s) in this study:

Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):

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

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

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

Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI

Executive Plaza North, Suite 7111

Bethesda, Maryland 20892

FAX 301-402-1584

Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

14 STATISTICAL CONSIDERATIONS

The primary objectives of this trial are to identify a potentially safe dose of lenalidomide, to confirm that the drug does not have an excessively high rate of toxicity in a moderately large cohort of patients, and to evaluate the efficacy of the agent.

Initially, there will be a small dose escalation portion of the trial. Based on a standard 3 to 6 patient per cohort dose escalation, the first 3 patients would be treated at a 15 mg dose, and then the next cohort of 3 patients will be treated at 20 mg provided there are 0 of 3 patients with unacceptable toxicity at the 15 mg dose. If 1 of 3 patients has dose limiting toxicity at 15 mg, then 3 more patients will be enrolled at that dose. If 1 of 6 has unacceptable toxicity, then accrual would escalate to the 20 mg dose. If 1 of 3 patients has dose limiting toxicity at 20 mg, then 3 more patients will be enrolled at that dose. If 1 of 6 has unacceptable toxicity, then accrual would escalate to the 25 mg dose. Three to 6 patients will be tested at the 25 mg dose. The dose selected for evaluation will be the maximum dose at which 6 patients are treated and no more than 1/6 has dose limiting toxicity. Provided that 25 mg is determined to be an acceptable dose, with no more

than 1/6 with dose limiting toxicity at this level, we would carry out the main objectives of the trial at this dose level.

The first primary objective is to rule out a 25% rate of grade 4 non-hematologic toxicity attributable to the study at the 25 mg dose level of lenalidomide. With respect to the stopping rule, grade 4 hematologic toxicity will be only be considered if the episode lasts for greater than or equal to 5 days. Grade 4 lymphopenia of any duration will not be counted. If an early stopping rule is not invoked, we will plan to enroll a total of 45 evaluable patients at the 25 mg dose and score each patient for the development of any grade 4 toxicity as described above during any cycle. This cohort of 45 patients will include the 6 patients treated as part of the initial dose escalation phase. If we enroll 45 patients and if 8 or more have grade 4 toxicity as described above, then the probability that the true rate of grade 4 toxicity is 10% is 7.6% while the probability that the true rate of grade 4 toxicity is 25% is 90.6%. Thus, the appearance of 8 or more patients with grade 4 toxicity as defined above will provide evidence that the true rate of toxicity is consistent with 25%, and this will be considered excessive.

The 90% and 95% confidence intervals will be constructed around the observed fraction of patients with grade 4 toxicity as defined above, and will be reported along with the observed incidence. If 8/45 are noted to have toxicity, the exact two-sided 90% CI bound extends from 10.6% to 27%, thus confirming that this rate of toxicity exceeds 10% and is consistent with as high as 27%, thus confirming that this rate of toxicity exceeds 10% and is consistent with as high as 27%. As an early stopping rule for toxicity, if anytime within the first 18 patients have been enrolled, 7 patients are found to have grade 4 toxicity as defined above, no further patients will be enrolled as soon as this can be determined, since the lower 80% one-sided confidence bound around 7/18 is 27.3%, which being greater than 25% would be considered demonstration of excessive toxicity. In fact, the lower 80% bounds range from 79% for observing 7 patients with early toxicity in the first 7 patients to 27% for observing 7 patients with early toxicity in 18 patients.

Efficacy will also be evaluated with respect to progression free survival (PFS). PFS curves will be compared between the ATTP study and the present one, although with low power to detect a meaningful difference. In addition, an early stopping rule based on efficacy will be incorporated, as follows:

A recent analysis of progression free survival for the patients enrolled on the ATTP trial found that the 6 month PFS probability was 89%, the 9 month PFS was 81%, the 12 month PFS was 75% and the 18 month PFS was 54%. It would be important that the present study including lenalidomide would have PFS probabilities which are similar to those of the ATTP trial. After all 45 patients have been enrolled and 18 months have passed since the last patient was enrolled onto the trial, a Kaplan-Meier curve will be constructed, and the results will be compared to those of the ATTP trial using a two-tailed log-rank test. Significant differences between the two trials will not be expected (and the present trial may even yield superior results based on experience in other diseases) since the two trials use extremely similar treatment regimens, but the results will be determined and discussed in the context of the non-randomized comparison being made. Because in the ATTP trial at 6 months, the 89% PFS result had a corresponding lower two-sided 80% confidence bound (one-sided 90% bound) of 82%, it would be considered tolerable or better if the present trial is able to demonstrate a 6 month PFS that exceeds 82%.

To ensure that an unexpectedly poor treatment outcome is not obtained, an interim, early evaluation for PFS will be made. After 18 patients have been enrolled and the 18^{th} has been

potentially followed for progression for 6 months (that is, 6 months have passed since his on-study date), an interim Kaplan-Meier curve will be constructed. As noted above, in the ATTP trial at 6 months, the 89% PFS result had a corresponding lower two-sided 80% confidence bound (one-sided 90% bound) of 82%. If the actual observed PFS probability of the present trial based on 18 patients is below 82% at the 6 month time point, then the trial will no longer enroll further patients since this would suggest that the PFS distribution may be below the lower one-sided 90% confidence bound of the prior trial, which would indicate a potential for a substantially inferior outcome. By the time this determination is made, approximately 25 to 30 total patients may have been accrued; however, such inferiority is not expected, and the determination will be more imprecise if the evaluation was made earlier or based on accrual of fewer than 18 patients.

Secondary endpoints will be evaluated as follows. Survival will be determined using the Kaplan-Meier method. Changes from pre-treatment to post-treatment in levels of circulating prostate cancer and apoptotic endothelial cells, and of molecular markers of angiogenesis will be obtained and tested for whether they differ from zero, using a Wilcoxon signed rank test. The changes in these parameters may also be evaluated with respect to their possible association with PFS or overall survival using a Cox model.

The primary objective of the expansion cohort is to determine if the use of a lower dose of lenalidomide will result in an acceptably high proportion of patients exhibiting a clinical response. At the highest dose of lenalidomide, a very high response rate was noted, but a large fraction of patients required a dose reduction because of toxicity. Thus, it would be desirable if reasonable efficacy could be noted at a lower dose of lenalidomide.

This portion of the study will be conducted using a MinMax Two-Stage Phase II Trial Design[45] in order to explore whether we can rule out an unacceptably low 60% of patients who experience a clinical response (CR+PR; p0=0.60) in favor of a higher 90% who have a clinical response (p1=0.90). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), this portion of the study will initially enroll 10 evaluable patients (including 3 previously enrolled during the initial dose escalation phase) and if no more than 7 of the 10 have a clinical response, then no further patients will be accrued. If 8 or more of the first 10 have a response, then accrual would continue until a total of 14 patients have enrolled at the lower dose. As it may take up to 3-6 months to determine if a patient has experienced a clinical response, a temporary pause in the accrual to this portion of the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 8-10 patients with a clinical response in 14 patients, this would be an uninterestingly low response rate, while if there were 11 or more patients with a response in 14 patients, then this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (60% response rate), the probability of early termination is 83%.

It is expected that up to 45 patients receiving lenalidomide at 25mg daily will enroll onto this trial plus 6 to 12 patients required for the run-in phase with lenalidomide at 15mg and 20mg once daily and up to eleven patients in the expansion cohort. In order to allow for a small number of inevaluable patients, the accrual ceiling will be set at 70 patients. Approximately 2 patients can enroll on this trial per month, the trial is expected to be able to complete accrual within 2 to 3 years at the most. Aggressive accrual will be pursued with a goal of 36 patients enrolled per year. We are currently enrolled in discussion with Georgetown University's Lombardi Cancer Center about potentially enrolling patients there if accrual at the NIH does not meet goals.

15 ACCRUAL TARGET TABLES

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	n/a	+	3	=	3
Not Hispanic or Latino		+	67	=	67
Ethnic Category: Total of all subjects	(A1)	+	70 (B1)	=	70 (C1)
Racial Category					
American Indian or Alaskan Native	n/a	+	0	=	0
Asian		+	1	=	1
Black or African American		+	14	=	14
Native Hawaiian or other Pacific Islander		+	1	=	1
White		+	54	=	54
Racial Category: Total of all subjects	(A2)	+	70 (B2)	=	70 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate:	**2**	pts/month	**Total Expected**	**68**	Min	**70** Max

16 HUMAN SUBJECTS PROTECTIONS

16.1 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.

16.2 PARTICIPATION OF CHILDREN

Children will not be eligible for this protocol.

16.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **16.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and 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 in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

16.4 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 metastatic 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 **5.4**.

16.5 RISKS/BENEFITS ANALYSIS

For patients with castration resistant 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 section **7**.

16.6 CONSENT AND ASSENT 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 on 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 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.

17 REFERENCES

1. Hudes GR, Greenberg R, Krigel RL, et al. Phase II study of estramustine and vinblastine, two microtubule inhibitors, in hormone-refractory prostate cancer. *J Clin Oncol.* Nov 1992;10(11):1754-1761.

2. Hudes GR, Nathan F, Khater C, et al. Phase II trial of 96-hour paclitaxel plus oral estramustine phosphate in metastatic hormone-refractory prostate cancer. *J Clin Oncol.* Sep 1997;15(9):3156-3163.

3. Pienta KJ, Redman BG, Bandekar R, et al. A phase II trial of oral estramustine and oral etoposide in hormone refractory prostate cancer. *Urology.* Sep 1997;50(3):401-406; discussion 406-407.

4. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* Oct 7 2004;351(15):1513-1520.

5. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* Oct 7 2004;351(15):1502-1512.

6. Horwitz SB. Taxol (paclitaxel): mechanisms of action. *Ann Oncol.* 1994;5 Suppl 6:S3-6.

7. Berchem GJ, Bosseler M, Sugars LY, Voeller HJ, Zeitlin S, Gelmann EP. Androgens induce resistance to bcl-2-mediated apoptosis in LNCaP prostate cancer cells. *Cancer Res.* Feb 15 1995;55(4):735-738.

8. McDonnell TJ, Troncoso P, Brisbay SM, et al. Expression of the protooncogene bcl-2 in the prostate and its association with emergence of androgen-independent prostate cancer. *Cancer Res.* Dec 15 1992;52(24):6940-6944.

9. Haldar S, Chintapalli J, Croce CM. Taxol induces bcl-2 phosphorylation and death of prostate cancer cells. *Cancer Res.* Mar 15 1996;56(6):1253-1255.

10. Friedland D, Cohen J, Miller R, Jr., et al. A phase II trial of docetaxel (Taxotere) in hormone-refractory prostate cancer: correlation of antitumor effect to phosphorylation of Bcl-2. *Semin Oncol.* Oct 1999;26(5 Suppl 17):19-23.

11. Picus J, Schultz M. Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. *Semin Oncol.* Oct 1999;26(5 Suppl 17):14-18.

12. Sartor O, Weinberger M, Moore A, Li A, Figg WD. Effect of prednisone on prostate-specific antigen in patients with hormone-refractory prostate cancer. *Urology.* Aug 1998;52(2):252-256.

13. Stirling D. Thalidomide: a novel template for anticancer drugs. *Semin Oncol.* Dec 2001;28(6):602-606.

14. Bauer KS, Dixon SC, Figg WD. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. *Biochem Pharmacol.* Jun 1 1998;55(11):1827-1834.

15. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A.* Apr 26 1994;91(9):4082-4085.

16. Minchinton AI, Fryer KH, Wendt KR, Clow KA, Hayes MM. The effect of thalidomide on experimental tumors and metastases. *Anticancer Drugs.* May 1996;7(3):339-343.

17. Bok RA, Halabi S, Fei DT, et al. Vascular endothelial growth factor and basic fibroblast growth factor urine levels as predictors of outcome in hormone-refractory prostate cancer patients: a cancer and leukemia group B study. *Cancer Res.* Mar 15 2001;61(6):2533-2536.

18. Ostendorf T, Kunter U, Eitner F, et al. VEGF(165) mediates glomerular endothelial repair. *J Clin Invest.* Oct 1999;104(7):913-923.
19. Dahut WL, Gulley JL, Arlen PM, et al. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol.* Jul 1 2004;22(13):2532-2539.
20. Figg WD, Arlen P, Gulley J, et al. A randomized phase II trial of docetaxel (taxotere) plus thalidomide in androgen-independent prostate cancer. *Semin Oncol.* Aug 2001;28(4 Suppl 15):62-66.
21. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med.* Nov 18 1999;341(21):1565-1571.
22. Muller GW, Chen R, Huang S-Y, et al. Amino-substituted thalidomide analogs: Potent inhibitors of TNF-[alpha] production. *Bioorganic & Medicinal Chemistry Letters.* 1999;9(11):1625-1630.
23. Miller AA, Case D, Harmon M, et al. Phase I study of lenalidomide in solid tumors. *J Thorac Oncol.* May 2007;2(5):445-449.
24. Moss R. A. MSG, Shelton G. ,Melia J., Petrylak D. P. A phase I open-label study using lenalidomide and docetaxel in androgen independent prostate cancer (AIPC). Paper presented at: Prostate Cancer Symposium 2007
25. Ning YM, Gulley JL, Arlen PM, et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol.* Apr 20 2010;28(12):2070-2076.
26. Huang X, Ning Y, Mulquin M, Madan R. Phase II trial of bevacizumab , lenalidomide, docetaxel, and prednisone in patients (pts) with metastatic castration-resistant prostate cancer *J Clin Oncol 29: 2011 (suppl; abstr 4574).*
27. Keizman D, Zahurak M, Sinibaldi V, et al. Lenalidomide in nonmetastatic biochemically relapsed prostate cancer: results of a phase I/II double-blinded, randomized study. *Clin Cancer Res.* Nov 1;16(21):5269-5276.
28. Idler I, Giannopoulos K, Zenz T, et al. Lenalidomide treatment of chronic lymphocytic leukaemia patients reduces regulatory T cells and induces Th17 T helper cells. *Br J Haematol.* Mar;148(6):948-950.
29. Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood.* Nov 1 2002;100(9):3063-3067.
30. Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. *J Natl Cancer Inst.* Apr 19 2006;98(8):516-521.
31. Armstrong AJ, Garrett-Mayer E, Ou Yang YC, et al. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. *J Clin Oncol.* Sep 1 2007;25(25):3965-3970.
32. Christian B. 26-Week intravenous toxicity study with rhuMAB VEGF in cynomolgus monkeys with a 12 week recovery1999: 97-194. Located at: Genetech Report, San Francisco.
33. Ryan AM, Eppler DB, Hagler KE, et al. Preclinical safety evaluation of rhuMAbVEGF, an antiangiogenic humanized monoclonal antibody. *Toxicol Pathol.* Jan-Feb 1999;27(1):78-86.

34. Ferrara N, Chen H, Davis-Smyth T, et al. Vascular endothelial growth factor is essential for corpus luteum angiogenesis. *Nat Med.* Mar 1998;4(3):336-340.
35. Margolin K, Gordon MS, Holmgren E, et al. Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. *J Clin Oncol.* Feb 1 2001;19(3):851-856.
36. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol.* Jan 1 2003;21(1):60-65.
37. Reese D, Fratesi, P, Corry, M. . A phase II trial of humanized anti-vascular endothelial growth factor antibody for the treatment of androgen-independent prostate cancer. *The Prostate J.* 2001(3(2)):65-70.
38. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med.* Jul 31 2003;349(5):427-434.
39. Levine MN. Prevention of thrombotic disorders in cancer patients undergoing chemotherapy. *Thromb Haemost.* Jul 1997;78(1):133-136.
40. Yang R, Thomas GR, Bunting S, et al. Effects of vascular endothelial growth factor on hemodynamics and cardiac performance. *J Cardiovasc Pharmacol.* Jun 1996;27(6):838-844.
41. Product label. *Taxotere® (docetaxel) Injection Concentrate*. Bridgewater, NJ: Aventis Pharmaceuticals Inc.; 2003.
42. Warr D, McKinney S, Tannock I. Influence of measurement error on assessment of response to anticancer chemotherapy: proposal for new criteria of tumor response. *J Clin Oncol.* Sep 1984;2(9):1040-1046.
43. Keil S, Behrendt FF, Stanzel S, et al. RECIST and WHO criteria evaluation of cervical, thoracic and abdominal lymph nodes in patients with malignant lymphoma: manual versus semi-automated measurement on standard MDCT slices. *RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin.* Sep 2009;181(9):888-895.
44. Schwartz LH, Mazumdar M, Brown W, Smith A, Panicek DM. Variability in response assessment in solid tumors: effect of number of lesions chosen for measurement. *Clin Cancer Res.* Oct 1 2003;9(12):4318-4323.
45. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials.* 1989;10(1):1-10.

18 APPENDICES

18.1 APPENDIX A: AGENTS METABOLISED THROUGH CYP450

Substrates			
Acetaminophen	Dapsone	Levobupivicaine	Risperidone
Alfentanil	Dehydroepiandrostendione	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

Substrates			
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	

Inhibitors			
Diltiazem	Ketoconazole**	Quinine**	
Dirithromycin	Metronidazole	Quinupristin and dalfopristin	

The specific pathways are CYP3A4 and CYP3A5. These pathways are only utilized by Docetaxel. Also, the fact that there are two potential pathways of metabolism allows for more flexibility in the utilization of substrates, inducers, and inhibitors. (i.e. if one pathway is affected, the other pathway may still adequately metabolize docetaxel)

18.2 APPENDIX B: MEDICATION CHECKLIST

	Medication	**Schedule**	☐
Day 1	**Decadron**	3 hours before Docetaxel	
	Decadron	1 hour before Docetaxel	
	Prednisone	AM	
	Lovenox injection	anytime	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 2	Prednisone	AM	
	Lovenox injection	anytime	
	Neulasta injection	24 hours after chemo.	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 3	Prednisone	AM	
	Lovenox injection	anytime	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 4	Prednisone	AM	
	Lovenox injection	anytime	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 5	Prednisone	AM	
	Lovenox injection	anytime	

	Medication	**Schedule**	☐
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 6	Prednisone	AM	
	Lovenox injection	anytime	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 7	Prednisone	AM	
	Lovenox injection	anytime	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 8	Prednisone	AM	
	Lovenox injection	anytime	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 9	Prednisone	AM	
	Lovenox injection	anytime	
	Lenalidomide	bedtime	
	Prednisone	PM	
Day 10	Prednisone	AM	
	Lovenox injection	anytime	

	Medication	**Schedule**	☐	
	Lenalidomide	bedtime		
	Prednisone	PM		
Day 11	Prednisone	AM		
	Lovenox injection	anytime		
	Lenalidomide	bedtime		
	Prednisone	PM		
Day 12	Prednisone	AM		
	Lovenox injection	anytime		
	Lenalidomide	bedtime		
	Prednisone	PM		
Day 13	Prednisone	AM		
	Lovenox injection	anytime		
	Lenalidomide	bedtime		
	Prednisone	PM		
Day 14	Prednisone	AM		Stop Lenalidomide after 14 days
	Lovenox injection	anytime		
	Lenalidomide	bedtime		
	Prednisone	PM		
Day 15	Prednisone	AM		
	Lovenox injection	anytime		
	Prednisone	PM		

	Medication	**Schedule**	☐
Day 16	Prednisone	AM	
	Lovenox injection	anytime	
	Prednisone	PM	
Day 17	Prednisone	AM	
	Lovenox injection	anytime	
	Prednisone	PM	
Day 18	Prednisone	AM	
	Lovenox injection	anytime	
	Prednisone	PM	
Day 19	Prednisone	AM	
	Lovenox injection	anytime	
	Prednisone	PM	
Day 20	Prednisone	AM	
	Lovenox injection	anytime	
	Prednisone	PM	
Day 21	Prednisone	AM	
	Lovenox injection	anytime	
	Prednisone	PM	
Evening before Chemotherapy	Decadron		

18.3 APPENDIX C: MEDICATION INSTRUCTION SHEET

Medication Instruction Sheet

The following medications should be taken every cycle:

Days 1-21 – **Prednisone** every morning and evening.
Lovenox injection anytime during the day

Day 2 – **Neulasta** 24 hours after Chemotherapy, please inject yourself

Days 1-14 – **Lenalidomide** every day for 14 days.

On the evening before and morning of your return for your clinic appointment, please take the following:

Evening before your clinic appointment- **Decadron**

Morning of your clinic appointment **(about 3 hours before chemotherapy)-Decadron**

1 hour before your Chemotherapy- **Decadron** (the nurses in the day hospital will help guide you when to take this last dose, so bring it with you to your clinic appointment)

Reminders:

1. If you miss a dose/day of your **Lenalidomide**, please notify your Research Nurse and DO NOT take an extra day of the medication, DO NOT take 2 on the same day. Just leave it in the container and return to your Research Nurse.

2. Please bring back the empty container of Lenalidomide and Prednisone when you return for your clinic appointment, DO NOT throw it away.

18.4 APPENDIX D: CELGENE PREGNANCY PREVENTION COUNSELING PROGRAM SITE COUNSELOR IDENTIFICATION FORM

NCI Protocol#: _____

- **Please provide at least two (2) counselors and fax back to 908.673.2779**
- **Use one form per counselor.**
- **Identified counselors must be a licensed healthcare professional (e.g. RN, PA, RPh, PhD, LPN, CNP or MD).**
- **If you have any questions, please contact tfranco@celgene.com**

General Information

Principal Investigator: _____Institution Name: _____
CTEP site ID: _____

Counselor Information
First Name: _____ Middle Initial:_____ Last Name: _____
License Type: (circle one) MD PhD PA CNP RN LPN RPh Other:_____
Email Address: _____
Phone: _____ Fax: _____
Institution Street Address: _____
City: _____ State/Region: _____
Zip/Post Code: _____ Country: _____
Previously approved as a _____ Counselor? □ No □ Yes If Yes, which Protocol: _____

18.5 APPENDIX E: LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Before starting study drug

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Male patients should not donate blood, semen or sperm during treatment or for at least 28 days following discontinuation of lenalidomide.
- Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

18.6 APPENDIX F: LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

MALE:

I counseled the Male patient regarding the following:

Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).

To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.

Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.

NEVER share study drug with anyone else.

Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.

Do not break, chew, or open study drug capsules.

Return unused study drug capsules to the study doctor.

Provide Lenalidomide Information Sheet to the patient.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

Maintain a copy of the Lenalidomide Education and Counseling Guidance Document in the patient records.

18.7 APPENDIX G: LENALIDOMIDE INFORMATION SHEET

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.

Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the babies of female monkeys who received the drug during pregnancy**.**

If you are a man:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

Men (including those who have had a vasectomy) must either abstain from sexual intercourse or use a condom during sexual contact with a pregnant female or a female that can become pregnant:

While you are taking lenalidomide

During dose interruptions of lenalidomide

For 28 days after you stop taking lenalidomide

Men should not donate sperm or semen while taking study drug and for 28 days after stopping lenalidomide.

If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if she gets pregnant.

Restrictions in sharing lenalidomide and donating blood:

Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.

Do not donate blood while you take lenalidomide and for 28 days after stopping study drug.

Do not break, chew, or open study drug capsules.

You will get no more than a 28-day supply of lenalidomide at one time.

Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

18.8 APPENDIX H: GUIDELINES FOR PROPHYLAXIS AND TREATMENT FOR HYPERSENSITIVITY REACTIONS (HSR) ASSOCIATED WITH DOCETAXEL

Initial Regimen	HSR Interventions Step 1	HSR Interventions Step 2	HSR Interventions Step 3
For ALL patients who have not experienced an HSR associated with Docetaxel	**For pts with a H/O a single HSR episode**	**For pts who experience a HSR after implementing Step 1 interventions**	**For pts with severe or repeated HSR episodes after implementing Steps 1 & 2 interventions**
PREMEDICATION WITH: **Dexamethasone** 8 mg PO for 3 doses at 12 h, 3 h, & 1 h before starting docetaxel *OR* **Dexamethasone** 8 mg IV 30 – 60 min before docetaxel for patients who miss ≥1 oral dexamethasone doses • Reference: study protocol, Section **5.2.1**	PREMEDICATION WITH: **Dexamethasone** 8 mg PO for 2 doses at 12 h & 3 h before starting docetaxel + **Dexamethasone** 8 mg IV 30 – 60 min before starting docetaxel + **Diphenhydramine** 50 mg IV push 15 – 30 min before starting docetaxel + **Ranitidine** 50 mg IV infusion 30 min before starting docetaxel		PREMEDICATION WITH: **Dexamethasone** 8 – 20 mg PO for 2 doses between 24 – 36 h and at 12 hours before starting docetaxel + **Dexamethasone** 20 mg IV 30 – 60 min before starting docetaxel + **Diphenhydramine** 50 – 150 mg IV push 15 – 30 min before starting docetaxel + **Ranitidine** 50 mg IV infusion 15 – 30 min before starting docetaxel
Docetaxel 75 mg/m^2* IV over 60 minutes†	**Docetaxel** 75 mg/m^2* IV over 1 – 2 hours†	**Docetaxel** 75 mg/m^2* IV over 4 hours • Given in two portions‡, as: Docetaxel 37.5 mg/m^2 IV over 2 hours, q.2 h for 2 doses	**Docetaxel** 75 mg/m^2* IV • Given in three portions‡, as follows: 1. Docetaxel 5 mg in 10 mL IV via syringe pump over 60 min, followed immediately afterward by:

Initial Regimen	HSR Interventions Step 1	HSR Interventions Step 2	HSR Interventions Step 3
For ALL patients who have not experienced an HSR associated with Docetaxel	**For pts with a H/O a single HSR episode**	**For pts who experience a HSR after implementing Step 1 interventions**	**For pts with severe or repeated HSR episodes after implementing Steps 1 & 2 interventions**
			2. Docetaxel 25 mg in 50 mL IV over 60 min, followed immediately afterward by: 3. Docetaxel 75 mg/m^2 (*minus* 30 mg) IV over 120 min

PRN Orders:

Hydrocortisone 100 mg IV push q.15 min for 2 doses, PRN docetaxel reaction

+

Diphenhydramine 50 mg IV push q.15 min for 2 doses, PRN docetaxel reaction

+

Ranitidine 50 mg IV, PRN docetaxel reaction

+

Hydromorphone 1 mg IV push q.15 min for 4 doses, PRN pain with docetaxel reaction

+

Aluminum **Hydrox**ide 200 mg + **Mag**nesium **Hydrox**ide 200 mg + **Simethicone** 20 mg chewable tablet

1 – 2 tablets q.3 hours, PRN epigastric discomfort (drug name in CRIS is cross-referenced with "Mylanta")

* Initial (unmodified) docetaxel dosage is identified. Consult the study protocol or a medically responsible investigator to determine whether docetaxel dose/dosage modification is indicated.

† For each docetaxel product, drug delivery will be attempted over the administration period indicated, but rate titration is permitted. If rate titration is needed to accommodate patient tolerance, the following escalation scheme is recommended:

Initial Rate:	25 mL/h for 5 minutes
Rate Escalation Steps:	
1st	50 mL/h for 5 minutes
2nd	100 mL/h for 5 minutes
3rd	200 mL/h for 5 minutes
4th	250 mL/h until completed

‡ Docetaxel stability is concentration dependent. All docetaxel products diluted within the range 0.3 – 0.74 mg/mL are labeled to expire 4 hours after preparation was completed.

CRIS Chemotherapy/Biotherapy Treatment Note

<table>
<tr><th>For patients WITHOUT a prior H/O HSR</th><th>For Step 1 HSR Interventions</th><th>For Step 2 HSR Interventions</th><th>For Step 3 HSR Interventions</th></tr>
<tr><td rowspan="2">Docetaxel _____ mg/m^2 (calculated dose = _____ mg) IV over 60 min</td><td>Docetaxel _____ mg/m^2 (calculated dose = _____ mg) IV over 1 – 2 hours</td><td>Docetaxel _____ mg/m^2 (calculated TOTAL dose = _____ mg) continuous IV infusion over 2 hours, every 2 hours for 2 doses</td><td>Docetaxel _____ mg/m^2 (calculated TOTAL dose = _____ mg) given in 3 portions, as follows:
#1 of 3: Docetaxel 5 mg IV over 60 minutes
#2 of 3: Docetaxel 25 mg IV over 60 minutes
#3 of 3: Docetaxel _____ mg (calculated TOTAL dose minus 30 mg from products #1 & #2, above) IV over 2 hours</td></tr>
<tr><td colspan="3">Because patient, _____, has a history of hypersensitivity reaction with docetaxel administration, they will receive pre-medication and docetaxel according to Step #_____ of the guidelines for Prophylaxis and Treatment for Hypersensitivity Reactions (HSR) Associated with Docetaxel.</td></tr>
<tr><td colspan="4">In the event of a hypersensitivity reaction associated with docetaxel administration:
1. Immediately STOP docetaxel administration.
2. Rapidly administer PRN doses of hydrocortisone & diphenhydramine.
3. Assess patient to determine whether additional PRN meds are indicated.
4. Reinitiate docetaxel after hypersensitivity signs and symptoms have completely resolved.
5. In the event of a hypersensitivity reaction, contact:
Dr. _____at 102-_____.
Anna Couvillon at 102-10744.</td></tr>
</table>

TAKE HOME Dexamethasone Orders for the Next Treatment Cycle

For patients WITHOUT a prior H/O HSR	For Step 1 HSR Interventions	For Step 2 HSR Interventions	For Step 3 HSR Interventions
Dexamethasone 8 mg PO for 3 doses at 12 h, 3 h, & 1 h before starting docetaxel	**Dexamethasone** 8 mg PO for 2 doses at 12 h & 3 h before starting docetaxel		**Dexamethasone** 8 – 20 mg PO for 2 doses between 24 – 36 h and at 12 hours before starting docetaxel

INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0195 PRINCIPAL INVESTIGATOR: Ravi Madan, M.D.

STUDY TITLE: A Phase 2 Trial of Bevacizumab, Lenalidomide, Docetaxel, and Prednisone (ART-P) for Treatment of Metastatic Castrate-Resistant Prostate Cancer

Continuing Review Approved by the IRB on 08/08/16
Amendment Approved by the IRB on 01/12/17 (X) Date posted to web: 01/25/17
Standard

INTRODUCTION

You are invited 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 and research team before you agree to the study.

Your doctors have told you that you have advanced prostate cancer that is not responding to hormonal therapy. 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, there is no guarantee that your cancer will respond. Benefit cannot be promised, nor can the chance of benefit be accurately predicted.

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.

REVISION COPY

Why is this study being done?

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. If you have been on the study more than 2 years, being treated with prednisone only and your disease is stable, your cycles may be 42 days long. Your treatment regimen will consist of four anticancer agents. We know that two of these agents (Prednisone and Docetaxel) have been used successfully in treating patients with prostate cancer, either when used alone or in combination with other agents. We have reason to believe that these anticancer effects can be increased by giving them in this specific combination.

There have been studies that demonstrate that the combination of docetaxel and prednisone increases survival for patients with prostate cancer. In a previous study at the National Cancer Institute, we combined docetaxel and prednisone with bevacizumab and thalidomide. The results of this study were promising; 52 of 58 patients saw their PSA levels decrease by at least half. Of the 33 patients who had prostate cancer that could be measured on imaging studies, 21 of them had a significant decrease in the size of their tumors. However, most patients in the study required a dose reduction of thalidomide due to its side effects. Lenalidomide, a drug similar to thalidomide, may have less severe side effects. Based on previous studies, lenalidomide is well tolerated in patients with solid tumors when used alone or in combination with docetaxel. We think lenalidomide may be a good substitute for thalidomide. We are also attempting to understand how these drugs work together and what side effects may commonly occur. All four drugs are approved by the U.S. Food and Drug Administration (FDA).

The first agent is docetaxel, a type of chemotherapy, which is used in the treatment of many types of cancer. Docetaxel will be given through a vein over 60 minutes 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, and a second dose 1 hour before the infusion, and a third dose 12 hours after the infusion. Docetaxel may cause fluid retention (edema) in some patients and dexamethasone helps to prevent this.

The second agent is prednisone, a steroid that has been used safely in the treatment of many diseases and is used in combination with docetaxel for the treatment of prostate cancer. Prednisone will be taken by mouth on each day of the cycle.

The third agent is bevacizumab. This drug is a man-made antibody that blocks the development and growth of new blood vessels. It has been shown to be effective in the treatment of many types of cancer including colorectal, breast and lung. Bevacizumab will be given through a vein, over 30 to 90 minutes on the first day of each 21day cycle following the infusion of docetaxel. Recently, data was reported from a large clinical trial (CALGB 90401) revealing that the addition of bevacizumab to docetaxel and prednisone did not increase overall survival when compared to docetaxel and prednisone alone in men with metastatic castrate resistant prostate cancer. While this trial failed to demonstrate an overall survival benefit for the addition of

bevacizumab, this combination did prolong the time before the prostate cancer progressed and increased the number of patients whose PSA and tumors responded to therapy. In the study, we are conducting (ART-P): the addition of lenalidomide to bevacizumab, docetaxel and prednisone is designed to improve bevacizumab's ability to kill cancer cells by targeting the same process of new blood vessel growth in a different but complementary way. It is our hope that the combination of lenalidomide and bevacizumab in addition to docetaxel and prednisone will be more potent than either drug given alone with docetaxel and prednisone.

The fourth agent is lenalidomide. This drug has shown an ability to block the development of new blood vessels. Lenalidomide has been shown to be effective for the treatment of multiple myeloma, a type of blood cell cancer. In prior clinical trials in patients with solid tumor cancer, some patients had a clinical benefit after taking lenalidomide by itself or in combination with docetaxel. The first 3-6 patients on the trial will receive 15 mg daily of lenalidomide. If this is well tolerated, the next 3-6 patients will receive lenalidomide at a dose of 20 mg daily. If this is well tolerated, all subsequent patients to be enrolled on the study will receive lenalidomide at a dose of 25 mg daily. Lenalidomide is a capsule that will be taken by mouth the first 2 weeks of each cycle. All patients will continue to receive lenalidomide at their original starting dose throughout their time on study. Patients in the expansion arm of the study will receive lenalidomide at 15 mg po daily.

The chance of developing death of some cells in a part of the bone of your jaw can be increased, while you are receiving bisphosphonate treatment for prostate cancer in the bones. This is called osteonecrosis of the jaw (ONJ). It is probable that the combination of drugs used in this clinical trial may increases your risk of developing this condition. You may experience exposed jaw bone, jaw/gum pain, swelling or infection. Therefore, you will be scheduled for dental exam and imaging study of your jaw bone before the start of the protocol therapy. You will also receive scheduled dental exams after cycle 5 and every 6 cycles thereafter. Appropriate treatment, including antibiotics, will be used if it is needed.

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.

It is possible that the combination of these drugs may increase your risk of developing a blood clot; therefore, we will ask you to give yourself or have a caregiver give you a daily injection of enoxaparin, a blood-thinning agent.

How many people will take part in the study?

Approximately 70 patients will participate in this study, which will be conducted at the NIH Clinical Center.

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

Before you begin the study:

You will need to have the following exams and procedures to determine if this study is suitable for you. These exams and procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of done them recently, they may not need to be repeated. This will be up to the study team.

- A complete medical history will be taken from you, a history of your cancer, and prior cancer treatments you have taken.
- You will be asked to give information about all drugs (including over the counter drugs, vitamins and herbal supplements) that you are currently taking.
- Your study doctor will do a complete physical examination, assess your ability to do physical activities, measure your blood pressure, heart rate, and respiration rate.
- You will be asked to have a 12-lead electrocardiogram (ECG) and a chest x-ray.
- A sample of your blood (approximately 2 tablespoon) and urine will be taken for laboratory testing.
- An evaluation of your cancer will be done. This will include a CT scan and bone scan.
- Mandatory research urine samples will be obtained prior to starting the study drug and at monthly clinic visits.

During the study:

If you choose to join this study you will return to NIH to begin the first treatment cycle. On this regimen, treatment cycles are generally 3 weeks (21 days) in duration. If you have been on the study for more than 2 years, being treated with prednisone only and your disease is stable, your treatment cycles may be 42 days in duration.

Cycle 1 and Cycle 2
Day 1

- On day 1 of the first and second treatment cycle, you will be asked to report to the NIH Clinical Center Outpatient Cancer Center.
- Samples of your blood (approximately 8 teaspoons) will be taken for laboratory testing before you take your first dose of study drug.
- Samples of your blood (approximately 6 teaspoons) will be taken for research prior to the first treatment dose, and prior to the treatment for cycles 2, 3 and 6, if possible. These samples will be used for various immune function testing, specifically looking at T-cell function.

- You will receive an intravenous infusion of docetaxel at a dose of 75 mg/m2.
- You will also receive an intravenous infusion of bevacizumab at a dose of 15 mg/kg.
- You will begin taking prednisone by mouth at a dose of 10 mg on the first day of each cycle and continue to take it daily throughout the cycle.
- You will also begin taking lenalidomide by mouth at a dose of either 15 mg or higher on the first evening of each cycle and continue to take it for the first two weeks of the three week cycle.
- You will be taught how to inject enoxaparin for the prevention of blood clots and take it every day of the cycle, including 7 days after stopping lenalidomide.
- You will be observed for any side effects that you may experience during and after the infusions of docetaxel and bevacizumab.

Cycle 1 and Cycle 2

Day 2

- You will be given a medicine called Pegfilgrastim to help keep your white blood cell count from dropping on the second day of each cycle, at least 24 hours after you receive the docetaxel.
- You will be asked to have a weekly blood count drawn at home during the cycle and the results faxed to the Outpatient cancer center.

During each Cycle

- We will ask you to return to NIH on or about day 21 or day 1 of the next cycle (if you are taking prednisone only you may return after 42 days and have blood drawn prior to coming to clinic. Labs are required for both clinical and research purposes.
- You will have scans (bone scan and possibly CT scan) prior to Cycle 3, and then every 3 cycles. After you have been on study for at least 2 years, scans may be done only if there is other evidence that your disease has worsened. Scan visits may take 2 days for all of the required testing to be completed and for the IV infusions to be administered. You will be given a medication check list and a medication instruction sheet to help you keep track of the medications you will take while away from the clinic.
- You will be asked to have a weekly blood count drawn at home and results faxed to the outpatient cancer center.
- We ask that you avoid ingestion of grapefruit juice while enrolled on study as this may adversely interact with one or more of the study drugs.

After Cycle 5

- Follow up dental evaluations will occur at every other restaging visit until cycle 17. Thereafter, they will be performed once annually.

Throughout your treatment PD (pharmacodynamic) studies (blood samples) will be drawn which allow for the evaluation of the following:

1. optimal dosing of medications

2. interactions between medications in your body

3. potential relationship between the way your body handles medications and clinical outcome

4. candidate blood tests that may reflect drug activity

5. immune function testing

Throughout your treatment it will be very important to keep us informed about any new symptoms you experience. We will repeat the scans after the second cycle, and then approximately every 3 cycles to determine if your cancer has responded. If you have been on the study for at least two years, you may have the scans only if there is other evidence that your disease has worsened. As long as you are tolerating the treatment and your cancer has not gotten worse, we will continue to give you treatment.

How long will you be in the study?

If you choose to join this trial, your participation will continue until either you or the study team decides that this experimental treatment is not helping you. The following are reasons the treatment may be stopped:

- You may request at any time to stop treatment.
- Bone scan or CT scan results showing clear evidence that the cancer has grown.
- Illness which would make it unsafe for you to receive further treatment.
- Severe side effects which last for more than 21 days.

Can you stop being in the study?

Yes. You can decide to stop at any time. Please tell your study team if you are thinking about stopping or decide to stop, we will tell you how to stop safely.

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 and Celgene 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.

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

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

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The medications used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. The docetaxel which is used in this study also contains ethanol or alcohol which may cause you to feel drunk during or after treatment. It may be necessary to avoid driving, operating any machinery or performing any activities that are dangerous for one to two hours after the infusion of docetaxel. Some medications such as pain relievers or sleep aids may interact with the alcohol in docetaxel and may worsen these effects.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Docetaxel:

(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Docetaxel, more than 20 and up to 100 may have:
• Swelling of the body • Hair loss • Change in nails • Rash, itching • Vomiting, diarrhea, nausea • Sores in mouth which may cause difficulty swallowing • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Tiredness • Numbness and tingling of the arms and legs • Fever • Absence of menstrual period • Swelling and redness of the arms, leg or face • Pain • Watering, itchy eyes

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Docetaxel, from 4 to 20 may have:
• Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body • Belly pain • Bruising, bleeding • Liver damage which may cause yellowing of eyes and skin • Kidney damage which may require dialysis • Scarring of the lungs • Blood clot which may cause swelling, pain, shortness of breath • Abnormal heart rate • Shortness of breath, wheezing • Chest pain

RARE, AND SERIOUS In 100 people receiving Docetaxel, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Liver damage which may cause yellowing of the eyes and skin

Bevacizumab:

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, more than 20 and up to 100 may have:
• High blood pressure which may cause headache or blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Low white cell count that may increase the risk of infection • Infection, including collection of pus in the belly or rectum • Abnormal heartbeat which may cause palpitations or fainting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Pain in the belly, rectum, chest, joints, muscles, or tumor • Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up of blood, or blood in urine • Bleeding from other sites, including the vagina or nose • Blockage of internal organs which may cause vomiting or inability to pass stool • Sores in mouth • Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Delay in healing of wounds or spontaneous opening of wounds • Weight loss, tiredness, or dizziness • Muscle weakness • Damage to organs which may cause loss of teeth or loss of motion • Headache • Numbness, tingling, or pain in the fingers or toes • Hoarseness, stuffy nose, or cough • Dry skin • Swelling and redness of the skin • Blood clot in limbs or lungs which may cause swelling, pain, or shortness of breath • Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS In 100 people receiving bevacizumab, 3 or fewer may have:
• Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes • Heart failure which may cause shortness of breath, swelling of ankles, or tiredness • Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair • A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair • Sores in the throat • Flesh-eating bacteria syndrome, an infection in the deep layers of skin • Bleeding in the tumor, brain, belly, or lungs which may cause confusion, blood in stool or coughing up blood • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis • Redness, pain or peeling of palms and soles

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in children or adolescents: abnormal bone changes which may interfere with growth.
- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Lenalidomide:

COMMON, SOME MAY BE SERIOUS **In 100 people receiving lenalidomide, more than 20 and up to 100 may have:**
• Anemia which may require blood transfusion • Constipation, diarrhea • Tiredness • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving lenalidomide, from 4 to 20 may have:**
• Nausea, vomiting • Chills, fever • Swelling of arms, legs • Infection, especially when white blood cell count is low • Weight loss, loss of appetite • Pain • Muscle spasms • Dizziness, headache • Difficulty sleeping • Cough, shortness of breath • Increased sweating • Itching, rash • Sores on the skin • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS **In 100 people receiving lenalidomide, 3 or fewer may have:**
• Heart attack • Liver damage which may cause yellowing of eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to organs in the body when donor cells attack host organs which may cause dry skin, or muscle weakness • Kidney damage which may require dialysis • Cancer of bone marrow caused by chemotherapy • Damage to organs which may cause infection, bleeding, may require transfusions or changes in thinking • Increased tumor size • A new cancer resulting from treatment of earlier cancer • Stroke which may cause paralysis, weakness • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Difficulty stimulating enough stem cells in the bloodstream for future transplant

Prednisone:

(Table Version Date: June 24, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Prednisone, more than 20 and up to 100 may have:
• In children and adolescents: decreased height • Loss of bone tissue • Mood swings • Skin changes, acne • Swelling of the body, tiredness, bruising • High blood pressure which may cause headaches, dizziness, blurred vision • Pain in belly • Increased appetite and weight gain • Weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Prednisone, from 4 to 20 may have:
• Cloudiness of the eye, visual disturbances • Glaucoma • Infection • Non-healing wound • Diabetes • Damage to the bone which may cause joint pain and loss of motion • Kidney stones • Heartburn

RARE, AND SERIOUS In 100 people receiving Prednisone, 3 or fewer may have:
• Bleeding from sores in the stomach • Broken bones

Pegfilgrastim:

(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Pegfilgrastim (Neulasta), more than 20 and up to 100 may have:
• Pain in bone

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Pegfilgrastim (Neulasta), from 4 to 20 may have:
• Anemia which may cause tiredness, or may require transfusion • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to the lungs which may cause shortness of breath

RARE, AND SERIOUS
In 100 people receiving Pegfilgrastim (Neulasta), 3 or fewer may have:
• Rupture of the spleen with bleeding in the belly

Enoxaparin:

COMMON, SOME MAY BE SERIOUS
• Swelling and redness at the site of the medication injection

OCCASIONAL, SOME MAY BE SERIOUS
• Bleeding • Nausea • Diarrhea • Confusion

RARE, AND SERIOUS
• Allergic reaction: itching or hives, swelling of the face or hands, swelling or tingling in the mouth or throat, chest tightness, trouble breathing. • Blood in the urine • Bloody or black, tarry stools • Chest pain, shortness of breath or coughing up blood • Irregular heartbeat • Numbness or weakness in arm or leg, or on one side of the body. • Sudden or severe headache, problems with vision, speech or walking. • Unusual bleeding or bruising. • Swelling in hands, ankles or feet. • Vomiting blood or material that looks like coffee grounds. • Heparin-induced low platelet count

As previously mentioned we will ask you to take 3 doses of dexamethasone (a steroid), around your docetaxel infusion. The first dose is 12 hours before docetaxel, a second dose 3 hours before the infusion, and a third dose 1 hour before the infusion. Dexamethasone will help prevent fluid retention as well as the chance of infusion reactions. Because of the short term use in this setting, serious side effects have not been observed. Some patients complain that they feel jittery or experience difficulty sleeping when taking dexamethasone. If this occurs, please tell the study team so we can make adjustments.

We have seen decreases in neutrophil counts (neutropenia) in most patients on the trial thus far. As such, all patients will take pegfilgrastim on day 2 of each cycle. Pegfilgrastim is a medication that can increase the number of neutrophils and reduce your risk of infection. It is given as an injection approximately 24 hours after the docetaxel infusion. Because there is a rare risk of having an allergic reaction to pegfilgrastim, we ask that you receive the first injection either at NIH or your local physician's office. It is very important that you use pegfilgrastim every cycle at the same time thereafter.

Since this combination of drugs together may 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, we believe this medication is necessary for this study and provides overall benefit to you.

Notify the study team immediately if any of the following occur, these can be symptoms of a blood clot:

- Sudden onset of swelling to one leg that may or may not be accompanied by leg pain (calf or thigh)
- Chest pain
- Shortness of breath

Side Effects reported by patients, but not proven to be caused by study drugs

Patients in this study have experienced dehydration (an excessive loss of body fluids) and imbalances of electrolytes (chemicals in the blood stream such as sodium, potassium, calcium, chloride and magnesium that help to regulate body functions). Symptoms of dehydration include dry mouth, loose skin, dizziness and lower urine output. Symptoms of electrolyte imbalances vary depending on which electrolyte levels are affected, but can include muscle spasm, weakness, twitching, convulsions, irregular heartbeat, confusion, blood pressure changes, numbness and fatigue. In this study, patients generally did not have symptoms, except dizziness, as a result of fluid or electrolyte imbalances.

Risk of Second Cancer:

Sometimes a second primary cancer arises after patients have undergone cancer therapy, including therapy using chemotherapeutic agents used to treat multiple myeloma. Recently, in clinical trials of patients with newly diagnosed multiple myeloma, a higher number of second cancers has also been reported in patients treated with high doses of chemotherapy (induction therapy) and/or stem cell transplant followed by prolonged (maintenance) lenalidomide therapy compared to those who received induction therapy and/or transplant without maintenance lenalidomide.

We do not know at this time whether prolonged lenalidomide therapy in this clinical setting actually increases the risk of second primary cancers. No increase in second primary cancers has been observed in patients receiving lenalidomide therapy who have relapsed multiple myeloma or other types of cancer.

We will be carefully monitoring these events (second primary cancers) in on-going studies of lenalidomide therapy and will inform you if there are any changes. We want you to be aware of this possibility and to continue to follow standard medical advice for prevention and early detection of other cancers during and after your treatment.

Pregnancy Risk:

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Preliminary findings from a monkey study appear to indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Lenalidomide is detected in trace quantities in human semen according to a

study. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

Lenalidomide is present at very low levels in human semen of healthy men for three days after stopping the drug according to a study. For patients who may not be able to get rid of the drug, such as people with kidney problems, lenalidomide may be present for more than three days. To be safe, all men should use condoms when engaging in sexual intercourse while taking lenalidomide, when temporarily stopping lenalidomide, and for 28 days after permanently stopping lenalidomide treatment if their partner is either pregnant or able to have children.

Patients should not donate blood during study treatment or for 28 days following discontinuation of lenalidomide.

You will be counseled at least every 28 days during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (or other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.

Because of these risks, all patients taking lenalidomide must read the following statements that apply to them according to gender and menopausal status.

FOR ALL MALES

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking lenalidomide or is exposed to lenalidomide.

_____: I have been told by my doctor that while taking lenalidomide and for 6 months after my last dose, I must NEVER have unprotected sexual contact with a female who can become pregnant. Because lenalidomide may be present in semen, my doctor has explained that I must completely abstain from sexual contact including oral exposure to semen with females who are pregnant or able to become pregnant, or I must use a latex condom every time I engage in any sexual contact with females who are pregnant or may become pregnant. My sexual partner must also use a highly effective form of birth control. I must do this while I am taking lenalidomide and for 6 months after I stop taking lenalidomide, even if I have had a successful vasectomy.

_____: I know I must inform my doctor if I have unprotected sexual contact with a female who is pregnant or can become pregnant or if I think, for ANY REASON, that my sexual partner may

be pregnant. Female partners of male patients taking lenalidomide should be advised to call their own physician immediately if they get pregnant.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are able to have children.

_____: I agree any unused drug supply will be returned to the research site at each visit.

_____: I know that I cannot donate blood, sperm or semen while taking lenalidomide and for 2 months days after stopping lenalidomide.

You will be counseled at least every 28 days during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (and other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules.

You should recognize that no method of birth control besides abstinence provides 100% protection from pregnancy.

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 this treatment for any signs which might signal the earliest stages of side effects so that appropriate intervention can be done.

What other choices do you have if you do not participate in this study?

It has been explained to you that you have prostate cancer that has come back after hormonal treatment. At this time, docetaxel combined with prednisone is the standard treatment for your cancer. Other treatment alternatives which can be considered for you now include:

- Getting treatment without being in a study.
- Taking part in another study.
- Getting no treatment.

- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

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

Will your medical information be kept private?

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.

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

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- The NCI Institutional Review Board.
- Genentech.
- Celgene.

What are the costs of taking part in this study?

While you are on study at the National Cancer Institute, we will pay for the medications and treatments associated with the study including commercially available agents. We do not assume the cost of your overall medical care. Any studies done outside of the NCI may require you or your insurance company to cover the cost of the service.

It is important to stress that your participation in this study does not constitute a promise of long term care at the NIH Clinical Center.

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

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

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

Who can answer your questions about the study?

You can talk to your study team about any questions or concerns you have about this study. Contact your Study Coordinator, Guinivere Chun, RN 240-760-6065, and/or Dr. Ravi Madan, the Principal Investigator at 301-480-7168.

If you have any complications when you are not in the Clinical Center (e.g., at home or in a local hotel), you may call the page operator at (301) 496-1211 and ask for the NCI Medical Oncology Branch physician on call or the NIH Patients' Rights Representative who will be available to answer questions concerning your involvement in this study or your rights as a research subject. This person is not directly associated with this study and can be contacted at (301) 496-2626.

Research Subjects' Rights

You will be told if no benefit occurs to you as a result of taking part in this treatment program and your participation in the trial will be stopped.

You will receive a copy of this informed consent for your own records. In addition, a copy of the informed consent is on file with the Medicine Oncology Branch of the National Cancer Institute and a copy will be made available to you whenever you want to see it. Your records will be kept confidential, with the exception that the FDA, and the staff of the National Cancer Institute, who may inspect and study your medical records.

Your participation in this study is entirely voluntary, and you may refuse to participate, or withdraw from this protocol at any time and receive care from a physician of your choice. Your participation in this study may be ended without your consent by the Principal Investigator or an Associate Investigator if they feel that it is medically unsafe for you to continue to receive experimental treatment.

It is important to maintain a relationship with your referring physician while you are on this study. Upon completing this study, you may be given the choice of taking part in other research protocols that may be appropriate for you. Otherwise, you will be returned to the care of your referring physician. If there is no research study that can help you, you will be returned to the care of your private doctor.

You may decide now to not receive treatment in this protocol, or you may choose at any time to stop the drug and withdraw from the protocol. In either case, you would be returned to the care of your referring physician. It is possible that participation in this study may render you ineligible to participate in other research studies that limit the number or types of treatment that have been given.

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.

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 A. Madan, M.D., Building 10, Room 13N240B, Telephone: 301-480-7168. 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.

   You may also call the Clinical Center Patient Representative at 301-496-2626.

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 AUGUST 8, 2016 THROUGH AUGUST 7, 2017. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	