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Part of the Keck School of Medicine of USC

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PROTOCOL #:	**4P-04-3**
TITLE:	**A PHASE II STUDY OF BORTEZOMIB (VELCADE®, PS-341) AND DOCETAXEL FOR PATIENTS WITH HORMONE REFRACTORY PROSTATE CANCER**
SITE:	**PROSTATE**
HISTOLOGY:	**ADENOCARCINOMA**
STAGE:	**Tx Nx M1 (D2) – Progressive, metastatic, hormone refractory**
MODALITY:	**CHEMOTHERAPY**
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PRECIS

In this protocol, we propose to evaluate the efficacy and toxicity of chemotherapy with docetaxel and bortezomib in men with symptomatic advanced prostate cancer. Patients with hormone refractory prostate cancer have a poor prognosis with a mean time to death of less than 12 months without treatment. Recent studies demonstrate the efficacy and tolerability of mitoxantrone-based and taxane-based chemotherapeutic regimens for this group of patients. Despite this the benefit in terms of overall survival is small and limited to those who respond to this therapy. All patients responding to chemotherapy eventually relapse. Studies at the Fox Chase Cancer Center, the University of Michigan, Columbia University and the South West Oncology Group have shown that the combination of a taxane and estramustine has first line activity. While not formally studied these regimens preliminary results from a trial underway at USC suggest considerable activity after mitoxantrone-based therapy failure. A major issue with estramustine-taxane regimens relates to the cardiovascular toxicity consequent upon the addition of estramustine to docetaxel. Consequently, many centers use docetaxel alone and there is a quest for an agent to combine with docetaxel for additive efficacy, acceptable safety profile and suitable dosing regimen. The combination of bortezomib (Velcade®) with docetaxel shows potential in fulfilling these requirements. Ongoing studies suggest at least additive activity with good longer term tolerability at therapeutic doses but the optimal dosing schedule is still to be determined. Current schedules involve 4 or more dosing days in a 21 day cycle. The dosing schedule in this study will see docetaxel given on day 1 with bortezomib on days 1 and 8 of a 21 day cycle. This study will test the primary hypothesis that this combination will result in a response $\geq$50% of cases as evaluated by serum PSA response rate while producing $\leq$10% grade 4 non-hematological toxicity by NCI CTC v. 3 criteria.

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1.0 Objectives and Study Design

1.1 Objectives

To perform a phase II trial of bortezomib (Velcade®) and docetaxel in patients with hormone refractory prostate cancer with the following objectives:

Primary: Determine the PSA response rate

Secondary:
Evaluate the pain response rate
Determine the safety of this combination
Assess the duration of pain responses
Determine the objective response rate as measured by improved physical examination and/or imaging studies

1.2 Study Design

Eligible patients will have analgesic medication adjusted to achieve stable and optimal pain control prior to commencement of the study. The study will take the form of a phase II trial: **37 patients** will receive docetaxel 75 mg/m^2 given on day 1 with bortezomib 1.6 mg/m^2 on days 1 and 8 of a 21 day cycle. The PSA, measurable disease and pain responses to therapy will be evaluated in all patients. Interim analysis will be undertaken after 24 patients are evaluable. Treatment will consist of up to twelve 21 day cycles of chemotherapy contingent on cessation criteria for cancer progression or therapy toxicity.

1.3 Cycle schedule

Days	**0**	**1**	**2**	**3-7**	**8**	**6–20**	**21**
Drug							
Bortezomib	No therapy	**1.6 mg/m^2**	No therapy	No therapy	**1.6 mg/m^2**	No therapy	No therapy
Docetaxel	No therapy	**75 mg/m^2**	No therapy	No therapy	No therapy	No therapy	No therapy
Dexamethasone	**8mg BID**	**8mg BID**	**8mg BID**	No therapy	No therapy	No therapy	**8mg BID**
Prednisone		5mg BID	5mg BID	5mg BID	5mg BID	5mg BID	5mg BID
Maintenance of castration (orchiectomy or LHRH agonist)	->	->	->	->	->	->	->

See section 7.2 for further detail.

2.0 Background and Hypotheses

2.1 Hypothesis

This study is premised upon the hypothesis that chemotherapy with bortezomib and docetaxel improves outcome in patients with hormone refractory prostate cancer. The primary outcome measure will be serum PSA response. Secondary outcome measures are changes in measurable or evaluable disease, and symptomatic improvement as measured by decreased pain score in the setting of stable or reduced analgesic requirements.

2.2 Background: Prostate cancer

Adenocarcinoma of the prostate is a major public health issue for patients, physicians and health care providers. With the exception of skin cancer, prostate cancer is the most prevalent and incident cancer in American men [1] and the second leading cause of cancer death [2]. The lifetime risk of developing prostate cancer has risen to the order of 1 in 5 [3, 4]. American Cancer Society data suggest that there were 179, 300 men diagnosed with and 37, 000 deaths from prostate cancer in the United States in 1999 [4]. The vast majority of these deaths occurred as a consequence of progressive metastatic hormone refractory prostate cancer (HRPC). In the setting of a population with increased longevity, it is likely that prostate cancer will become more clinically prevalent in the future.

Hormone therapy is the cornerstone of first-line therapy for advanced disease**.** However, the effect of androgen ablative therapy is transient in virtually all cases with a duration of response of 12 – 36 months in most cases. At relapse patients characteristically develop increased serum PSA concentrations, progressive disease on imaging studies and symptomatic deterioration. Unfortunately, progress in improving the survival of patients with HRPC has been slow and the interval between development of HRPC and death is usually between 6 and 18 months. Radiation therapy is useful for the palliation of local bone pain but does not improve survival time. Attempts at using hormonal agents that act on non-androgen steroid hormonal pathways such as estrogen or progesterone have met with little success and at times significant toxicity [5-8]. Once the patient becomes hormone refractory, disease classically progresses to be fatal in around 12 months. Recent advances in the supportive and chemotherapeutic therapy of these patients have improved quality of life for these patients and may impact survival but more efficacious and durable therapies are required.

2.3. Chemotherapy for hormone refractory prostate cancer

Many different **cytotoxic agents** have been used in **hormone refractory prostate cancer** in an attempt to palliate symptoms and improve survival [9]. While no therapy has been demonstrated to increase survival, physicians using chemotherapy in patients with HRPC have believed that significant improvement in symptoms occurred in many of

these patients [10-12]. Recently, **mitoxantrone-based** chemotherapeutic regimens have definitively demonstrated symptomatic and health related quality of life improvement in patients with HRPC in two phase III trials [13-16]. Mitoxantrone-based regimens has become the first line standard of care for patients with symptomatic progressive HRPC. The **taxanes** (paclitaxel, docetaxel) have activity in HRPC when used alone or in combination with other cytotoxic agents [17-19]. Taxanes have been combined with **estramustine** with possible synergistic effect but at the cost of significant procoagulant derived side effects. Another important issue in taxane-based therapy in prostate cancer is dose scheduling, with differential side effects between dosing every 3 weeks and dosing at shorter intervals such as every week or two out of every 3 weeks. The best schedule for disease response has not been definitively determined. Efforts at improving front line therapy are important and several multicenter trials are currently accruing to determine what approach should be first line standard care. Concurrently new approaches that improve the response to first line therapy with increased efficacy, diminished toxicity and better selection of patients for individual therapy are major goals. Regardless of the first line approach used in hormone refractory prostate cancer, eventually all patients relapse [9, 20]. While efforts directed at improving first line therapy for HRPC based on mitoxantrone are of interest [21], a large number of patients would benefit from the development of effective alternative first line or second line chemotherapeutic strategies.

As a single agent estramustine has not demonstrated benefit over continued or alternate hormonal therapy in HRPC [5]. However, in combination with cytotoxic agents estramustine appears to contribute to response [22-25], although published studies to prove this conclusively are currently lacking. Recent reports from phase I and phase II trials suggest that the combination of estramustine and docetaxel is well tolerated and produces a decrease of >50% in serum PSA in more than 50% of HRPC cases treated [26-33]. Studies at several other centers [31, 34-36] have shown that the combination of a taxane and estramustine has first line activity in HRPC. Longer follow-up on at least one study suggests that the combination may improve survival at least compared to historical controls [36], although this is far from proven and many clinicians use docetaxel as a single agent because of potential side effects from estramustine (see below). The Southwest Oncology Group SWOG recently tested the combination of estramustine and docetaxel tested against mitoxantrone. In a phase III study titled Docetaxel and Estramustine versus Mitoxantrone and Prednisone in Men with Androgen Independent Prostate Cancer: Results of Southwest Oncology Group Intergroup Protocol 99-16 were reported at ASCO 2004. It was concluded that Docetaxel/estramustine demonstrated an increase in overall survival, progression free survival, PSA response by 50%, and an increase in objective response rate. It was concluded that Docetaxel and Estramustine combination could be considered a reference regimen for the treatment of androgen-independent prostate cancer.

A second large study supporting a non-Estramustine combination was presented at ASCO 2004. TAX 327 A Phase III multi-center comparison of docetaxel given weekly or every three weeks + prednisone with mitoxantrone + prednisone in patients with

hormone-refractory prostate cancer. Over 1000 men were randomized on this study producing results that were statistically significant for response rates, pain response, PSA decline, and quality of life for the Docetaxel and Prednisone arm on a q 3-week schedule.

Docetaxel

Docetaxel (Taxotere™) is an anti-neoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Bcl2 function is implicated in the maintenance of microtubule integrity [37] and taxane action on the microtubule may be dependent on the phosphorylation of Bcl-2 or Bcl-XL [17, 38, 39]. Recent work suggests that variation in β-tubulin expression may predict response to docetaxel, with higher levels of expression correlating with decreased response to therapy [40, 41].

Bortezomib

The proteasome is a final degradative enzyme that has important functions in the catabolic pathway for numerous intracellular regulatory proteins. It achieves this by tagging protein and peptide degradation by adding ubiquitin moieties to the amine residue attached to the amino acid lysine in the molecules structure. Bortezomib (Velcade®) is a potent, specific and reversible proteasome inhibitor with postulated anticancer effects through modulation of apoptotic (e.g. Bcl-2 down-regulation [43]) and cell cycle pathways (e.g. $p27^{Kip1}$ and $p21^{Cip1}$ up-regulation [44, 45]) as well as NF-κβ stabilization and inhibition of angiogenesis [46, 47]. The anti-neoplastic effects of bortezomib may be due to several mechanisms. Bortezomib induces apoptosis in cells that overexpress Bcl-2. It may also inhibit cell growth signaling pathways and inhibit cellular adhesion molecule expression. Based on studies done at the National Cancer Institute, bortezomib has cytotoxic activity in a variety of xenograft tumor models and *in vitro* and *in vivo* assays. A study in the PC-3 human prostate xenograft model was conducted that showed administration of bortezomib given to male nude mice demonstrated significant decreases in tumor volume. Bortezomib dosed at 0.3 or 1.0mg/kg/dose was given intravenously for 4 consecutive weeks to mice with tumor volumes of approximately 100mm3. One week after the last dose at 48 days, mice administered bortezomib at 0.3 or 1.0mg/kg/dose had reduction of tumor volume of 44% and 65% respectively.

In vitro data demonstrates synergy between bortezomib and gemcitabine as well as with fluoropyrimidines [48]. Bortezomib and gemcitabine are synergistic in a xenograft model of pancreatic cancer [49]. Bortezomib demonstrates induction or restoration of fluoropyrimidine sensitivity in select patients with colorectal cancer refractory to 5FU [50]

and of thalidomide response in some patients with previously thalidomide-refractory myeloma [51].

Docetaxel works through a mechanism of microtubule assembly enhancement which inhibits the depolymerization of tubulin thereby blocking cells in the M phase of the cell cycle and inhibiting cell division. This hypothetically should increase the apoptotic effect of bortezomib. Further *in vitro* data demonstrates synergy between bortezomib and the taxanes [48, 52] as well as the ability of bortezomib to reverse taxane resistance [53]. In vitro data also suggest that administration of taxanes before bortezomib produces more pronounced changes in the levels of key molecules such as p27 and a higher apoptotic index and cell kill than if bortezomib is given first [52]. These data have resulted in two phase I studies (see below) directed at evaluating the safety of the combination of docetaxel and bortezomib in lung cancer and prostate cancer. In the hormone-refractory prostate cancer trial dosing was scheduled so that docetaxel was administered on day 1 and 8 with bortezomib administered a day after bortezomib on days 2 and 9 of a 21 day cycle. Some PSA and clinical responses are reported from this phase I trial in heavily pretreated patients suggesting that the combination is promising. However, since this trial was conceived more has been learned about the pharmacokinetics of bortezomib, in particular the fact that the drug accumulates in extravascular tissue with repeated dosing probably due to protein binding. This suggests that while the sequence effect of bortezomib and docetaxel may be important in cell culture, it may be less so in clinical practice. Recent work from M. D. Anderson suggests that, in the clinical setting, bortezomib should be administered before or concurrent with docetaxel. In contrast to this clinical phase I/II studies of the combination report rapid PSA responses soon after commencement of therapy with dosing regimens where bortezomib is given after docetaxel. In addition, the regimen of day 1, 2, 8 and 9 administration of chemotherapy within a 21 day cycle is likely to have practical limitations for patients and increased cost compared less frequent dosing. The current regimens testing the combination involve dosing of one drug or another on between and 4 and 6 separate days in the 21 day cycle. Hence there is a need for a rationalization of dose scheduling for this combination.

Phase I studies with bortezomib are complete or ongoing to delineate DLT and MTD in a number of settings including:

- **alone**:

a. 1.04 mg/m2 twice weekly for 4 weeks with 2 weeks off in heavily pre-treated hematological malignancies. DLT's included thrombocytopenia, fatigue, hypokalemia and hyponatremia [54].
b. MTD of 1.56mg/m2 twice weekly for 2 weeks with 1 week off alone in solid tumors DLT was grade 3 sensory neuropathy and grade 3 diarrhea [55].
c. MTD of 1.6mg.m2 once weekly for five weeks of a 35 day cycle in solid tumors. DLT diarrhea and hypotension. Preliminary single agent activity in HRPC was observed (Panpandreou et al. JCO 2004).

- with **gemcitabine**:

d. A single phase I study of bortezomib and gemcitabine is ongoing and demonstrates that bortezomib at a dose of 0.7 mg/m2 on days 1, 4, 8, and 11 with gemcitabine 1000 mg/m2 on days 1 and 8 every 21 days is feasible. DLT not reached. [56]

- with **5-fluorouracil** :

e. A completed phase I study of bortezomib and 5FU with leucovorin demonstrated that a that bortezomib at a dose of 1.0 mg/m2 twice weekly with 5FU 500 mg/m2 and leucovorin weekly for four weeks with a two week break was the MTD in heavily pretreated colorectal cancer patients. DLT was grade 3 diarrhea and abdominal cramping [50].

- with **docetaxel** (Millennium on file):

1. An phase I trial of bortezomib to dose 1.3 mg/m2 on days 1, 4, 8, and 11 with docetaxel 75 mg/m2 on days 1 every 21 days in predominantly non small cell lung cancer patients. DLT reached at docetaxel 75 mg/m2 and bortezomib 1.3 mg/m2 - fatigue.
2. A phase I study in metastatic breast cancer of bortezomib at a dose of 1.3mg/m^2 on days 1, 4, 8, and 11 of a 21 day cycle with docetaxel 75mg/m^2 every 21 days
3. An ongoing phase I/II trial of bortezomib to dose 1.6mg/m2 on days 1 and 8 with docetaxel 35mg/m2 on days 2 and 9 every 21 days in hormone refractory prostate cancer. DLT not reached (Dreicer, Cleveland Clinic and collaborators).

- with **mitoxantrone** (Millennium on file):

Ongoing phase I/II trial in hormone refractory prostate cancer

- with **prednisone**

Ongoing phase I/II trial in hormone refractory prostate cancer

- with **pegylated liposomal doxorubicin**:

Completed phase I of bortezomib 1.3 mg/m2 days 1, 4, 8, and 11 with pegylated liposomal doxorubicin 30 mg/m2 on days 1 every 21 days. DLT was thrombocytopenia and hand/foot syndrome [57].

- With **thalidomide:**

Ongoing phase I trial in myeloma patients failing autologous bone marrow transplantation with bortezomib 1.0 mg/m2 days 1, 4, 8, and 11 and daily thalidomide to 150mg in a 21 day cycle [51].

Further studies are evaluating the potential of bortezomib to increase response to standard cytotoxic therapy in a variety of solid tumors.

Phase II data from two studies show that bortezomib at a dose of 1.3mg/m2 on days 1, 4, 8, and 11 every 21 days has significant single agent activity in multiple myeloma refractory to first-line therapy [58] and multiple agents [59]. The grade 3 toxicities observed in these studies related to asymptomatic cytopenia and sensory neuropathy. In a phase II study completed in indolent non-Hodgkin's lymphoma patients, bortezomib at a dose of 1.5mg/m2 on days 1, 4, 8, and 11 every 21 days showed significant activity with reversible cytopenias and neuropathy as the grade 3 toxicities [60]. A common theme of the early studies of bortezomib has been grade 1 or, less commonly, grade 2 fatigue, however, this has not resulted in a significant numbers of patients refusing to continue therapy.

Bortezomib and docetaxel in hormone refractory prostate cancer

The study described above (Dreicer, Cleveland Clinic and collaborators) using day 1 and 8 scheduling of docetaxel are the only current trial experience with this drug combination in HRPC. Data from the phase I components of these studies suggest high rate of PSA response with rapid falls in PSA, an experience emulated by a number of clinicians with out of trial, non indication use of the combination. This suggests that the combination may have sufficient activity to warrant inclusion in randomized studies against standard chemotherapeutic approaches for HRPC. When these approaches have included a taxane they have most commonly included docetaxel on a once every three week schedule and recent data from the TX327 studies show that docetaxel given every 3 weeks produces a superior survival to docetaxel given on a weekly schedule. To allow comparison, data on three weekly docetaxel with two doses of bortezomib within the 21 day cycle (to facilitate patient acceptance and lessen cost) are needed.

2.4 Justification for Doses Proposed

The combination of bortezomib and docetaxel has been tested for safety in a variety of settings including classical phase I studies and those focused on individual primary sites such as breast, prostate and lung cancer. In prostate cancer, dosing at up to 1.6mg/m2 with docetaxel at 35mg/m2 twice in a period of 21 days is safe and effective. These studies have employed dosing of bortezomib either before or concurrently with docetaxel. Bortezomib dosing at 1.3mg/m2 on days 1,4,8 and 11 reached DLT when combined with docetaxel 75mg/m2 every 21 days in the classic phase I trial undertaken at a selection of institutions including those within the California Cancer Consortium. Similar data have been generated in a heavily pretreated population of breast cancer patients. On this basis, a bortezomib dose of between 1.3 and 1.6mg/m2 twice in a 21 day period with docetaxel 75 mg/m2 on day 1 should be safe. Recent large studies have used three weekly dosing of docetaxel and therefore to facilitate integration into a competitor arm data on the safety and efficacy of bortezomib in combination with a three weekly docetaxel schedule are needed.

Hence we will use the following schedule on a 21 day cycle:

Docetaxel 75mg/m2 IV over 1 hour on day 1
Bortezomib 1.6mg/m2 IV push on days 1 and 8
Prednisone 5mg twice daily orally every day (days 1 through 21 inclusive)

Dose de-escalation (level -1) to a bortezomib dose of 1.3mg/m2 on days 1 and 8 will be utilized for individuals experiencing level 4 non-hematological toxicity, non-deffervescent (reversible) grade 3 toxicity or neutropenic fever. This de-escalation will be considered for the reminder of the cohort if toxicity is excessive at the scheduled interim analysis.

3.0 Pharmaceutical Information

3.1 Bortezomib (Velcade®)

DESCRIPTION AND USE:
Bortezomib (Velcade®) is a water soluble dipeptididyt boronic acid (chemical name: [(1R)-3-methyl-1-[[(2S)-1-oxo-3phenyl-2-[(pyrazinlycarbonyl)
amino]propyl]amino]butyl] boronic acid, molecular weight: 384.24, chemical formula: $C_{19}H_{25}BN_4O_4$, brand name: Velcade®, Millennium Pharmaceuticals, Cambridge, MA) is an antineoplastic agent constituted of a monomeric boronic acid. Bortezomib (Velcade®) is currently approved by the United States Food and Drug Administration (US FDA) and it is registered in Europe for the treatment of multiple myeloma patients who have received at least 2 prior therapies and have demonstrated disease progression on the last therapy.

HOW SUPPLIED:
Bortezomib for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing bortezomib and mannitol at a 1:10 ratio. For example vials containing 3.5 mg of bortezomib contain 35 mg of mannitol.

STORAGE:
Vials should be stored refrigerated at controlled room temperature.

STABILITY:
To date, stability data indicate that the lyophilized drug product is stable for at least 12 months when stored under the recommended conditions.

ADMINISTRATION:
Study drug will be supplied in vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted within eight hour before dosing with 3.5 mL of normal saline (0.9%), Sodium chloride injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted bortezomib should be administered promptly and in no case more than eight hours after reconstitution. Bortezomib should be administered by push bolus intravenous injection over 3-5 seconds. This will occur on days 2 and 8 in this protocol.

Bortezomib is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing bortezomib solution. The pharmacist should prepare bortezomib using a vertical laminar flow biological cabinet (hood) and proper aseptic techniques. It is recommended that gloves and protective garments be worn during bortezomib preparation. If BORTEZOMIB solution contacts the skin, was the skin immediately and thoroughly with soap, water, and

diluted hydrogen peroxide. If bortezomib solution contacts the mucous membranes, flush thoroughly with water.

MECHANISM OF ACTION AND PHARMACODYNAMICS:
Bortezomib is a novel molecule that acts as a potent (Ki = 0.6 nM) and reversible proteasome inhibitor. The proteasome is a final degradative enzyme that has important functions in the catabolic pathway for numerous intracellular regulatory proteins. These include I kappa B kinase/nuclear factor-KB, p53 and cyclin dependent kinase inhibitors p21 and p27. Bortezomib acts by specifically and selectively binding tightly to the active site of proteasome. The anti-neoplastic effects of bortezomib may be due to several mechanisms. Bortezomib induces apoptosis in cells that overexpress Bcl-2. It may also inhibit cell growth signaling pathways and inhibit cellular adhesion molecule expression.

PHARMACOKINETICS:
Bortezomib is rapidly cleared from the plasma after intravenous injection. It is highly protein bound and distributed to second space compartments. The terminal half life of the drug is 9-15 hours. No completed studies in patients with liver or renal impairment are available.

Bortezomib: Safety

The *most common* side effects of VELCADE (ie, incidence ≥10%) observed in subjects are weakness, fatigue, general discomfort, GI effects such as abdominal pain, constipation, diarrhea, nausea, vomiting and loss of appetite, painful sensations or numbness and tingling in hands and feet which may not resolve after discontinuation of VELCADE, flu-like symptoms (fever, chills, muscle cramps and/or aches), decreases of platelets, neutrophils/white blood cells (WBC) and red blood cells, skin rash and itching, decreases in blood pressure, fluid retention, dizziness, changes in heart rate and rhythm, pain in limbs, bones, joints, muscles, and/or back or general pain, shortness of breath, cough, upper respiratory tract infection, pneumonia, headache, blurred vision, altered sense of taste, insomnia, anxiety, nosebleed, and herpes zoster.

Less common side effects of VELCADE (ie, incidence <10%) observed in subjects are deterioration in kidney and liver function, decrease in blood sodium or blood potassium, hepatitis, severe bleeding including central nervous system (CNS) and GI bleeding associated with thrombocytopenia and blood clotting changes, tumor lysis syndrome (TLS), transient small bowel obstruction in subjects who had prior major abdominal surgery, low blood sugar in a few diabetic subjects receiving oral anti-diabetic medication, and acute development or exacerbation of congestive heart failure in patients with risk factors for or existing heart disease.

Although *rare* (ie, incidence <1%), VELCADE may cause allergic reactions (fever, severe skin rash, joint swelling, and pain) and anaphylactic shock. Complications arising from these VELCADE toxicities may result in death.

Further details on the potential risks of VELCADE may be found in the Investigator Brochure.

3.2 Docetaxel

DESCRIPTION AND USE:
Docetaxel (chemical name: (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5b-20-epoxy-12a,4,7b,10b,13a-hexahydroxytax- 11-en-9-one 4-acetate 2-benzoate, trihydrate, empiric formula: C43H53NO14• 3H2O, molecular weight: 861.9, brand name: Taxotere®, (Aventis Pharmaceuticals Products Inc., Bridgewater, NJ) is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel is commercially available and has been widely used in a range of solid tumours including lung, breast, ovarian and head and neck cancers. Docetaxel is FDA approved for the treatment of metastatic breast cancer , non small cell lung cancer, and Androgen Independent Prostate Cancer.

PREPARATION AND ADMINISTRATION PRECAUTIONS
TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

If TAXOTERE concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

TAXOTERE for Injection Concentrate requires <u>two</u> dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the TAXOTERE for Injection Concentrate and the diluent vials contain an overfill.

A. Preparation of the Initial Diluted Solution

1. Gather the appropriate number of vials of TAXOTERE for Injection Concentrate and diluent (13% Ethanol in Water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of TAXOTERE for Injection Concentrate. **<u>If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.</u>**
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to

assure full mixture of the concentrate and diluent. Do not shake.

4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) 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.

B. Preparation of the Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10mg docetaxel/mL) with a calibrated syringe and inject into a 250mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74mg/mL.

   If a dose greater than 200mg of Taxotere is required, use a larger volume of the infusion vehicle so that a concentration of 0.74mg/mL TAXOTERE is not exceeded.

2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE for Injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXOTERE dilution for infusion should be administered intravenously as per protocol under ambient room temperature and lighting conditions.

Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

STABILITY:

TAXOTERE infusion solution, if stored between 2 and 25ºC (36 and 77ºF) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the administration time).

HOW SUPPLIED:
TAXOTERE for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in Water for Injection) vial. The following strengths are available:

TAXOTERE 80 MG (NDC 0075-8001-80)
TAXOTERE (docetaxel) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 and diluent for TAXOTERE 80 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

TAXOTERE 20 MG (NDC 0075-8001-20)
TAXOTERE (docetaxel) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

STORAGE:
Store between 2 and 25°C (36 and 77ºF). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

HANDLING AND DISPOSAL:
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Supply – Docetaxel is available commercially from Aventis, Bridgewater, NJ.

ADMINISTRATION:
Following pretreatment with dexamethasone, docetaxel is infused intravenously over one hour**.** Do not give docetaxel therapy to patients with baseline neutrophil counts of < 1500 cells/mm^3 or platelet counts of < 100, 000 cells/mm^3. The starting dose of docetaxel for this study is 75 milligram per square meter of body surface area on day 1 of each 21 day cycle.

PHARMACODYNAMICS:
Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

PHARMACOKINETICS:
The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase I studies. The area under the curve (AUC) was dose proportional following doses of 40–80 mg/ m^2 and 70-115 mg/m^2 with infusion times of 1 to 2 hours in two separate studies [61]. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β and δ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

A study of 14C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

A population pharmacokinetic analyses have been undertaken based on 535 patients treated with docetaxel at a dose of 100 mg/m^2. Pharmacokinetic parameters derived from this analysis were very close to those from phase I studies. The pharmacokinetics of docetaxel was not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with mild to moderate liver enzyme elevation (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, included a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. On this basis, Aventis Pharmaceuticals recommends that patients with combined abnormalities of transaminase and alkaline phosphatase or elevated serum bilirubin should not be treated with Docetaxel.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the in vitro binding to

plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies show that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on in vitro findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding.

Docetaxel: Safety

Serious side effects
Bone marrow suppression, which is most often manifests as transient neutropenia, is the major potential life threatening toxicity related to docetaxel therapy. Anemia and thrombocytopenia may also occur but are less common and rarely manifest a life threatening toxicity from docetaxel. Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% of the 92 patients premedicated with 3-day corticosteroids. Hypersensitivity reactions requiring discontinuation of the docetaxel infusion were reported in 5 out of 1260 patients with various tumor types who did not receive premedication, but in 0/92 patients premedicated with 3-day corticosteroids. Patients with a history of severe hypersensitivity reactions should not be re-challenged with docetaxel.

Common Symptoms
Nausea and vomiting are common in patients not given antiemetic pretreatment with ondansetron, trapisetron or similar drugs. The use of these drugs renders vomiting uncommon and minimizes nausea. Fluid retention manifests usually by edema of the lower limbs is a common but self limiting side effect of docetaxel. Most patients treated with docetaxel have subtotal alopecia which recovers after therapy. Some patients experience transient fevers and myalgias following the administration of docetaxel.

3.3 Concomitant Medications

Concomitant medications to control the side effects of therapy will be given.

Premedication
The patients will be given dexamethasone orally for 24 hours prior to the dose of docetaxel. In addition, intravenous dexamethasone will be administered prior to intravenous chemotherapy on day 1 along with antiemetic therapy in the form of trapisetron, granisetron, dolasetron or ondansetron or similar agent. Each of these drugs may be continued in oral form for up to 48 hours after chemotherapy. Further management of side effects by the treating physician including further antiemetics,

corticosteroids or benzodiazepines for nausea and/or vomiting is encouraged as needed. However, the need for this intervention should be determined by experience on prior cycles and not given for anticipated side effects. Routine antiemetics will not be given on days 2 and 8 prior to administration of bortezomib.

Dexamethasone decreases incidence and severity and delays the onset of late-occurring fluid retention and also may decrease the incidence and severity of acute hypersensitivity reactions. Dexamethasone 4-8 mg po bid x 3 days, starting 12-24 hours before the planned Taxotere infusion has been an effective schedule.

Other concomitant medication

Administration of any other cytotoxic, hormonal or radiation is not permitted. Patients should not receive any other investigational drugs from 30 days prior to enrollment until 30 days after the final dose of study drugs. Patients requiring radiation therapy for painful lesions will be considered as having evidence of progressive disease and will be taken off study. **Bisphosphonates are permitted** provided administration commenced prior to trial entry and continues in accordance with manufacturers guidelines are institutionally accepted practice. Any toxicities related to the use of Bisphosphonates should be resolved prior to study entry or clearly documented as a preexisting condition at baseline.

Patients will receive full supportive care during the trial, including transfusion of blood products, treatment with antibiotics, antidiarrheals and analgesics when appropriate.

Colony stimulating factors for bone marrow support should not be used prophylactically to prevent neutropenia. Intervention with these agents as part of treatment for febrile neutropenia is acceptable provided dose reduction occurs as per the protocol. Colony stimulating factors should otherwise be used as detailed in the American Society of Clinical Oncology guidelines.

Patients must be withdrawn from antiandrogen therapy prior to the study. For flutamide and nilutamide this should occur 28 days and for biclutamide 42 days prior to registration to remove the potential for withdrawal effect. LHRH agonist therapy (leuprolide, goserelin or similar) will be continued in all patients except those previously treated with surgical bilateral orchiectomy.

3.4 Drug Accountability and Drug Ordering

Once the patient's eligibility has been established and the individual has been registered, docetaxel will be supplied from commercial sources. Bortezomib will be supplied by Millennium at no cost to the patient or study.

4.0 Staging Criteria

STAGING OF ADENOCARCINOMA OF THE PROSTATE
(Modified AJCC/TNM system 1997) [62]

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1: Clinically inapparent tumor not palpable nor visible by imaging
- T1a: Tumor incidental histologic finding in 5% or less of tissue resected
- T1b: Tumor incidental histologic finding in more than 5% of tissue resected
- T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)*

T2: Tumor confined within prostate
- T2a: Tumor involves one lobe
- T2b: Tumor involves both lobes

T3: Tumor extends through the prostatic capsule
- T3a: Extracapsular extension
- T3b: Tumor invades seminal vesicle(s)

T4: Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

*Note: Tumor found in 1 or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in regional lymph node or nodes

Regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Distant lymph nodes are outside the confines of the true pelvis and their involvement constitutes distant metastasis. They can be imaged using ultrasound, computed tomography, magnetic resonance imaging, or lymphangiography

Distant metastasis (M)

MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis*
M1a: Nonregional lymph node(s)
M1b: Bone(s)
M1c: Other site(s)

*Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced

Histopathologic Grade (G)

GX Grade cannot be assessed

G1 Well-differentiated (slight anaplasia)

G2 Moderately differentiated (moderate anaplasia)

G3-4 Poorly undifferentiated or undifferentiated (marked anaplasia)

Stage Grouping

Stage I	T1a N0 M0 G1
Stage II	T1a N0 M0 G2, G3-4
	T1b N0 M0 Any G
	T1c N0 M0 Any G
	T1 N0 M0 Any G
	T2 N0 M0 Any G
Stage III	T3 N0 M0 Any G
Stage IV	T4 N0 M0 Any G
	Any T N1, M0 Any G
	Any T Any N M1 Any G

5.0 Eligibility Criteria

5.1 Inclusion Criteria

- Patient must have had a histological or cytological diagnosis of adenocarcinoma of prostate and currently must have metastatic disease (stage TxNxM1) that is unresponsive or refractory to hormone therapy. Patients must have metastatic prostate cancer deemed to be hormone refractory by one or more of the following (despite androgen ablation and anti-androgen withdrawal where applicable):
  - Progression of measurable disease assessed within 28 days prior to registration.

  OR
  - Progression of non-measurable (i.e. bone scan or PET scan) disease assessed within 42 days prior to registration.

  OR
  - Rising PSA – defined as at least 2 consecutive rises in PSA documented over a reference value (measure 1). The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2^{nd} beyond the reference level) to be greater then the second measure and it must be obtained at least 7 days after the 2^{nd} measure. Patient must have a PSA concentration of at least 5 ng/ml in addition to increasing PSA to be eligible.

  Note: The PSA result (done within 28 days prior to registration) need not be elevated above the normal range for inclusion provided other criteria for progression are met and the serum PSA is at least 2 ng/ml.
- Must have received prior hormonal therapy and have a castrate level of testosterone (less than 100ng/ml within 90 days of entry to the study). Patients treated with orchiectomy are eligible. If patients have been treated with non-steroidal anti-androgens, the patients must have ceased taking flutamide or nilutamide at least 28 days prior to enrollment and at least 42 days prior to enrollment for biclutamide. Either method of castration can have been supplemented with nonsteroidal antiandrogen (e.g. flutamide, biclutamide, nilutamide). Patients may have been treated with "second-line" hormonal therapy such as ketoconazole, aminoglutethimide and/or estrogen therapies but these must have ceased at least 7 days prior to commencement of study therapy.
- May have received at most one prior chemotherapy for hormone refractory prostate cancer provided they have not received docetaxel or Bortezomib for that indication or otherwise within 2 years of trial entry.
- Prior radiation therapy is allowed but it must have been to less than 25% of total body bone marrow (see Appendix 4). Prior use of samarium is permitted, but patients can not have received strontium. (>10 days must have elapsed since completion of RT with recovery from side effects. Soft tissue disease irradiated in the prior 2 months is not and may not be designated as measurable disease).

- Creatinine ≤1.5x the institutional upper limit of normal (within 28 days prior to registration)
- Hepatic function

  Total Bilirubin ≤ ULN

  AST **and** ALT **and** Alkaline Phosphatase must be within the range allowing for eligibility. In determining eligibility the more abnormal of the two values (AST or ALT) should be used.

	AST or ALT:			
ALK PHOS:	**≤ ULN**	**>1x but ≤1.5x**	**>1.5x but ≤5x**	**>5x ULN**
≤ ULN	Eligible	Eligible	Eligible	Ineligible
>1x but ≤2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but ≤5x	Eligible	Ineligible	Ineligible	Ineligible
>5x ULN	Ineligible	Ineligible	Ineligible	Ineligible

- Adequate bone marrow function. Complete blood count with differential must be done within 14 days prior to registration

  Absolute neutrophil count $\geq$ 1,500/mm^3

  Hemoglobin $\geq$ 8.0 g/dl

  Platelet count $\geq$ 100,000/mm^3
- ECOG performance status 0-3. (For patients with PS of 3, cause must be due to pain secondary to bone metastases to be eligible)
- Patients should (for good medical practice) have stabilization of their analgesic medications for at least one week prior to receiving study medication (sections 7.1 and 9.1).
- No other chemotherapy, biological response modifiers, RT, radioisotope therapy (e.g. samarium or strontium), corticosteroid, or concomitant hormonal therapy may be given during protocol treatment.
- Bisphosphonate therapy is permitted provided it commences prior to study entry and is maintained at recommended dosing intervals.
- Completed baseline McGill Pain Questionnaire and Pain Medication Log prior to registration. The nurse or CRA must complete MPQ and PML cover sheet for baseline assessment prior to registration. If unable to complete questionnaires in English or Spanish, patient can be registered without contributing to QOL study).
- Men of childbearing potential must be willing to consent to using effective contraception while on treatment and for a reasonable period (90 days) thereafter.
- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

5.2 Exclusion Criteria

- Myocardial infarction or angina pectoris within one year of registration
- History of brain metastases, treated or untreated. (Patients with neurological symptoms must have CT or MRI brain negative for metastatic disease within 56 days prior to registration). Patients who have recovered from spinal cord compression and are clinical stable may enter the study provided they fulfill other criteria.
- Not recovered from major infections and/or surgical procedures, or has significant active concurrent other medical illness precluding protocol therapy or survival.
- Known or anticipated severe hypersensitivity reaction to bortezomib, boron, mannitol, docetaxel or polysorbate 80.
- Other prior malignancy (except patients who have had another stage I or II malignancy currently in complete remission or other cancer with no evidence of disease for greater than 5 years from accrual to the current trial. Patients with basal or squamous cell carcinoma of the skin that have been treated with curative intent can be accrued to this trial 30 days after treatment. Solar keratoses treated topically do not preclude entry).
- Patient has ≥Grade 2 peripheral neuropathy within 14 days before enrollment.
- Prior therapy with docetaxel or paclitaxel
- Prior treatment with more than one prior chemotherapy for hormone refractory prostate cancer
- Ongoing therapy with drugs known to inhibit P4503A4 drug metabolism including:
  Macrolide antibiotics: erythromycin, troleandomycin, azithromycin
  Imidazole antifungal agents: ketoconazole, itraconazole, fluconazole
  HIV protease inhibitors
  Immunosuppressive agents: cyclosporin, FK-506
- Ongoing therapy with drugs known to induce P4503A4 drug metabolism including: Phenobarbital, phenytoin, carbamazepine, griseofuvin and rifampin.

6.0 Stratification/Descriptive Factors

This is a single arm study.

7.0 Treatment Plan

7.1 Treatment overview

In this pilot phase II study to be conducted at USC/Norris Comprehensive Cancer Center and LAC-USC Medical Center patients with TxNxM1 prostate cancer that have symptomatically progressed following hormonal therapy will be evaluated for response to and toxicity from chemotherapy with bortezomib and docetaxel. Registration will occur only after all criteria are met. The primary endpoint of the study is PSA response with symptomatic response, RECIST response and therapeutic toxicity assessment as secondary endpoints. The dosing schedule will involve therapy over 21 day cycles. On day 0 dosing with dexamethasone 8 mg twice daily will commence and continue for 3 days. On day 1 docetaxel with be given intravenously over one hour. On day 1 bortezomib will be given as an intravenous push dose over 3-5 seconds and the patient observed for one hour for adverse effects particularly hypotension. The day 1 dosing of bortezomib will be repeated on day 8. Patients will commence prednisone 5mg twice daily orally on or before day1 and take it each and every day until study treatment ends. On day 21 dexamethasone dosing will restart for the subsequent cycle and continue for 3 days. The physician has the option of reducing the dose of dexamethasone if it is producing side effects. If this is the case then the dose may be reduce to 4 mg BID for three days and then subsequent further reduced by dosing only for 2 days starting on day 0 with doses given on day 1 (docetaxel administration day) but not day 2. No dose escalation will occur but toxicity may result in treatment delay and/or dose reduction. Withdrawal from therapy will occur on the basis of progressive disease after the completion of the second 21 day cycle of chemotherapy, unacceptable toxicity, patient election or death. Patients will self assess their disease related pain on a weekly basis by maintaining a diary which records the Present Pain Intensity (PPI) score as well as analgesic usage. Pain Medication Log and McGill Pain Questionnaire will be undertaken prior to each cycle of chemotherapy and, if appropriate, at withdrawal from the study. Serum PSA estimations will be undertaken with each cycle of chemotherapy, 4 weeks after cycle 6 and then 3 monthly until 12 months after registration. For patients with measurable or non-measurable soft tissue or bone disease, appropriate imaging will be repeated prior to the third cycle of chemotherapy and then 4 weeks after the sixth cycle unless clinical status dictates otherwise.

7.2 Dosage and schedule

Dexamethasone	8mg PO q12 hours on days 0, 1 and 2 in every 21 day cycle and Dexamethasone 10mg IV or PO (witnessed) 30 minutes prior to docetaxel administration.
Docetaxel q21 days	75mg/m^2 of body surface area intravenously over 60 min on day 1
Bortezomib	1.6 mg/m2 of body surface area intravenously over 3-5 seconds on day 1 and day 8 of a 21 day cycle

Prednisone 5mg twice daily orally every day

Maximum of 12 cycles will be administered. 1 cycle = 21 days.
Dose escalation: Nil
Continuation of therapy: Treatment to continue for a maximum of 12 cycles for patients who experience stabilization, PR or CR.

7.3 Pain and Analgesia assessment

Including the following measures:

a. Analgesic consumption - Assess prior to registration, every cycle through a maximum possible 12 cycles, and then, at 1 yr. post-registration using the Pain Medication Log. Record all analgesics used for the 24-hr period prior to each return to the clinic for treatment.
b. Assess pain at interview prior to registration, every cycle through 12 cycles, and then, at 1 year post-registration using the Pain Questionnaire (Appendix 3).
    - If patient goes off-treatment before cycle 6, administer the Pain Medication Log (Appendix 7) and Pain Questionnaire (Appendix 3) at study exit.
    - If Medication Log (Appendix 3) and Pain Questionnaire (Appendix 3) are not done, this must be indicated with a reason on the log or questionnaire cover sheet.

Criteria for removal from protocol treatment

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- A treatment cycle delay or bortezomib interruption of >3 weeks
- Patient request
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease at any time

- Treatment delay >3 weeks due to toxicity or completion of the trial.

7.4 Toxicities and Dose Modification

Docetaxel

Dose modifications for docetaxel will only be done for blood counts, biochemical liver dysfunction, neurological (including fatigue) and cutaneous toxicities and for stomatitis or diarrhea but not for other toxicities which need to be managed.

Myelosuppression

Dosage modification for docetaxel related to blood counts is based on day 22 and "any time during cycle" absolute neutrophil and platelet count of the preceding cycle for the next and additional courses. The succeeding cycle of bortezomib and docetaxel must not be administered until neutrophil count is >1,000 cells/mm^3 and platelet count >100,000 cells/mm^3. If counts are below these levels, recheck weekly and retreat using parameters outlined below. Dose modification is for the next cycle and all subsequent cycles. If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued. Doses reduced for toxicity should not be re-escalated back to starting level.

Colony stimulating factors for bone marrow support should not be used prophylactically to prevent neutropenia. Intervention with these agents as part of treatment for febrile neutropenia is acceptable provided dose reduction occurs as per the protocol. A second course of treatment with colony stimulating factors will require removal from the study.

Time point	Parameter	Criteria	Modification
Day 1 in each cycle	ANC and/or Platelets	<1000 cells/mm^3 < 99,999 cells/mm^3	Docetaxel dose is decreased by 25%
Any time during cycle	ANC	<500 cells/mm^3 plus >38.5 degree Celsius or <500 cells/mm^3 for = 7 days	Docetaxel dose is decreased by 25%
Any time during cycle	Platelets	<75,000 cells/mm^3 plus bleeding	Docetaxel dose is decreased by 25%

If a patient qualifies for a third drop in dose then they should be removed from the study.

Bortezomib dosage will not be modified for myelosuppression.

Anemia

There are no specific recommendations for the management of anemia.

Hypersensitivity Reactions

No dose reductions will be made.

Management of Hypersensitivity Reactions

Severity of Symptoms	**Treatment Guidelines**
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	· consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient · then, complete Taxotere infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	· interrupt Taxotere infusion · give diphenhydramine 50 mg IV with or without hydrocortisone 100 mg IV; monitor patient until resolution of symptoms · resume Taxotere infusion after recovery of symptoms; depending on the physician's assessment of the patient, Taxotere infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate*, (e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the 1-h infusion rate)* · depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, *(e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate)*
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	· immediately discontinue Taxotere infusion · give diphenhydramine 50 mg IV with or without hydrocortisone 100 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms · the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
Anaphylaxis (NCI grade 4 reaction)	· NO FURTHER STUDY DRUG THERAPY

Late-occurring hypersensitivity symptoms (e.g., appearance within 1 week after treatment of a localized or generalized pruritus), give symptomatic treatment with oral anti-histamine. May also give additional PO or iv anti-histamine for the next cycle of treatment, depending on intensity of reaction. No dose reduction to be made. Inform and monitor patient of risk for recurrent reactions.

Fluid Retention (Docetaxel)

a. No dose reduction is planned.
b. New onset or symptomatic edema or other signs of increasing fluid retention: Treat with PO diuretics. Suggested diuretic therapy: (1) Dyazide 1 cap PO daily increased to 1 cap TID if needed. (2) Furosemide 40 mg PO daily + K + supplementation, if not responsive to dyazide. (3) Furosemide 20 mg PO daily + metolazone 2.5 mg PO daily + K + supplementation, if still not responsive after a 2-wk trial. (4) Further therapy customized depending on clinical situation.

Abnormal Liver Function Tests (Docetaxel)

Both AST and ALT should be drawn. The more abnormal of the two values (AST or ALT) should be used in determining the dose.

	AST or ALT:			
ALK PHOS:	**≤ ULN**	**>1x but ≤1.5x**	**>1.5x but ≤5x**	**>5x ULN**
≤ ULN	Full Dose	Full Dose	Full Dose	Hold*
>1x but ≤ 2.5x	Full Dose	Full Dose	Reduce Dose#	Hold*
>2.5x but ≤ 5x	Full Dose	Reduce Dose#	Hold*	Hold*
>5x ULN	Hold*	Hold*	Hold*	Hold*

#Reduce dose by 25%

*Hold until recovered, maximum 21 days, then re-treat at a 25% dose reduction.

"Recovered" is defined as meeting the study baseline eligibility criteria.

Bilirubin: TAXOTERE® should not be administered to patients with serum total bilirubin >ULN. If serum total bilirubin is >ULN on treatment day, hold TAXOTERE® until serum total bilirubin is ≤ ULN (maximum 21 days), then re-treat at a reduced dose.

Cutaneous Toxicity (Docetaxel)

a. Gr 2 cutaneous toxicity: No change. If occurring at the time of scheduled re-treatment, hold treatment until ≤Gr 1 for a maximum of 3 wks and re-treat with no dose reduction. If no recovery to ≤Gr 1 within 3 wks, off-study.
b. Gr 3 or 4 cutaneous toxicity occurring at the time of scheduled re-treatment: Hold treatment until ≤Gr 1 for a maximum of 3 wks and re-treat with 25% dose reduction. If no recovery to ≤Gr 1 within 3 wks, off-study.
c. If Gr 3 or 4 cutaneous toxicity occurs during the cycle, and there is recovery at time of scheduled re-treatment, re-treat with 25% dose reduction.

Diarrhea (Docetaxel and/or Bortezomib)

a. Gr 1 or 2 diarrhea (=6 loose stools/24 hrs): Treat prophylactically in subsequent cycles with loperamide 2 tab or diphenoxylate in addition to 1-2 tablets after each loose stool, no dose reduction.
b. Gr 2 diarrhea despite prophylactic treatment for more than 7 days: give loperamide or diphenoxylate HCl with atropine SO4, dose reduce bortezomib by 25%.

c. Gr 3-4 diarrhea: Off study. Octreotide is recommended until diarrhea abates.

Stomatitis (Docetaxel)
If stomatitis > grade 1 is present on day 1 of any cycle, treatment (both drugs) should be withheld until stomatitis has resolved to grade 1 or less. If Gr 3/4 stomatitis occurs, the dose of docetaxel should be reduced 25% for subsequent cycles.

Peripheral Neuropathy (Docetaxel or Bortezomib)

Both docetaxel should be reduced by 25% and bortezomib by 0.3mg/m^2 per dose for Gr 1 with pain or Gr 2 neuropathies and the dose delayed until resolution to Gr 1. Treatment (both drugs) should be discontinued for Grade 4 neuropathy or if more than 2 reductions in bortezomib dose are required.

Recommended Dose Modification for VELCADE-related Neuropathic Pain and/or Peripheral Sensory Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE by 0.3mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a further reduced dose of VELCADE by 0.3mg/m^2 and change treatment schedule to once per week.
Grade 4 (Permanent sensory loss that interferes with function	Discontinue VELCADE
NCI Common Toxicity Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

Other Non-Hematologic Toxicity

For Gr 3 and 4 toxicities, treatment should be withheld until the toxicity resolves to Gr 1 or less, then reinstituted (if medically appropriate) at a 25% (docetaxel) or 0.3mg/m^2 (bortezomib) dose reduction in either or both drugs based on attributed toxicity. If treatment is withheld for longer than 3 weeks due to Gr 3 or 4 toxicity of any type, the patient will be withdrawn from study.

Questions regarding attribution and dose modification must be discussed with the Principal Investigator, Dr. David Quinn.

7.5 Adverse event reporting

7.5.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product. For a marketed product, this includes any failure of expected pharmacological action.

The term "adverse event" could include any of the following events which develop or increase in severity during the course of the study:

a. Any signs or symptoms whether thought to be related or unrelated to the condition under study;
b. Any clinically significant laboratory abnormality or laboratory abnormality that requires medication or treatment. If the patient requires medication or treatment, the laboratory abnormality is to be recorded on the adverse event CRF page;
c. Any abnormality detected during physical examination that was not recorded on the pretreatment physical exam.

It is the primary responsibility of the Investigator to report all serious adverse events (SAEs) as defined below to the appropriate regulatory bodies (i.e. local IRB).

All patients will be followed for 60 days after the last dose of chemotherapy for the purpose of reporting SAEs. Any SAE involving a patient in the study, including death due to any cause that occurs during the study period and for up to 60 days after the last dose of chemotherapy, must be reported to appropriate regulatory bodies (i.e. local IRB). All "serious" events must be followed with appropriate medical management until resolved or stabilized. All AEs with possible relationship to chemotherapy in the Investigator's opinion will be followed for 60 days after the last chemotherapy dose or until resolved or stabilized.

Reporting Safety Information

Periodic observation and open-ended questions will be used to assess patients for the occurrence of adverse events during the clinical trial.

All adverse events or other signs and symptoms which occur from the administration of the first dose of study drug until 30 days after the final dose of

study drug will be recorded on the CRF (except as noted in Section 7.4.4). Intensity will be graded according to toxicity criteria in Appendix 2.

Any non-serious adverse event (see section 7.5.1 for definition and handling of serious adverse events) that has not resolved or returned to baseline after the final dose of study drug will be followed until 30 days after the final dose of the study drug. Adverse events continuing beyond this time should be followed by the investigator or treating physician in accordance with standard medical practice.

Recording Abnormal Laboratory Findings as Adverse Events

Abnormal laboratory values will be recorded on the laboratory CRF pages. A laboratory abnormality per se will not be recorded as an adverse event unless it constitutes a serious adverse event that requires prompt reporting (e.g. requires inpatient hospitalization), represents the primary reason for treatment/study discontinuation or is associated with a clinical diagnosis. In the case of the latter, the clinical diagnosis (e.g. renal failure), not the laboratory abnormality (e.g. raised creatinine) should be recorded as an adverse event on the CRF (and serious adverse event form, as appropriate).

Events Exempt from Recording as Adverse Events

The following events will not be recorded as adverse events:

a. Lack of efficacy
b. Medical or surgical procedures (if a condition that leads to a procedure is an AE then the condition, no the procedure, will be recorded as an AE)
c. Laboratory abnormalities except for expected toxicities as indicated in Section 7.4.

7.6 Serious Adverse Events

7.6.1 Definition of a Serious Adverse Event

A **serious adverse event** (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive

treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The definition of "related" is that there is a reasonable possibility that the drug caused the adverse experience.

Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity or carcinogenicity.

A fatal or life-threatening event, regardless of cause, which occurs within 30 days of the last dose of study drug, or after 30 days, and is a result of delayed toxicity due to administration of the study drug, will be reported as an SAE.

7.6.2 Reporting of a Serious Adverse Event

Any serious adverse event, regardless of causality, occurring from enrollment until 30 days after the final dose of study drug must be promptly reported to Aventis and Millennium. Any serious adverse event occurring after this time is thought to be associated with prior treatment with study drug must also be promptly reported. Serious adverse events must be followed until resolved or deemed irreversible.

All serious, related adverse events will be reported and documented on MedWatch Form FDA 3500A (www.fda.gov/medwatch/getforms.htm) and forwarded directly to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department as well as Millennium *Product* Safety.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

These reports may be sent by **FAX** or **E-MAIL to:**

Reports by **FAX** should be sent to
Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department
FAX: (908) 231-4827
Telephone: (617) 551-2972
AND Millennium Product Safety
Fax: (617) 551-3746,
within 24 hours of receipt by investigator.

FAX transmission should include the following on the provided IIT SAE REPORT, fax cover form (below):

Investigator-Initiated (IIT #) study number: #16164
Study Title: Phase II Study to Evaluate Bortezomib and Docetaxel as therapy for patients with hormone refractory prostate cancer
Name of Principal Investigator: David Quinn, M.D., Ph.D

Reports by **E-MAIL** should be sent to:
GPEmailbox@aventis.com AND
E-mail: productsafety@mpi.com,
within 24 hours of receipt by investigator.

E-Mail transmission should include the following:

Investigator-Initiated (IIT #) study number: #16164
Study Title: Phase II Study to Evaluate Bortezomib and Docetaxel as therapy for patients with hormone refractory prostate cancer
Name of Principal Investigator: David Quinn, M.D., Ph.D

For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

Report by telephone to the Principal Investigator (see page 1) within 24 hours at (323) 865 3000 (fax to 323 865 0089 or email to diquinn@usc.edu are acceptable if contact cannot be made by telephone):

a. All life threatening events (grade IV) which might be due to drug administration.
b. All fatal events occurring from enrollment until 30 days after the final dose of study drug, and any death occurring after this time that is judged possibly related to prior treatment with study drug.
c. First occurrence of any grade III toxicity.

Toxicities of a level of grade 3 or more defined in Appendix 2 will also be reported to the USC / Norris Comprehensive Cancer Center IRB within 5 days. All adverse events that are serious, unexpected, and definitely, probably, or possibly related, or of undetermined relationship to the study drug must be reported to the IRB.

If for any reason a patient is withdrawn before completing the study, the reason for withdrawal must be entered on the End of Study case report form (CRF) and other appropriate CRFs must be completed. All data on the patient prior to discontinuation will be made available to Aventis, Millennium or its designees.

The institution (USC) will send Millennium copies of all serious adverse event (SAE) reports regardless of association with the Drug(s) and regardless of whether the SAE is considered expected by the investigator within five (5) business days of the report being sent to the applicable regulatory agency or the occurrence of the serious adverse event if a filing is not required. Therefore, this request is made irrespective of whether an Investigational New Drug (IND) or foreign equivalent is required. Additionally, Millennium requests copies of any correspondence or telephone conversation logs with regulatory authorities regarding all SAEs, arising in the course of the Clinical Trial, within five (5) business days of such report or correspondence being sent to the regulatory authorities or the occurrence of the logged telephone conversation with such regulatory authorities, whichever occurs earlier. Millennium's Product Safety Department will send to the Investigator-Sponsor a monthly listing of the SAE reports received for site verification. Institution and/or Principal Investigator will be responsible for forwarding such reports to Sub-investigator(s).

For both serious and non-serious adverse events, the investigator must determine both the intensity of the event and the relationship of the event to drug administration.

Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 3.0, as a guideline, wherever possible. The criteria are provided in the study manual and also are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to drug administration will be determined by the investigator responding yes or no to the question: Is there a reasonable possibility that the adverse event is associated with the drug?

8.0 Patient evaluation

The investigations undertaken reflect standard of care assessments for patients with hormone refractory prostate cancer.

8.1 Pretreatment Studies

a. Complete history and physical examination.
b. Height, weight, BSA
c. ECOG status
d. Blood chemistry including liver panel (chem 24 to include Glucose, Na, K, Cl, CO2, Tbili, Alk Phos, ALT, AST, calcium, albumin) and lactate dehydrogenase.
e. CBC, differential, (including absolute neutrophil count) , platelet count PT-INR/PTT
f. Serum PSA
g. Serum testosterone
h. Chest x-ray, unless patient has had CT of chest
i. EKG
j. CT scan abdomen and pelvis (add chest CT if chest x-ray abnormal or clinically indicated and CT or MRI of brain if clinically indicated) plus pretreatment quantification of disease on imaging modalities deemed measurable (within 28 days of registration)
k. Whole body bone scan (within 42 days of registration)
l. Pain Medication Log
m. Pain Questionnaire (appendix 3)
n. Toxicity assessment

8.2 Evaluation During Treatment

The patient will have the following undertaken prior to commencement of each cycle of chemotherapy (i.e. every 21 days):

a. Appropriate history and physical examination.
b. Weight, BSA
c. ECOG status
d. Blood chemistry including liver panel to include Glucose, Na, K, Cl, CO2, Tbili, Alk Phos, ALT, AST, calcium, albumin
e. CBC, differential (including absolute neutrophil count), platelet count.
f. Serum PSA
g. Pain Medication Log
h. Pain Questionnaire (Appendix 3)
i. Toxicity assessment

In addition, prior to the third cycle of chemotherapy imaging procedures undertaken at baseline that demonstrated measurable or non-measurable disease will be repeated.

8.3 Evaluation Post-treatment

Four weeks following the last cycle of chemotherapy and each subsequent three monthly review visit for responding patients, the following will be undertaken:

a. Physical examination.
b. Blood chemistry including liver panel to include Glucose, Na, K, Cl, CO2, Total bilirubin, Alkaline Phosphatase, ALT, AST, calcium, albumin
c. CBC, differential, (including absolute neutrophil count), platelet count.
d. Serum PSA
e. Pain Medication Log
f. Pain Questionnaire (Appendix 3)
g. KPS

In addition, four weeks following the last cycle of chemotherapy imaging procedures undertaken at baseline that demonstrated measurable or evaluable disease will be repeated. Further imaging procedures will then be performed only of clinically indicated, except if the physician opts to continue therapy to a total of 12 cycles where imaging procedures undertaken at baseline must also be repeated four weeks after the completion of cycle 12.

8.4 Study Calendar

Parameter				
	Pre-Study	**Day 1 each cycle[2]**	**Post-Rx (at 21 days)**	**F/U visit[1]**
History	**X**	**X**		
Physical exam	**X**	**X**	**X**	**X**
Weight, PS	**X**	**X**	**X**	**X**
CBC[5]	**X**	**X**	**X**	**X**
CMP to include Glucose, Na, K, Cl, CO2, Total bilirubin Alk Phos, ALT, AST, calcium, albumin [5]	**X**	**X**	**X**	**X**
CT or MRI of brain (if clinically indicated)	**X**			
LDH, PT INR / PTT and Testosterone	**X**			
CT or MRI of chest (if CXR abnormal or clinically indicated)	**X**			
EKG[3]	**X**			
CXR[3]	**X**			
CT Abdomen and Pelvis[3,6]	**X**		**X[7]**	
Bone Scan[4,6]	**X**		**X[7]**	
Serum PSA	**X**	**X**	**X**	**X**
Pain Medication Log (App 3)	**X**	**X**	**X**	**X**
Pain Questionnaire (App 3)	**X**	**X**	**X**	**X**
Therapy with bortezomib and docetaxel + prednisone		**X**		
Toxicity assessment	**X**	**X**	**X**	

1. Follow-up visits will be every three months for 2 years, then every six months for three years, then yearly

2. Each cycle is 21 days of therapy

3. Must have EKG, chest X-ray and CT scan of abdomen and pelvis (within 28 days prior to registration). Chest X-ray may be omitted if a CT of the chest is undertaken.

4. Must have bone scan (within 42 days prior to registration)

5. Prestudy laboratory tests within 28 days of registration, LDH, PT INR. PTT and testosterone at base line only

6. Prior to 3rd cycle, repeat and every 6 weeks if measurable or non-measurable disease at baseline. Patients with partial responses by RECIST criteria should have confirmatory imaging done 4-6 weeks after the first recorded objective.

7. If given 12 cycles, repeat imaging studies 4 weeks after completion of cycle 12, otherwise repeat 4 weeks after the last cycle of therapy.

9.0 Criteria for Evaluation and Endpoint Definitions

Sites distant to USC have agreed to fax to 323 865 0089 copies of USC Toxicity Assessment Worksheet and Case Report Forms within 8 days of the beginning of each cycle where toxicity and response are assessed. Data will be stored centrally at USC for this study.

The primary outcome measure in this trial will be PSA response rate. Secondary outcome measures will be the pain response rate, the response rate as measured by improved imaging studies, and safety.

Evaluable for pain response. Patients will be considered evaluable for a pain response if the baseline analgesic use was determined, and at least 4 weekly assessments of PPI and analgesic score are available from any 8-week period from the period after the initiation of therapy until discontinuation of study medication. If patients develop increased pain which precludes completion of these forms then the patient will be deemed to have progressed.

Evaluable for PSA and/or measurable response. Patients will be considered evaluable for PSA response if the baseline PSA was determined and >5 ng/ml. and at least two assessments of PSA are available from the period after the initiation of therapy until discontinuation of study medication. Patients will be considered evaluable for measurable response if they have had a further imaging procedure subsequent to that performed at study baseline.

Evaluable for toxicity: All patients will be evaluable for toxicity if they have received any study drug.

9. 1 PSA Response

The primary endpoint in this study will be PSA response, defined below. In addition, PSA doubling time will be calculated.

For purposes of this study, patients should be reevaluated for PSA response every 21 days. A confirmatory PSA level should be obtained 3-4 weeks following initial documentation of a PSA response.

9.1.1 Definitions: PSA response

PSA response and PSA progression are defined below, using the criteria of Bubley *et al.* (1999). On case report forms, PSA response will be recorded in a field distinct from clinical progression. After study entry, disease activity evaluation will be made and recorded using the following criteria:

9.1.1.1 PSA Normalization (PSA-N): PSA-N will be recorded on case report forms for any evaluation where the PSA level is undetectable (<0.1ng/ml, if the assay used is the Tosoh assay – otherwise, it will depend on the level of detectability based on method of determining PSA – is this correct?). If the PSA-N response is confirmed by a second measurement at least 3-4 weeks later, the patients best PSA-response will be considered PSA-N

9.1.1.2 PSA Partial Response (PSA-PR): A PSA-PR will be recorded if the PSA decreases by at least 50% from the baseline (pretreatment, within

14 days of start of treatment) value. If confirmed by a second measurement at least 3-4 weeks later, the patient's best PSA-response will be PSA-PR.

9.1.1.3 PSA Progression: In patients whose PSA levels never decreased: PSA progression is defined as a 25% increase over the baseline (pretreatment, within 14 days of start of treatment), **and** an increase in the absolute value in the PSA value of 5 ng/mL, relative to the baseline PSA level – and which is confirmed by second value 3-4 weeks later.

In patients whose PSA levels initially decreased: PSA progression is defined as a 25% increase over the nadir (defined as the lowest PSA value observed – based on the baseline value [which should be Day 0, day of treatment start, or within **14** days of start of treatment if Day 0 is not available] and on all values obtained since start of treatment) **and** an increase in the absolute value of the PSA value of 5 ng/mL, relative to the nadir – which is confirmed by a second value 3-4 weeks later.

9.1.1.4 PSA Progressive Disease (PSA-PD): A best response of PSA-PD will be recorded for those patients who did not achieve a confirmed PSA-N or PSA-PR and who experienced PSA progression within 3 months of start of treatment.

9.1.1.5 PSA Stable Disease: Patients who remain on-treatment for a minimum of 3 months and whose PSA levels do not meet the criteria for either PSA-N, PSA-PR or PSA progression during that time, will be classified as having a best response of PSA-SD.

9.1.1.6 Confirmatory Measurement**:** To be assigned a status of PSA-N or PSA-PR, changes in PSA must confirmed by repeat assessment that should be done 4 weeks after the criteria for response were first met. In the case of PSA-SD, follow-up measurements must have met the PSA-SD criteria every 3 weeks.

9.1.2 Other PSA-Based Definitions

- PSA Response Duration: PSA response duration is calculated from the date of the first ≥ 50% decline in PSA till the first documentation of PSA progression.

- Time to PSA Progression (TTP-PSA): TTP-PSA is measured from the start of treatment until the date of the first documentation of PSA progression.

9.2 RECIST criteria

For the purposes of evaluating the soft tissue tumor response, patients should be reevaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response. An additional set of imaging studies will be done 4 weeks after the last cycle of chemotherapy.

Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee {Therasse et al, 2000}. Changes in only the largest diameter (one-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.2.1 Measurable disease

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

9.2.2 Non-measurable disease

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

9.2.3 Target lesions

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

9.2.4 Non-target lesions

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

9.3 Response Criteria and 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.

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

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 when both methods have been used to assess the antitumor effect of a treatment.

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

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.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria

9.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

9.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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

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

9.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 9.3.1).

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

Note:

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

- X 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 lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see section 9.3.3).

9.4.2 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 recurrent disease is objectively documented.

9.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.5 Progression-Free Survival

Progression-free survival will be defined as the interval from study entry to progression as define by RECIST criteria.

9.6 Response Review

Response review will occur at two levels:

1. Measurement at each institution is undertaken by the clinical investigator in addition to the standard radiology report produced. Each institution within the California Cancer Consortium undertakes peer review of any designated partial or complete response.
2. The consortium undertakes regular random centralized consensus audits of radiology from trials undertaken.

9.7 Definition of pain response

Prior to receiving any study drugs, patients will have an initial adjustment and stabilization of their analgesic medications. This to achieve optimal pain control with the initial adjustment. The patient's pain will be considered stable provided there is no significant (e.g. >25% dosage change or new pain agent or modality) increase in number or frequency or strength of pain medications taken in a 5-7 day period prior to study entry.

Since the treatment of patients with HRPC is palliative, the effects of drug therapy on the symptoms related to their disease are important. Patients will self assess their disease related pain by answering questions on the Pain questionnaire (Appendix 3) [64-66] as well as analgesic usage (Appendix 3) on the first day of each cycle.

The PPI scale has verbal descriptors (0 = no pain, 1 = mild pain, 2 = discomforting pain, 3 = distressing pain, 4 = horrible pain, and 5 = excruciating pain); patients will be asked on on the first day of each cycle to clarify the average pain level during the previous 24 hours, using the PPI scale. The quantity of analgesics will be converted to morphine equivalents for determination of the analgesic score.

Patients may take analgesics for acute inter-current problems such as headaches, which will not be attributed to tumor pain. The baseline values of PPI and analgesic score will be the values obtained most recently before the initiation of study drugs.

The criteria for the Pain Response and Progression are as follows:

Response: A 2-point or more reduction in item 4 from baseline (or complete loss of pain if baseline score was <2), maintained for at least 4 weeks, in the setting of stable or decreasing analgesic score (also compared to the baseline). Response will be based on at least four weekly pain questionnaire and analgesic score

determinations in a 6 week period. A stable analgesic score is defined as a ≤25% increase from baseline score. There should be no progressive disease (as defined in sections 9.4 and 9.5 below) prior to or during the PPI response period.

Progression : A 2-point or more increase from baseline or best pain response, in the setting of stable or increasing analgesic medication usage. Alternatively, a 50% increase in analgesic score with no change or any increase in PPI score coupled with other evidence of disease progression (as defined in section 9.4 and 9.5 below).

Duration of pain response

Duration of pain response will be calculated for all patients who are responders by the pain criteria (section 9.1). It is calculated from the start of the treatment until date of pain progression (section 9.1).

9.8 Toxicity definition

The safety and toxicity of this regimen at the doses and schedule used in this protocol will be evaluated. All signs and symptoms will be recorded in the patient's case report form (CRF). Toxic effects of chemotherapy will be assessed using the expanded NCI Common Terminology Criteria for Adverse Events (CTCAE 3.0) in Appendix 2.

10.0 Statistical Considerations

Design of the clinical trial

This is a two-stage Phase II study to evaluate bortezomib and docetaxel as therapy for patients with hormone refractory prostate cancer.

Study Design and Justification of Sample Size:
Since the entry criteria for this trial are, in part, PSA based**,** the primary endpoint in this trial will be tumor response as determined by PSA criteria [67]. However, imaging to document disease with a bone scan and CT of chest, abdomen and pelvis will be undertaken to document disease at baseline and repeated every two cycles of therapy (every 6 weeks) to evaluate the response to bortezomib and docetaxel in this setting. A two stage minimax design suggested by Simon will be used [68]. Based on studies of single agents for the treatment of hormone refractory prostate cancers, a PSA response rate of 25% or less would be disappointing, while a true PSA response rate of 50% or greater would be considered promising and would encourage further study of bortezomib and docetaxel and prednisone in this setting with this schedule. In the first stage, accrual will continue until 17 patients are evaluable for response. If 5 or fewer responses are observed, accrual will stop with the conclusion that the regimen with PS341 is not promising for further study. If 6 or more

responses are observed in the first 17 patients, an additional 20 patients will be accrued during the second stage of the study. Fourteen (14) or more responses out of 37 patients will be considered as evidence warranting further study of the regimen providing other factors, such as toxicity and survival, also appear favorable. If 13 or fewer responses out of 37 patients are observed, further study of this regimen of PS341 and docetaxel may not be warranted.

With this design, the probability of falsely declaring a regimen with a 25% response rate as warranting further study is 0.05 (alpha) and the probability of correctly declaring an agent with a 50% response rate as warranting further study is 0.90 (power).

Stopping rules will not be applied for secondary endpoints.

Toxicity Monitoring

We expect the regimen to be well tolerated. Nonetheless, toxicity will be monitored on an ongoing basis according to guidelines based on the sequential probability ratio test. Unacceptable toxicity for the purposes of this analysis will be defined as treatment related death, grade 4 non-hematological toxicity or grade 4 hematological toxicity requiring platelet transfusion or hospital admission for treatment of neutropenic fever over 38.5 degrees Celsius. Clear evidence that the chance of unacceptable toxicity is greater than 20% will lead to suspension of accrual. The decision to continue unchanged, modify the regimen, or terminate the trial will be based on a careful review of all patients treated to date, all toxicities experienced, the response to therapy, the time to progression and overall survival to date. The rules given below will trigger such a review (and are based on the sequential probability ratio test with the theoretical parameters set to α=0.10, β=0.10, p_o=0.20, p_a=0.40). At the completion of the study, all toxicities will be summarized and reported. During the conduct of the trial, when unacceptable toxicity is observed, the number of patients (X) who have experienced unacceptable toxicity will be compared to the number of patients (N) who are evaluable for toxicity. If the number of patients, N, is greater than N_X, the number given in the bottom row of the table below, then accrual will continue. If N is less than or equal to N_X, then accrual will be suspended for review of the data.

Table: Criteria for Suspending Accrual to Evaluate Toxicity											
X: # pts with unacceptable toxicity	4	5	6	7	8	9	10	11	12	13	14
Nx: Suspend trial of # evaluable pts. (N) is ≤ Nx	≤ 5	≤ 9	≤12	≤16	≤19	≤23	≤26	≤29	≤33	≤36	≤37

These rules were selected to ensure a reasonable chance that the trial would not be suspended if the true chance of unacceptable toxicity were less than 20% and a reasonable chance that it would be suspended if the true chance were 40% to 45%. The table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval.

True Chance of Unacceptable Toxicity	15%	20%	25%	35%	40%	45%
Probability of Suspending Accrual to Review Toxicities	0.02	0.07	0.20	0.64	0.82	0.94

Analysis of Clinical Endpoints:
The outcome status (in terms of toxicity, response (PSA, pain, and RECIST), reason off study, progression-free survival, and survival) of all patients who are registered, will be reported. Patients who complete 21 days of therapy or who experience any Grade 2 or greater toxicity will be included in the analysis of toxicity. Patients with measurable PSA- who complete 21 days of therapy, or who terminate treatment for reasons of toxicity or progression, will be included in analysis of PSA response, and in any decision to terminate the study early. All eligible patients who begin treatment will be included in the analysis of survival and progression-free survival.

All PSA, pain, and RECIST responses will be reported. Response rates will be calculated as the percent of evaluable patients whose best response is a CR or PR, and exact 95% confidence intervals will be calculated for this estimate. The overall survival and time to progression will be summarized using the Kaplan-Meier product-limit estimators.

All toxicities observed will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI Common Toxicity Criteria and nadir or maximum values for the laboratory measures), time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities by type and severity. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented, as well, to describe the patients treated in this Phase II study

Criteria for removal of Patients

- Disease progression
- Study Closure
- Unacceptable adverse event(s)
- Patient decision to withdraw from the study, or
- In the judgment of the investigator, further treatment would not be in the best interest of the patient

Women and Minorities

Women do not get prostate cancer.

Accrual to the protocol will necessarily include the large pool of cancer patients in the Los Angeles basin area but may not reflect the ethnic mix in the catchment area of USC/Norris or LAC+USC noted below. Every attempt will be made to recruit patients

representative of the ethnic mix in Southern California. As noted below, we have been particularly successful at USC/LAC and Norris at the recruitment of members of minorities to clinical trials.

Ethnic Distribution on Clinical Trials at USC/Norris, USC/LAC and affiliates in 1998

	LA County Patients with Cancer - 1998	Patients on USC Cancer Trials
Non-Hispanic white	62%	441 - 43.4%
Hispanic	16%	398 - 39.2%
Black	12%	61 - 6%
Asian	5%	106 - 10.4%
Pacific Islander/Other	4%	10 - 1%
TOTAL	100%	1016 - 100%

11.0 Patient registration

11.1. Registration Guidelines

Patients will be registered on this protocol by faxing the USC/Norris Clinical Investigations Support Office at 323 865 0089 (fax) ((323) 865-0451 (phone)) and submitting the study name, patients initials and the USC/Norris, LAC+USC or other local institution patient identification number. Registration will occur when the USC/Norris data managers receive a complete registration packet consisting of the Informed consent form and the Registration/Eligibility worksheet.

11.2 Registration Forms

One copy each of the Informed Consent form, Registration/Eligibility worksheet, and flow chart should be submitted at time of registration.

12.0 Ethical and Regulatory Considerations

12.1 General:

All institutional, NCI, and Federal regulations concerning the Informed Consent form will be fulfilled.

12.2 Institutional Review Board Approval

It is required that a valid Institutional Review Board approves the conduct of this clinical study, together with the Investigator's informed consent document, prior to study initiation.

This study is IND exempt ***(must confirm this statement upon receipt of IND status letter)***, however, the minimum standards of conduct and requirements for informed consent defined in the FDA regulations should be adhered to.

This protocol must be reviewed and approved by a valid Institutional Review Board (IRB) prior to initiation of the study. Until written approval by the IRB has been received by the Investigator, no subject may undergo any procedure solely for the purpose of determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by Aventis before implementation.

12.3 Informed Consent

The Investigator will obtain informed consent from each subject enrolled in the study, in accordance with the U.S. Food and Drug Administration (FDA) regulations 21 CFR Parts 50.20 - 50.27 and the laws and regulations of the country in which the investigation is being conducted.

The IRB, Millennium and Aventis must approve the informed consent document to be used by the Investigator. It is the responsibility of the Investigator to ensure that informed consent be obtained from the subject or his/her guardian or legal representative before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the first dose of study medication.

12.4 Clinical Laboratory Tests and Normal Laboratory Values (NLV)

Clinical laboratory tests should be performed by the same laboratory throughout the study.

The normal ranges of the laboratory that will perform the tests required by the protocol must be transmitted to Aventis. If the investigator feels the patient requires additional testing at an outside laboratory, the normal ranges of each laboratory that will perform the tests required by the protocol must be transmitted to Aventis, along with CLIA certification, and the name and address of the laboratory indicated on a revised FDA 1572.

Any change in normal laboratory values during this study will be transmitted to Aventis.

12.5 Monitoring

Monitoring with occur as outline in the USC quality assurance committee and data safety monitoring policy. Aventis and Millennium will NOT be monitoring this study. However, requests by regulatory agencies to inspect study sites could possibly be made after notification. The Investigator agrees to allow inspectors from regulatory agencies to review records and is encouraged to assist the inspectors in their duties, if requested.

12.6 Case Report Forms (CRFs)

Subject source documents are the physician's subject records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital's or the physician's chart, the information collected on the CRFs must match those charts. In some cases, a portion of the source documents for a given subject may be the CRFs.

It is the Investigator's responsibility to ensure completion and to review and approve all CRFs. If an Investigator Approval Form is used, it must be signed by the Investigator. Individual CRFs may be signed by the Investigator or a Subinvestigator. These signatures serve to attest that the information contained on the CRFs is true. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The CRFs will be printed on NCR ("no carbon required") paper to permit multiple copies. The bottom copy is to be retained at the site for the Investigator's study file. All questions should be answered using a black ink ballpoint pen. If certain data are not available, not done, or not applicable: "NAV," "ND," or "NAP," respectively, will be entered in the appropriate space.

Twenty-four hour clock should be used for all time entries. (NOTE: 24:00 hours will be entered as 23:59.) Changes and/or additions to data entered on original CRFs must be made in the following manner: The original entry will be lined out with a single line drawn through the error (not erased or "whited out") so as to leave it still legible. The correction will be entered using a black ink ballpoint pen, initialed, and dated by the person making the correction. The Investigator or delegate (e.g., sub-investigator or study coordinator), may enter corrections on original CRFs. The monitoring team may make changes to the copies of CRFs based on information supplied by the Investigator and documented in the study file.

12.7 Disposition of Clinical Supplies

Commercial supplies of drugs will be used and standard records maintained by Norris and USC-LAC pharmacies accessible for review, if required.

12.8 Maintenance of Records

The Investigator will retain a copy of all study documents, including reports to the IRB and to Aventis in accordance with the FDA or local regulations, whichever are the more stringent.

The Investigator will maintain study documents:

a. for a minimum of two years following approval of the last marketing application of the investigational product in any International Conference on Harmonization (ICH) region;
   -Or-
b. for a minimum of two years following discontinuation of clinical development of the investigational product in any ICH region;
   -Or-
c. for any longer period that is specified by the regulatory requirements of the country in which the study site is located.

If the Investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or to Aventis Inc. The Investigator must obtain Aventis written permission before disposing of any records.

12.9 End of Study Documentation

At the completion of the study and following analysis of the data,

12.10 Changes in Protocol

Changes to the protocol (after Signatures of Agreement are obtained) that affect the decision of the IRB (e.g., more extensive procedures, increased risk to subjects, changes in the subject population, additional safety information, etc.) must be documented in the form of an amendment. This amendment must be signed by the appropriate Aventis personnel and the Investigator, and approved by the IRB before it may be implemented. If the amendment is minor or reduces the risk to the subject, the chairperson of the IRB alone may approve it. IRB approval is not necessary for protocol clarifications that consist of minor protocol changes such as correcting typographical errors, rewording for clarity, changes in monitoring personnel, or for other changes to the protocol that do not affect the conduct of the study, including changes in the plan for statistical analysis. The only circumstances in which the amendment may be initiated without IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB in writing within five (5) working days after the implementation.

13. References

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Appendix 1 - Performance Scale

ECOG Scale

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work or office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair

Appendix 2

This study should utilize the revised NCI Common Toxicity Criteria (CTC version 3.0). The criteria can be downloaded from the CTEP web page (http://ctep.info.nih.gov).

The CTC 3.0 does not have to be appended to the protocol, but all appropriate treatment areas should have access to a copy of them.

Appendix 3 – Pain Assessment and Pain Medication Log (modified from SWOG Form #137050)

The Present Pain Intensity (PPI) scale has verbal descriptors (0 = no pain, 1 = mild pain, 2 = discomforting pain, 3 = distressing pain, 4 = horrible pain, and 5 = excruciating pain); patients will be asked on the first day of each cycle to clarify the average pain level during the previous 24 hours, using the PPI scale.

PAIN MEDICATION LOG

Patient No. _____ **Study No. USC 4P-04-3 /** _____

Patient Name: _____ **Institution:** _____

Physician: _____

Treatment Number: ☐ **Pre-Study** ☐ **Cycle 3** ☐ **Cycle 5** ☐ **Cycle 7** ☐ **OTHER Cycle**
☐ **Cycle 2** ☐ **Cycle 4** ☐ **Cycle 6** ☐ **Cycle 8**

INSTRUCTIONS:

The Pain Medication Log allows you to count your pain medications for the 24 hours before you come for a clinic visit. At the beginning of the study, the nurse will write the names of any pain medications you are taking in column 1 and the dose in column 2. You should tell the nurse about any pain pills you are taking that are not listed in your medical chart. When you enter the study, you will need to remember how many pills you took for the 24 hours before coming to the clinic. You will put this information in column 3 of the Log. After the first time, you will record pain medications in column 3 of your copy of the Log, covering the 24 hour period before your clinic visit. If over time, you take a pain pill not listed on the Log, please write its name in column 1 of the Log and bring the bottle with you for your clinic visit the next day. The nurse will always complete columns 2 and 4. Thank you for your cooperation.

Date Log Started:

Column 1	**Column 2**	**Column 3**		**Column 4**
Name of Pain Medication (Nurse and Patient)	**Dose (mg) (Nurse)**	**Number of pills you took with each dose Tally / Total**		**Total mg of Pain Medication (Nurse)**

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Their analgesic usage will be assessed using the following form:

Examples of Non-Narcotic, Weak Opioid, and Strong Opioid Pain Medications

Category 1 *Non-Narcotic*	*Category 2: Moderate Pain* *Weak Opioid (Constrained by Dose-Limiting Side Effects)*	*Category 3: Moderate to Severe Pain* *Strong Opioid (Strength Dose Dependent)*
NSAIDS Aspirin Ibuprofen	**Oxycodone** alone (e.g., 5mg) or in combination with other agents: Percocet®, Roxicet®, Endocet® or Tylox® Combination Doses (opioid/non-opioid): **2.5/325; 5/500; 5/325; 10/325; 7.5/325; 7.5/325; 10/650**	**Continuous-Release Opioid** OxyContin MS-Contin
Celecoxib (Celebrex)	**Hydrocodone** Combinations combinations**:** Vicodin® Combination Doses (opioid/non-opioid): **2.5/500; 5/500; 5/325; 7.5/750; 10/650**	Morphine Short acting oral, long acting oral, IV preparations
Naprosyn	**Codeine** Oral and liquid preparations (Don't count cough syrup)	**Methadone**
	Codeine Combinations: Tylenol #3® (30/300)	Fentanyl Transdermal,(Duragesic®) Transmucosal,(Actiq®) Intravenous
Diclofenac	**Propoxyphene** combinations: Darvocet-N 100 (100mg/650mg acetaminophen) Darvocet-N 50(50mg/325mg acetamnophen) Darvon-N aspirin325mg, propoxyphene 100mg, caffeine30mg	**Meperidine** (Demerol) Oral and IV preparations
Piroxicam (Feldene®)	**Tramadol** (Ultram®)	**Hydromorphone** (Dilaudid®) Oral and IV medication
Valdecoxib(Bextra®)		
NEUROPATHY Gabapentin (Nerontin®)		
Amitriptyline		
Nortriptyline		
Corticosteroids		
Acetminophen (Tylenol®)		

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Appendix 4 - Marrow Distribution in the Adult

Anatomic Site	% Total Red Marrow
Head	13.1
Cranium	12.0
Mandible	1.1
Upper limbs	8.3
2 humeri	2.0
2 scapulae	4.8
2 clavicles	1.5
Sternum	2.3
Ribs	7.9
Vertebrae	42.3
Cervical	3.4
Thoracic	14.1
Lumbar	10.9
Sacrum	13.9
Lower limb girdle	26.1
2 os coxae	22.0
2 femoral head and necks	4.0

(from Ellis RE. The distribution of active bone marrow in the adult. Phys Med Biol 5:255 - 258, 1961)

Appendix 5

Aventis Pharmaceuticals
Global Pharmacovigilance and Epidemiology
200 Crossing Boulevard
P.O. Box 6890
Mailstop BX4 – 412-i
Bridgewater, NJ 08807
Fax: 908-231-4827

Aventis
Pharmaceuticals Inc.

Fax IIT SAE REPORT
To: Global Pharmacovigilance and Epidemiology

Fax: 908-231-4827	
Date:	Pages:
From:	Phone:

IIT#:	**16164-Quinn**
Study Title:	**A Phase II Study to Evaluate Bortezomib and Docetaxel as Therapy for Patients with Hormone Refractory Prostate Cancer**
PI Name: Insert PI name	**David Quinn, MD, PhD**
Causality:	**All serious, related adverse events will be reported and documented on MedWatch Form FDA 3500A (www.fda.gov/medwatch/getforms.htm) and forwarded directly to Aventis Pharmaceuticals. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.** **For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.**
Check one:	
	Unrelated: The adverse event is clearly NOT related.
	Unlikely to be related: The adverse event is doubtfully related.
	Possibly related: The adverse event may be related.
	Probably related: The adverse event is likely related.
	Definitely related: The adverse event is clearly related.

Appendix 6

July 1st, 2008

1.0 Institutional Oversight and Protocol Audits

The Quality Assurance Committee (QAC) of the USC/Norris Comprehensive Cancer Center (USC/NCCC) has responsibility for the oversight of clinical trials conducted as part of the USC/NCCC research activities. All clinical protocols involving cancer patients or asking a cancer-related question are required to undergo scientific review by the USC/NCCC Clinical Investigations Committee (CIC). No cancer-related clinical trial may be activated without CIC review and approval; the USC Institutional Review Board (IRB) will not review a cancer-related clinical protocol that has not been reviewed and approved by the CIC. At the time of the CIC review, those studies that are classified as a clinical trial (i.e. involving an intervention) - thereby requiring QAC monitoring – are identified.

It is the responsibility of the study principal investigator (PI) to monitor the progress of each of his or her trials on an ongoing basis. The QAC will then review, on a monthly basis, all reported serious adverse events as well as all major study violations. In addition, at set intervals – depending on the class of the trial – the QAC will review the overall progress of the trial, including the cumulative toxicity, response to treatment and outcome, and adherence to protocol. Occasionally, for a randomized Phase II trial or for a multi-center trial Phase II/Pilot Trial or a study with potentially higher than average risk to patients, a formal Data and Safety Monitoring Committee (DSMC) will be formed to oversee the progress of the study. All Phase III trials are required to have a DSMC comprised of members that are not involved in the conduct of the trial. It is the responsibility of the CIC to review the monitoring plans at the time of the initial review of each protocol. These plans must include criteria for suspending the trial in the event of excessive toxicity, as well decision rules for terminating based on efficacy endpoints.

1.1 Annual Review

All open, in-house trials are reviewed once a year by the USC/Norris Comprehensive Cancer Center (USC/NCCC) Quality Assurance Committee (QAC). This annual review includes the following: evaluation of the current accrual relative to the planned total accrual and planned interim analyses; examination of all reported violations; examination of all reported AE's; review of past audits and correspondence with the trial principal investigator (PI); review of results of current audit (by an outside agency or by the USC/NCCC QAC); review of previous correspondence between the PI and the QAC. Based on these reviews, the QAC will decide one of the following: recommend that the study continue unchanged and review in 12 months; request an explanation or a plan for change – to address an identified problem - before a final decision is made by the QAC; recommend a specific amendment or change to address an identified problem; recommend termination of the study. If the PI does not respond within 30 days (by the next QAC meeting) a letter is sent to the USC/NCCC Clinical Investigations Committee (CIC) with a recommended action. The PI then has 30 days to appeal to the CIC or the

CIC will decide on an appropriate action. The results of all annual reviews, as part of the QAC minutes, are submitted to the CIC at the next CIC meeting.

1.2 Protocol Audits

All open, in-house (i.e. USC initiated) trials that are not monitored by another agency (e.g. Theradex) are audited by the USC/Norris Cancer Center Quality Assurance Committee (QAC) once a year. In addition, selected in-house protocols that are monitored by Theradex, will also be audited by the QAC. The review is done on the anniversary month of the initial IRB review date. Members of the Cancer Center involved in clinical research are asked to serve as auditors; generally one M.D. and one other person are asked to audit each patient selected. 20% of patients accrued during the past 12 months – and a minimum of 2 patients – are selected. Criteria for selection include: major response observed, treatment at the MTD of a Phase I trial, or some inside information that there might have been a problem. If none of these criteria are met, then patients are selected randomly. The audit involves a review of the hospital chart (i.e. source documentation) and evaluates the following: documentation of eligibility (including failure to obtain appropriate informed consent, and deviations from assessment of eligibility that would either (i) render that patient ineligible or (ii) make it impossible to establish eligibility – as well as the actual status of the patient); documentation of adherence to protocol-specified treatment and follow-up; evaluation of toxicity; and evaluation of response or other outcome.

Failure to report violations or required SAE's is viewed as very serious. Responsible data managers and research nurses are counseled (by the CISO Associate Director) and the PI is requested to propose a plan to avoid such breeches in the future. SAE's are forwarded to the IRB and the CIC is informed.

For all audited protocols (even those with no or minor issues), a report is created summarizing the results of the audit and, if appropriate, suggestions are provided for improving the conduct of the trial. Copies of all audit reports are sent to the CIC for review.

1.3 Review of Serious Adverse Events

If an adverse event (AE) is judged to be a serious adverse event (SAE), then the procedures to report the SAE depend on the drugs or the intervention in the protocol. For example, if the trial involves an investigational agent, then the PI must report certain SAE's to the study sponsor/supporter within 24 hours and to the USC IRB within 5 days. If the trial involves drugs that are commercially available and that have been extensively studied (e.g. the use of methotrexate, doxorubicin, vinblastine, and cisplatin as adjuvant therapy for bladder cancer), then only SAE's that result in death or that are unexpected, life-threatening, and thought to be possibly, probably or definitely associated with one of the drugs would be reported to the FDA and the USC IRB. The details regarding the

specification of reportable AE's and the procedures for reporting the SAE's are given in the protocol.

The QAC will review all toxicities and AE's that are reported to the IRB. All toxicities that are reported outside to agencies (e.g. the NCI, FDA, Office of Biotechnology, or the supporting pharmaceutical company) must also be reported to the IRB. The forms that are used to report toxicities or adverse events to the IRB (which may include adverse events that are not reported to any outside agency) are computer generated and tied to the USC/NCCC clinical trials database. Therefore at each QAC meeting, all adverse events and toxicities reported to the IRB since the last QAC meeting are listed and reviewed. At the time of the QAC review, a list of all past reported AE's for the open protocols is also available for reference.

This review of SAE's and other reported AE's is done by the QAC on a monthly basis. For investigational agents, this QAC review is used to verify that the appropriate agencies and sponsor/supporter have been notified in a timely fashion with the appropriate documents, as well as to examine the pattern of SAE's to date. For commercially available drugs, this monthly QAC review will be able to identify patterns of unexpected or increased toxicity.

The QAC will flag for follow-up, patterns of severe or relatively frequent AE's. Based on the pattern of reported AE's, the QAC will make recommendations on whether the study should continue unchanged, should be amended or modified, or be suspended, based on unacceptable risk to the trial participants – as well as considering the criteria in the protocol for suspending the trial in the event of excessive toxicity. These recommendations are forwarded to the CIC for action. If the CIC recommends suspension (temporary or permanent), the CIC will be responsible for notifying the IRB, as well as the sponsor/supporter (the NCI or the pharmaceutical company).

Finally, one function of the audits (see below) is to verify that all required reporting of AE's has occurred.

1.4 M**onitoring protocol violations**

Data managers and research nurses are required to report major protocol violations to the QAC. This is done by completing a computer form – thereby ensuring that the information is stored in the USC/NCCC clinical trials database. Major violations are defined as:

(a) deviation from protocol treatment by 10% of dose, delay in treatment of a month beyond the prescribed amount, failure to hold a drug for reasons of toxicity, or administration of an inappropriate drug
(b) departure from the follow-up schedule (i) leading to an inadequate assessment of toxicity or (ii) compromising the assessment of the outcome measures.

These reported violations are then reviewed and discussed at the next QAC meeting. Repeat violations and patterns are flagged. A memo is sent to the PI, requesting a plan to avoid these violations in the future. Sometimes the QAC will suggest a specific modification of procedures or protocol amendment. If the PI does not respond or if the violations continue, the QAC will report this to the CIC with a recommendation to either close the study or suspend accrual until the problems can be resolved. In practice, because of the close co-operation between the QAC and the CISO leadership, problems can be addressed on a one-to-one basis, usually bringing in the data manager or research nurse – and formal action is not required.

1.5 Monitoring accrual

The USC/NCCC clinical trials database is used to document the registration of all patients who are enrolled onto CIC-approved clinical trials. Thus at any given time, the clinical trials database should be up-to-date (within 24 hours) of accrual to studies.

At the monthly QAC meetings, all studies that have not accrued any patients during the preceding 12 months are flagged. A memo is sent to the PI requesting an explanation for the lack of accrual. If the explanation is not satisfactory, or if no response is received, a second memo is sent informing the PI that the protocol will be presented to the CIC with the recommendation for closure. At that time, the PI may appeal the closure to the CIC, but in the past, the CIC has consistently supported the QAC recommendation.

1.6 Monitoring study progress and interim analyses

Each protocol is required to describe the plans for interim analyses and stopping rules (for Pilot, Phase II and Phase III trials) or the rules for dose expansion, escalation, and de-escalation (for Phase I trials). In addition all Phase II and III trials must have criteria for suspending the trial in the event of excessive toxicity. The proposed plans and rules are reviewed by the CIC; no trial is activated without appropriate procedures in place – as assessed by the CIC. For each protocol, at the time of activation, a very brief summary of the proposed design (generally the total target accrual and the planned times for analysis) is stored in the clinical trials database. Every month, the design and the current accrual is reviewed for every open in-house protocol (approximately 40-50 at any given time). For every study that has reached the time for the scheduled interim analysis, a copy of the report summarizing the analysis, with the rationale for continuing (or discontinuing) the study is requested and (once obtained) is stored in the official protocol folder in the CISO office. Studies that do not supply an adequate summary of the interim analysis will be closed. The procedure for closing is the same as that described above: a memo is first sent to the PI requesting either a copy of the interim analysis report or an explanation of an issue; if no response is received or the response is not adequate, a second memo is sent informing the PI that the QAC will request that the CIC close the protocol. The PI then has 30 days to correct the situation or present an acceptable plan to the CIC, or the CIC will close the study.

At the monthly review, if a protocol has exceeded its planned total accrual (this very, very rarely happens) the PI will be notified of this, and the QAC will request that the CIC close the protocol.

2.0 Adherence to Protocol – Responsibilities of the Principal Investigator Study Team

It is the responsibility of the Principal Investigator (PI) to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting are all performed as specified in the protocol. When a study is opened at two institutions, the PI at each institution will assume the responsibilities for the day-to-day monitoring of the trial, as described below.

2.1 Eligibility

The PI will review the patient eligibility (with assistance from the Research Nurse – who will assemble the required source documents, and do an initial review) prior to registering the patient on study.

2.2 Informed Consent

Prior to registering the patient on study, the study research nurse will review the informed consent, to ensure that the patient has signed and dated the form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses. The dates of all persons signing the consent must agree and must be before or on the date of study entry. If the informed consent is signed and the patient is registered on the same day that treatment is started, then the time of signature and treatment start must also be included.

2.3 Treatment

The PI is responsible for ensuring that treatment is given per protocol. If treatment is administered by another physician, the study research nurse will review the treatment orders with the PI. Regardless of who the treating physician is, there will be only one research nurse for the study at the LAC+USC Medical Center and one research nurse for the study at the USC/Norris Cancer Center. The PI will review the status of each patient on-study, with the research nurses and treating physicians, on an on-going basis.

2.3 Evaluation of Safety

Generally it is the study research nurse who schedules the visits to evaluate toxicity to treatment, who initially interviews the patient to discuss the symptomatic side effects of the treatment, and who initially reviews the lab results. At the USC/Norris Comprehensive Cancer Center, the Informatics Core has developed toxicity forms that tailor the collection of side effects and toxicity information for each protocol and allow

the comparison of past toxicities with the current side effects. These are presented to the treating physician who will decide on the appropriate course of action – follow-up with additional tests or treatment. The PI will review the toxicity assessment and changes in schedule on an on-going basis.

2.4 Evaluation of Treatment Response

The study research nurse will schedule the tests or scans that are necessary to evaluate response to treatment. Although the treating physician will evaluate the results to establish the response, it is the responsibility of the PI to review all the scans and tests of all the patients to confirm the initial assessment of the response.

2.5 Data Management

2.5.1 Patient Charts

All written source documents are maintained in the patient chart which is stored in the Department of Medical Records at the hospital. X-rays and other images are stored in the Department of Radiology. These are the permanent, official documents for each patient on-study. A copy of the signed informed consent, physician's notes, orders, test results and pathology notes are maintained in the patient chart.

It is usually the responsibility of the data manager to ensure that the patient chart contains all the required documents.

2.5.2 Research Charts

To facilitate adherence to the protocol schedule and data management, research charts are often created to collect copies of the informed consent, relevant notes, orders and results that are in the hospital chart. Protocol calendars, worksheets, checklists, and completed case report forms may also be kept in the research chart. While the research charts do not contain the official, original documents, they do contain copies of all documents that are required for the study. These are maintained in the Clinical Investigation Support Office until the study is completed and the results are published and no further need is anticipated. These are then stored off-site.

It is usually the responsibility of the data manager to ensure that the research chart contains all the required documents.

2.5.3 Case Report Forms

It is the responsibility of the data manager to complete the required case report forms. For in-house trials, paper versions are stored in the research chart; for

certain protocols, the information is directly entered into the Cancer Center clinical trials database. If errors are identified and corrected, a copy of the source document is attached with an explanation of the change, the date of the correction and the person making the correction.

It is the responsibility of the PI to review the research chart once the patient has completed treatment. At this time, the PI will review the all the toxicities experienced by the patient, as well as the overall response to treatment. A final check-list/verification is provided for the PI to indicate that she or he has reviewed the eligibility, treatment, toxicities and overall response. The case report forms are kept in the Research Chart.

3.0 Agency Reporting and Regulatory/Administrative Issues

3.1 IRB Review and Review by NCI-CTEP or FDA

3.1.1 Initial Review and Approval

The trial will not be activated and no patients will be enrolled in the trial until the study has received final approval from all supporting agencies, as well as the USC IRB. It is the responsibility of the study PI to verify that all stipulations have been met and that the official approval documents have been received.

3.1.2 Protocol Amendments

All modifications to the study plan or protocol document must be submitted to the USC IRB, as well as to all the supporting agencies (Aventis, Millennium etc.) for review and approval. It is the responsibility of the study PI to ensure that the appropriate agencies have been informed of the proposed amendments and that these have been reviewed and approved. Until final approval is received, no patients may be treated according to the modified plan.

3.1.3 Serious Adverse Event and Toxicity Reporting

Procedures and requirements for reporting toxicity are described explicitly in the protocol. In the protocol, the following are specified:

(1) the definition of a serious adverse event (SAE)
(2) the agencies, in addition to the USC IRB, who are to be notified
(3) the information required and the procedures for notification
(4) the time frames for reporting the SAE's

3.1.4 SAE Reporting with Multi-Institutional Studies

For studies in which two or more institutions enroll patients and an investigator at the USC/Norris Cancer Center is the study PI, the following additional procedures are described in the protocol:

(1) requirements for other institutions to report SAE's to USC – and the required time frame
(2) procedures for USC to notify other institutions of SAE's experienced at any of the participating institutions

3.2 Drug Tracking and Accountability

The USC School of Pharmacy and the Norris Hospital Department of Pharmacy Services provide investigational drug support services, including those services that are FDA-mandated such as drug tracking and accountability. Investigational drugs for patients treated on protocol, at the L.A. County General Hospital or Women's Hospital, are managed and dispensed from a central facility located in the Norris Hospital. The services provided include distribution and control of investigational drugs, as well as research support. Prior to the initiation of any protocol involving an investigational agent, it is the responsibility of the PI to meet with a Research Pharmacist to arrange all aspects of drug procurement, dispensing, tracking and accountability. A Research Pharmacist is present at all CIC reviews and will flag those trials which have not adequately addressed the necessary issues. These protocols will not be approved (and forwarded to the IRB) unless the delinquent issues have been addressed.

3.2.1 Distribution and Control of Investigational Drugs

All aspects of drug tracking and accountability are coordinated with the central pharmacy facility at the Norris Hospital. For example, when a new prescription involving an investigational drug, is submitted to the pharmacy, a copy of the signed informed consent is also required to verify the status of the patient and the protocol. Services provided include:

3.2.1.1 Procurement, storage, and inventory control of investigational drugs

3.2.1.2 Preparation and dispensing of investigational drugs

3.2.1.3 Maintenance of comprehensive inventory control and dispensing records for at least two years after an IND is terminated or its new drug application (NDA) is approved

3.2.1.4 Maintain a computerized cross-reference system on investigational drugs that cross-references protocol number, drug name, patient name, principal investigator, and ordering investigator

3.2.1.5 Insure compliance with FDA, NCI (or other supporting agency), JCAH, ASHP, Federal and State of California regulations and USC/Norris Hospital Policies and Procedures for inventory control and dispensing of investigational drugs

3.2.1.6 Provide the Principal Investigator and research staff with investigational agent inventory and dispensing summaries as needed

3.2.1.7 Maintain a Quality Assurance Monitoring program

3.2.1.8 Provide necessary investigational drugs inventory control documentation and logs for both internal and external Quality Assurance audits by MCI, cooperative group, and other supporting agencies.

3.2.2 Research Support

In addition, the central research pharmacy facility will provide the following services to support the research aspects of the protocols:

3.2.2.1 Review all proposed intramural Cancer Center protocols and provide input regarding all aspects of use of investigational agents (completeness and accuracy of agent background section, procedures on preparation and administration of agents, impact of pharmacokinetics and preclinical animal toxicology data on agent, schedule of administration, trial design, etc.)

3.2.2.2 Provide PI and Protocol File investigational drug inventory and dispensing summaries on a quarterly basis

3.2.2.3 Participate in intramural Quality Assurance audits

3.2.2.4 Assist center investigators in external Quality Assurance audits by supporting agencies

3.2.2.5 Provide special services as needed (such as maintaining codes and preparing/dispensing placebo treatments for double-blind trials, etc.).

3.3 Final Reports

The study PI will comply with the reporting requirements of the supporting agency and will file the final report (with the FDA or NCI) as required. The protocol will describe when the final analyses will begin after accrual is completed. A copy of the dataset that was used to produce the final analyses will be stored for future reference.

July 1st, 2008