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Award Number: DAMD17-01-1-0069

TITLE: The Clinical Development of Thalidomide as an Angiogenesis Inhibitor Therapy for Prostate Cancer

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CONTRACTING ORGANIZATION: University of Texas
M. D. Anderson Cancer Center
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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The purpose of this award is to evaluate the: 1) **Safety and toxicity of neo-adjuvant thalidomide therapy** prior to radical prostatectomy in patients with locally advanced prostate carcinoma (PCa), assessed by wound healing and peri-operative bleeding; 2) **Efficacy of neo-adjuvant thalidomide treatment,** as measured by the rate of tumor reduction / PSA decline while on thalidomide therapy; 3) **Qualitative measurements of the *in vivo* effect of thalidomide therapy on the Endothelial and Epithelial compartment (PCa cells).**

Significance: The ability to assess *in vivo* the effects of thalidomide as well as identify surrogate markers of anti-angiogenic activity is invaluable to the design of new effective therapy and will result in the accelerated introduction of angiogenesis inhibitors into the clinic.

This clinical trial has been approved by the U.T.-MDACC IRB. During the 2001-2202 year the trial was reviewed twice by the HSRRB and we amended the protocol according to the HSRRB's recommendations. We recently were also able to solve one of the remaining issues, the re-imbursement for potential research-related injuries (given that there were no moneys dedicated for this in this award) and we are now ready and eager to proceed with the study after obtaining final HSRRB approval.

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Introduction

The purpose **of this award is to evaluate the:**

1) **Safety and toxicity of neo-adjuvant thalidomide therapy prior to radical prostatectomy in patients with locally advanced prostate carcinoma (PCa),** assessed by wound healing and peri-operative bleeding. Up to 40 patients will be treated in this study.

2) **Efficacy of neo-adjuvant thalidomide treatment**, as measured by the rate of tumor reduction / PSA decline while on thalidomide therapy;

3) **Qualitative measurements of the *in vivo* effect of thalidomide therapy on the**
a) Endothelial compartment: (MVD, endothelial cell apoptosis, tissue and circulating (serum/urine) levels of pro-angiogenic molecules (VEGF, Transforming growth factorb1 {TGFb1}, bFGF) and IL-6, IL-8.
b) Epithelial compartment: Apoptosis / proliferation in PCa cells, and correlate with pathological findings at the time of prostatectomy.

Our **hypothesis** is that neo-adjuvant treatment with thalidomide will inhibit neo-angiogenesis in the primary organ (prostate) as well as at sites of possible micrometastases and may reduce PCa recurrence post-operatively.

This design of neo-adjuvant angiogenesis inhibition is a useful strategy of identifying intermediate markers of activity, which may accelerate drug development.

Body

The Clinical Development of Thalidomide as an Angiogenesis Inhibitor Therapy for Prostate Cancer .

Task 1. **Assess the safety and toxicity** of neo-adjuvant thalidomide treatment in patients with locally advanced PCa who undergo RRP (months 1-20).

- Up to 40 patients with clinical stage T1c-T2c, Gleason score $\geq$ 7 and PSA>10 or clinical stage T3 will be treated with 6 weeks of thalidomide (escalating weekly from 200 mg/day up to 600 mg/day). If there is no evidence of disease progression at 6 weeks (by PSA and TRUS criteria), patients will be treated with 6 more weeks of thalidomide (600 mg/day) and then will proceed to RRP. Safety will be assessed using the endpoints of: a) excessive peri-operative bleeding (more than 5 units of PRBC transfusions during the first 24 hours post-operatively) or b) abnormal wound healing (fascia dehiscence). Based on historical rates of 8% for excessive bleeding and 2% fascia dehiscence at RRP a maximum adverse event rate of .10 is desired.

Accomplishements

This clinical trial has been approved by the U.T.-MDACC IRB.

During the 2001-2202 year the trial was reviewed twice by the HSRRB and we amended the protocol according to the HSRRB's recommendations.

We recently were also able to solve one of the major remaining issues, the re-imbursement for potential research-related injuries. Given that there were no moneys dedicated for this in this award and the fact that MDACC does not provide compensation for research-related injuries, we worked with Celgene and came to an agreement that Celgene will provide re-imbursement for injuries related to the investigation in this study (the use of thalidomide).

We have obtained MDACC- IRB approval of this amendement and we are now ready and eager to proceed with the study after obtaining final HSRRB approval.

Task 2. **To assess the efficacy** of neo-adjuvant treatment with thalidomide in patients with locally advanced PCa who undergo RRP (months 1-24).

- This is a phase II trial of neo-adjuvant thalidomide prior to RRP in patients with newly diagnosed locally advanced PCa. The design of Thall, Simon and Estey (14-15) will be used. For the purpose of sample size determination and safety monitoring, **patient success, S, is defined as stable disease (no increase in tumor mass) at 6 weeks, followed by $\geq$ 25% tumor shrinkage, compared to baseline mass or $\geq$**

50% decline in serum PSA (with no tumor progression) at 12 weeks. At 12 weeks, once S is evaluated, all patients will undergo RRP. The adverse event, A, pertains to surgery, and is defined as either excessive bleeding or fascia dehiscence (see task 1). **A success probability of .20 or larger will be considered clinically promising,** and **a maximum adverse event rate of .10 is desired.**

Accomplishements

Pending. The safety and efficacy of the thalidomide treatment will be assessed this year as soon as we proceed with the study.

Task 3. **Obtain qualitative measurements of the *in vivo* effect of therapy** (months 1-36).

TRUS prostate tumor measurement and prostate biopsies will be obtained pre- treatment, at 6 weeks (biopsy optional at that time) and at the time of the surgery. Serum and urine samples will be obtained weekly x 3 weeks (during escalation phase of thalidomide), then at 6, 12 weeks, pre- and post-operatively. Serum PSA will be measured pre-therapy, at 6 and 12 weeks on therapy, 3 weeks post-RRP and every 3 months thereafter. Bone marrow (BM) aspirate and biopsy will be obtained pre- and post-treatment (optional) with thalidomide and the effect of the therapy on bone marrow endothelial cells will also be assessed. We will look at the effects of therapy on:

- **Endothelial compartment:**

- Prostate (cancer and normal gland) MVD will be assessed immunohistochemicaly by staining with anti-CD31 antibody (16). Correlate with Gleason score and compare matched pre- and post-treatment samples.
- Endothelial cell (EC) apoptosis in normal prostate, prostate cancer, bone marrow biopsy (by Dual fluorescent labeling technique in CD-31 positive cells [TUNEL])
- Expression of bFGF, VEGF by PCa epithelium and prostatic stroma (by immunohistochemistry and / or in-situ hybridization (5,6,17).
- Modulation of circulating endothelial markers (18-21) (serum: E-selectin and Thrombomodulin) by ELISA.
- Modulation of serum: VEGF, TGFb1, IL-6 / Il-8, urine: bFGF levels and BM supernatant: VEGF,
IL-6/IL-8 levels will be measured by ELISA (6,17, 22-24).

- **Epithelial compartment:**

- Tumor size (by TRUS)

- PSA modulation on thalidomide therapy and freedom from biochemical relapse after surgery.
- Apoptosis in prostate cancer cells (by TUNEL)
- Proliferation index of PCa cells (by PCNA or Ki67)

and we will determine whether expression of tissue or circulating pro-angiogenic molecules and cytokines correlate with: a) pathological findings at surgery (Gleason score, MVD changes, pathologically organ confined prostate cancer, rate of positive surgical margins and / or lymph node metastases) and could serve as surrogate markers for antiangiogenic activity in prostate cancer.

Accomplishements

Pending evaluation of the pathology specimens of patients treated on study.

Key Research Accomplishements

- Approval of the study by the MDACC-IRB
- Review of the study by the HSSRB, revisions made according to HSSRB recommendations and approved by MDACC
- Secure re-imbursement by private sponsor for potential research-related injuries.

Unfortunately solving the re-imbursement issue proved to be the most time-consuming issue since there were no funds allowed in the award to cover for potential research-related injuries. We feel very confident that with these issues solved now, we can proceed with rapid patient accrual (we do see a lot of patients with newly diagnosed locally advanced prostate carcinoma in our center) and complete the study within the next 2 years.

Reportable Outcomes

Too early.

Conclusions

It proved really more time-consuming than anticipated to secure financial coverage for potential research-related injuries, but we also learned from this process.

We used this time to perfect our techniques in non-protocol patient specimens for evaluation of the pathological endpoints.

Since we had not solved all the issues we did not use any of the award money that we received. The money is kept available for the studies as we proceed with initiation of the study.

References

Appendicies

See attached

THE UNIVERSITY OF TEXAS
M. D. ANDERSON CANCER CENTER
DIVISION OF CANCER MEDICINE

A TOLERANCE AND EFFICACY TRIAL OF PREOPERATIVE THALIDOMIDE TREATMENT FOLLOWED BY RADICAL RETROPUBIC PROSTATECTOMY (RRP) IN SELECT PATIENTS WITH LOCALLY ADVANCED PROSTATE CANCER

STUDY CHAIRMAN: Daliani

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THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Protocol Abstract Page

SHORT TITLE:	NEOADJUVANT THALIDOMIDE IN PROSTATE CANCER
FULL TITLE:	A TOLERANCE AND EFFICACY TRIAL OF PREOPERATIVE THALIDOMIDE TREATMENT FOLLOWED BY RADICAL RETROPUBIC PROSTATECTOMY (RRP) IN SELECT PATIENTS WITH LOCALLY ADVANCED PROSTATE CANCER
STUDY CHAIRMAN:	DANAI DALIANI, M.D.
DEPARTMENT:	GENITOURINARY MEDICAL ONCOLOGY
PHONE:	(713) 792-2830
BOX:	427
STUDY CO-CHAIRMAN:	
PROTOCOL PHASE:	II

Abstract

Objectives: (MAXIMUM 2000 CHARACTERS)

1. To determine the efficacy (rate of tumor reduction and PSA decline) of pre-operative treatment with thalidomide in patients with locally advanced prostate carcinoma.

2. To determine the safety and toxicity (excessive bleeding, wound healing problems) of preoperative therapy with thalidomide in patients with locally advanced prostate carcinoma who undergo RRP

3. To obtain qualitative measurements of thalidomide's effect *in vivo* on:

   a) endothelial cells / neo-vascularity /angiogenic growth factors:
   - Assessment of neovascularity (MVD)
   - Dual flourescent labeling technique to evaluate apoptosis in CD-31 positive cells (TUNEL)
   - bFGF, VEGF, EGF and TGF expression by PCa epithelium and prostatic stroma
   - Modulation of endothelial markers (serum: E-selectin and Thrombomodulin)
   - Modulation of serum VEGF and urine bFGF levels, and Changes in tumor blood flow

b) epithelial compartment:
- Apoptosis in prostate cancer cells (TUNEL)
- Proliferation (PCNA)

c) quality of life

Rationale: (MAXIMUM 2000 CHARACTERS) (Be as concise as possible)

Clinically locally-advanced prostate cancer has a disease specific death rate of 75%. Both external beam radiation therapy (EBRT) and radical prostatectomy have been used to treat clinical stage T3 prostate cancer; either alone or in combination, these modalities have significant limitations in their ability to eradicate locally advanced prostate cancer. New vessel formation is essential to cancer progression including prostate cancer. Weidner et al. (1993) showed a correlation between microvessel count and metastatic prostate cancer. This study appears to support the theory that the degree of angiogenesis is an important predictor of disease progression.

Treatment with an angiogenesis inhibitor may reduce the extension of the tumor outside the capsule of the prostate and potentially eradicate small volumes of extra-prostatic disease.

Thalidomide is a sedative hypnotic agent that has been shown to alter adhesion molecule expression, suppress tumor necrosis factor-κ (TNF increase IL-10 production, downregulate IL-6, and inhibit basic fibroblast growth factor (bFGF)- and vascular endothelial growth factor (VEGF)- induced angiogenesis in the rabbit cornea micropocket assay as well as in a murine model of corneal vascu-larization. VEGF or bFGF are two strong angiogenic growth factors implicated in prostate cancer progression in vivo.

Thalidomide has shown some evidence of clinical activity in patients with metastatic androgen independent prostate cancer. Approximately 30% of 45 treated patients with overt metastatic Androgen Independent PCa had some "clinical benefit" without significant side effects [among them one individual had improvement in bony lesions (documented on bone scan over an 8 month period) that resulted in clinical improvement and another patient had a PSA decline of >50% that corresponded with symptomatic improvement and less pain medications. In addition, several individuals have had minor reductions of soft tissue masses as documented by CT scan] (NCI study, Figg et al, personal communication).

It is postulated that the efficacy of anti-angiogenic agents, such as thalidomide, will be seen in both the primary organ as well as the metastatic sites. However, angiogenesis

is site-specific and the effects of different agents may be variable in different tissues – organs.

The safety of treatment with thalidomide at the doses proposed has been established in a pilot study conducted by our department in patients with advanced metastatic renal cell carcinoma.
The safety of pre-operative treatment with a different angiogenesis inhibitor (fumagillin analog) has been established in our previous trial (DM96-140), although the results may not be necessarily comparable due to a different mechanism of action and much longer half-life of thalidomide compared to the fumagillin analog.

This pre-operative trial will assess: a) the safety of treatment with thalidomide before radical prostatectomy, b) screen for evidence of biologic activity (rate of PSA decline and tumor reduction with thalidomide), and c) obtain preliminary information concerning the effect of the treatment on tissue and serum markers of known angiogenic factors as well as the effect of the treatment on the epithelial compartment (apoptosis/proliferation markers) that will help us design future combination therapies.

Eligibility: (List Major Criteria)

Inclusion:

1. Prostatic adenocarcinoma without evidence of regional or distant metastases, clinical stage T1c-T2c with Gleason score $\geq$ 7 on initial biopsy or clinical stage T3. (chemohormonal vs hormonal protocol remains first priority for patients with T1c-T2 disease).
2. Negative bone scan and CT abd/pelvis.
3. Life expectancy of at least 10 years.
4. Surgical candidate for radical prostatectomy and ECOG performance status of $\leq$2.
5. Patients must have not other concurrent malignancies (within the past 5 years, with the exception of non-melanoma skin cancer or treated superficial transitional cell carcinoma of the bladder).
6. Peripheral granulocyte count $\geq$ 1,500/mm3, platelet count of $\geq$ 100,000/mm3 and Hb$\geq$ 10.0 gm/dl, adequate hepatic function with a bilirubin $\leq$ 1.5 mg % and SGPT $\leq$ 2.5x the upper limits of normal, and adequate renal function defined as serum creatinine $\leq$ 1.5 mg% or creatinine clearance > 40 ml/min.
7. Patients with biochemical hypothyroidism will have their thyroid hormone replaced concurrent with starting the study. Patients with clinical hypothyroidism should have their thyroid replaced prior to starting this study.

8. Informed consent indicating that patients are aware of the investigational nature of the study, in keeping with the policies of the institution. The only approved consent form is appended to this protocol.
9. Patients must be willing and able to travel to UT-MDACC for re-evaluation as necessary per protocol.
10. Patients should be counseled about the possibility that thalidomide may be present in the semen and must use a latex condom every time they have sexual intercourse with a woman during therapy and for 4 weeks after discontinuing thalidomide, even if they had a successful vasectomy.

Exclusion:

1. Patients who have received any prior hormonal-, immuno-, radiation or chemo-therapy for prostate carcinoma are excluded from the trial. Prior herbal and/or homeopathic medication is allowed if discontinued at least 2 weeks prior to study entry. PC-SPES is considered hormonal therapy.
2. Patients with history of substantial non-iatrogenic bleeding diathesis and patients with macroscopic hematuria or active GI bleeding are not eligible.
3. Patients with uncontrolled cardiac, respiratory, hepatic, renal, neurologic or psychiatric disorder are excluded from the trial.
4. Patients with NCI grade 2 or greater peripheral neuropathy of any cause (clinically detectable), or receiving anti-convulsive medications are not eligible for this trial.
5. Patients who are receiving sedative/hypnotic agents which cannot be discontinued (if necessary) are not eligible for this study.
6. Patients positive for HIV are excluded from this trial.

Is there an age limit? **OYes ●No**

Why? Please explain.

Treatment/Study Plan:

Patients will be treated as outpatients with thalidomide orally on a daily basis. The starting dose will be 200 mg/day (in the evening), and can be escalated by 200 mg/day every week to a maximum of 600 mg/day. One treatment cycle will be 42 days. The treatment cycle will be repeated in "responding" patients for a maximum of 3 months and then patients will proceed to radical prostatectomy. Patients will be considered as "responding" if they show stable intraprostatic lesion by bidimentional measurements (TRUS) after the first 6 weeks of thalidomide without PSA progression and if they experience more than 25% reduction in bidimentional measurements of the intraprostatic lesion(s) and/ or stable or lower PSA after 12 weeks of treatment. Follow-up evaluation by digital rectal exam and TRUS will be performed at 6 and 12 weeks of

treatment. CT scan (tumor perfusion protocol) of the prostate will be performed before and after thalidomide treatment. Biopsy of the prostate tumor will be obtained (optional) at 6 weeks of the therapy. Radical prostatectomy will be performed upon completion of the thalidomide treatment (+/- 3 days) provided the patient is not suffering any toxicity that necessitates delaying the surgery.

Disease Group: Locally Advanced Prostate Cancer

Treatment Agent: Thalidomide

Statistical Considerations:

This is a phase II trial of neo-adjuvant thalidomide prior to radical retropubic prostatectomy (RRP) in patients with newly diagnosed locally advanced prostate cancer. The design of Thall, Simon and Estey (199, 1998) will be used. For the purpose of sample size determination and safety monitoring, patient success, S, is defined as stable disease (no increase in tumor mass) at 6 weeks, followed by $\geq$ 25% tumor shrinkage, compared to baseline mass or $\geq$ 50% decline in serum PSA (with no tumor progression) at 12 weeks. At 12 weeks, once S is evaluated, all patients will undergo RRP. The adverse event, A, pertains to surgery, and is defined as either excessive bleeding (> 5 units of blood required during the first 24 hours post surgery) or fascia dehiscence. A success probability of .20 or larger will be considered clinically promising, and a maximum adverse event rate of .10 is desired. Formally, denote the success probability by p_S, the adverse event rate by p_A, and assume the historical probabilities of the four possible combinations (No S, No A), (No S, A), (S, No A), (S, A) follow a Dirichlet prior with parameters (720,80,180,20), which implies historical (H) mean rates for $p_S(H)$ and $p_A(H)$ of 10% and 20% as noted above, with independence of the two events S and A. For the probabilities under the experimental regimen (E) studied in this trial, we assume a Dirichlet prior with the same mean but parameters that sum to 4. The two safety monitoring criterion will be to stop the trial if either $Pr[p_S(H) < p_S(E) \mid data] < .01$ or $Pr[p_A(H) < p_A(E) \mid data] > .95$. A maximum of n=40 patients will be treated which, if 8/40 (20%) successes are observed, will yield a 90% posterior credibility interval running from .11 to .31. Applying these monitoring criteria after each cohort of 4 patients has been treated and evaluated, the trial will be terminated if the observed [#successes]/[# patients evaluated] $\leq$ 0/16, 0/20, 0/24, 1/28, 1/32, or 2/36, or if the observed [#adverse events]/[# patients evaluated] $\geq$3/4, 4/8, 4/12, 5/16, 5/20, 6/24, 7/28, 7/32, or 8/36. The operating characteristics of this design are as follows:

True ps pa	Early Stopping Probability	Sample Size Quartiles
.20 .10	.11	40 40 40
.20 .20	.59	16 32 40
.20 .30	.93	12 12 20
.05 .10	.79	16 28 36

References:

Thall, PF, Simon, R and Estey, EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in Medicine* 14, 357-379, 1995.

Thall, PF and Sung, HG: Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. *Statistics in Medicine* 17, 1563-1580, 1998.

Data Monitoring Committee

Does this protocol require monitoring by a Data Monitoring Committee? **○Yes ●No**

Which DMC has oversight?

Describe the Schedule for Interim and Final analysis:

Patient/Participant Evaluation: (MAXIMUM 4000 CHARACTERS) (Pretreatment and Interim Testing)

	Pre-Study	Q 1 Week On Escalation	At 6 Weeks	Pre-Prostatectomy	Post Prostatectomey
History, Physical, PS	X	X	X	X	as indicated
Quality of Life	X		X	X	1,3,6 mos and q 6 mos x 5 yrs
Toxicity	X	X	X	X	3 mos
DRE	X		X	X	3,6 mos and q 6 mos x 5 yrs
Step sect TRUS/Doppler	X		X	X	as indicated
Staging biopsies	X		X+		*
PSA	X		X	X	1, 3, 6 mos and q 6 mos x 5 yrs
PAP	X				as indicated
CBC, diff, Plat	X	[a]	X	X	as indicated
Chemical Survey[b]	X	[a]	X	X	as indicated
TSH, T4, T3	X		X		

Serum transferase level	X		X	X	
PT/PTT	X		X	X	as indicated
HIV test[c]	X				
Urine analysis/creatinine	X		X	X	3 mos
Electrocardiogram	X				
Bone Marrow Asp/Bx	X			X+	
Chest X-ray	X				
Bone Scan	X				X[d]
CT abdomen/pelvis	X			X	as indicated
Tumor neovascularity	X		X	X	X (at surgery)
Tissue Angiogenic Factors	X		X	X	X (at surgery)
Tissue Apoptosis Markers	X		X	X	X (at surgery)
Serum E-Selectin	X	X	X	X	X**
Serum Thrombomodulin	X	X	X	X	X**
Serum IL-6	X	X	X	X	X**
Serum VEGf	X	X	X	X	X**
Urine (bFGF/Creatinine)	X	X	X	X	X**
Entry info into PDMS	X		X	X	X

a If indicated
b BUN, creatinine, glucose, alk. phosphatase, total bilirubin, calcium, total protein, albumin, phosphorus, uric acid, SGPT, SGOT, Na, K, lactic dehydrogenase, chloride, bicarbonate, Mg
c HIV test results are acceptable if obtained within 6 months prior to study enrollment
d Yearly starting when elevated PSA is detected, or earlier if clinically indicated.
* TRUS guided biopsy of vesico-urethral anastomosis if PSA > 0.3
** On the fourth post-operative day (+/- 2 days)
+ Optional
++ Can be performed by the patient's treating urologist at home

Any studies necessary to completely evaluate malignant and concurrent non-malignant diseases and drug toxicity must be obtained and recorded at baseline and before each course as appropriate.

Biosafety:

Does this study involve the use of Recombinant DNA Technology? If Yes, contact the IBC coordinator for information at 713-745-1697.	OYes ●No
Does this study include any products manufactured or produced at MD Anderson Cancer Center?	OYes ●No
Does this protocol include a PK study with a new radiolabeled compound? If Yes, contact the chair of the Radioactive Drug Research Committee at 713-794-1052.	OYes ●No

Where Will Study Be Conducted:

- ● A) Only at MDACC
- O B) MDACC + Community Programs (CCOP/Network)
- O C) Independent Multicenter Arrangements

Estimated Accrual:

It is estimated that accrual will be **3-4** participants per month.

Total Accrual at M.D. Anderson Cancer Center **40**

Total accrual will be: **40**

Basis of Study:

This protocol is performed on
- O an Inpatient Basis
- O Outpatient Basis
- ●Both Inpatient AND Outpatient Basis

Length of Stay: (MAXIMUM 250 CHARACTERS) **(What is the length & frequency of hospitalization)**

Four days (routine for prostatectomy)

Return Visits: (MAXIMUM 250 CHARACTERS) **(How often must participants come to MDACC)**

Every week for the first 3 weeks of the treatment and at 6 weeks into the treatment, and 3 months post-prostatectomy.

Home Care: (MAXIMUM 250 CHARACTERS) **(Specify what (if any) treatment may be given at home)**

None

Name of Research Nurse/Data Manager Responsible for Protocol:

Pauline Dieringer RN / Darlene Montgomery

Public Display of Protocol on the Office of Protocol Research Web Site:	
The Office of Protocol Research maintains a website (www.clinicaltrials.org) listing protocols actively accruing patients. No information is given about drug dose or schedule. Would you like this protocol listed on this website?	●Yes ONo
If this protocol has a corporate sponsor, we also need to get the sponsor's written approval to post the trial on the website. Shall OPR send a letter requesting this permission to your sponsor?	●Yes ONo ON/A

Space Requirements for Clinical Trials:

Will implementing this protocol require additional space (clinical, office, departmental)? OYes ●No

CCSG:

Indicate the Cancer Center Support Grant (CCSG) -- NCI Core Grant Program that this protocol relates to (choose from the attached list next to the abstract on the ORA Forms database: GU Cancers

Sponsorship and Support Information:

Sponsor or Supporter:	Celgene Inc.
Grant Number:	
Is this Protocol listed on any Federal	OYes ●No
Grant or Foundation Funding Application?	
Sponsor or Supporter Contact: Telephone:	Andrew Zeitlin, M.D.
Fax Number: E-Mail:	Office: (732) 271-4135
	Fax: (732) 271-4184
	azeitlin@celgene.org
Who is supplying the drug(s) or device(s)?	Celgene
Funds Supplier:	

The Code of Federal Regulations at 21 CFR § 312.2(b)(1) describes when it is acceptable to conduct a clinical trial using commercially-available drugs without FDA oversight via the IND process. The criteria that must be met for the protocol to be exempt from the IND requirement are:

- the data are not going to be submitted to the FDA to expand the label for the drug
- the investigation is not going to be used to change the advertising for the drug
- the investigation will be conducted in compliance with federal regulation related to informed consent and good clinical practice.

The main criterion that requires the most scrutiny is the following:

- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

To ensure that all protocols conducted at UTMDACC have the appropriate regulatory oversight, please complete the following questions:

Based on your responses to the following questions, if your protocol needs to be conducted under an IND or an IND Exemption request needs to be sent to the FDA, you will be notified or asked for additional information.

Is your protocol being conducted under an IND? ●Yes ONo

(If Yes, just answer next question)

Who is the IND sponsor and what is the IND number? MDACC 56,533

(If No, answer all the rest of the questions)

Please list below the drugs or other therapies you are using in your protocol and the dose and route of administration for which they are approved:

Please list below the drugs or other therapies and the dose and route of administration you plan to use in your protocol:

Please briefly describe the difference in the patient population you will be treating and the patient population for which the drugs in your study have been approved. Are there any differences between the two that would cause the patient population in this protocol to be at greater risk?

1.0 OBJECTIVES

1.1 To determine the efficacy (rate of tumor reduction and PSA decline) of pre-operative treatment with thalidomide in patients with locally advanced prostate carcinoma.

1.2 To determine the safety and toxicity (excessive bleeding, wound healing problems) of preoperative therapy with thalidomide in patients with locally advanced prostate carcinoma who undergo RRP.

1.3 To obtain qualitative measurements of thalidomide's effect *in vivo* on:

a) endothelial cells / neo-vascularity /angiogenic growth factors:
- Assessment of neovascularity (MVD)
- Dual flourescent labeling technique to evaluate apoptosis in CD-31 positive cells (TUNEL)
- bFGF, VEGF, EGF and TGF expression by PCa epithelium and prostatic stroma
- Modulation of endothelial markers (serum: E-selectin and Thrombomodulin)
- Modulation of serum VEGF and urine bFGF levels, and
- Changes in tumor blood flow

b) epithelial compartment:
- apoptosis in prostate cancer cells (TUNEL)
- proliferation (PCNA)

c) quality of life

2.0 BACKGROUND:

In the United States, prostate cancer is the most common cancer and the second leading cause of male cancer death (Landis et al). Many patients with prostate cancer are curable with local therapy as local treatments continue to evolve to minimize morbidity (Zinke H et al).

The optimal treatment though for patients with locally advanced prostate cancer (clinical T3) remains to be defined. External beam radiation therapy (EBRT) alone has a significant local and distant failure rate for locally advanced prostate cancer. Zagars et al report in their series with a median follow-up of 17 months, that 17% and 60% of patients with a pretreatment PSA 4-40 ng/ml or > 40 ng/ml respectively developed a rising PSA profile (Zagars GK et al, 1992). In the Stanford University series, over 50% of patients followed greater than 1 year after completion of

radiotherapy have an increasing PSA (Stamey TA et al, 1989) indicating cancer progression. In the Stanford experience, over 90% have positive prostate biopsies if random TRUS guided biopsies are performed following radiation therapy (Kabalin JN, et al). If traditional disease endpoints are used (i.e., change in bone scan, digital rectal examination or prostatic acid phosphatase; excluding PSA and random biopsy data), the 15 year disease-free survival for clinical stage T3 patients treated with definitive radiation therapy is only 25-40% (Zagars GK, 1987, Bagshaw Ma, et al). Furthermore, evidence exists that locally recurrent prostate cancer following radiation therapy is of higher grade than the index cancer (Wheeler JA, et al, Cumming A, et al). These data suggest that if radiation therapy fails to eradicate the cancer, clonal evolution occurs over time favoring progressive loss of differentiation (this change in grade probably also occurs with locally recurrent prostate cancer following surgery although there are no studies yet documenting it).

At the same time, radical prostatectomy alone for clinical stage T3 disease also has significant limitations. The reported 10- and 15-year survival rates for clinical stage T3 disease treated with radical prostatectomy are 12-60% and 20-28% respectively. The reported local recurrence rates for pathologic stage T3 patients range from 10-41% (Stamey TA, et al, 1992). In many of these patients, radical prostatectomy alone is not curative because of local tumor extension outside of the prostate gland resulting in positive surgical margins. Positive margin rates of 23-33% have been reported for patients with clinically organ-confined prostate cancer undergoing radical prostatectomy (Rosen Ma, et al, Stamey TA, 1990, Catalona WJ, et al). Although there are no good studies documenting the positive surgical margin rate for clinical stage T3 patients, it is presumably significantly higher. In addition, post-operative PSA measurements following radical prostatectomy have demonstrated that a substantial number of these patients have clinically unrecognized recurrence (Stein A, et al, 19991); in one recent report 66% of patients with positive surgical margins had a detectable post-operative PSA (Frazier Ha, et al, 1993).

Similarly, patients with high grade tumors on initial biopsy have a high risk for extracapsular disease: patients with T1c-T2 tumors and Gleason's score 8-10 have a 92% risk for extracapsular extension (Partin AW, et al 1994), while patients with T2b-T2c tumors, Gleason's score of 7 and serum PSA > 10 have a > 73% risk for extracapsular extension of their disease (Partin AW, et al 1993).

Radiotherapy has been combined with radical prostatectomy in neoadjuvant and adjuvant settings to improve the local control rates for patients with pathologic T3 disease. The use of radiotherapy in a neoadjuvant setting has been limited because of an unacceptably high surgical complication rate (Pontes JE, et al). Radiotherapy is commonly used in an adjuvant setting for those patients with pathologic T3 disease (especially those who are found to have positive surgical margins following radical prostatectomy). In those patients with a detectable PSA following radical prostatectomy, only 27-29% exhibit a decrease in their PSA to

undetectable levels (Klein EA, et al, Hudson MA, et al). Although some of these patients may have metastatic disease outside of radiation portals, adjuvant radiotherapy following radical prostatectomy appears to eradicate disease in only a small percentage of patients.

Androgen ablation combined with radiation therapy delays progression of disease more than radiation therapy alone in patients with locally advanced prostate cancer (Pipelich MV, et al, Bolla M, et al) and is considered the current "standard of care" for these patients. Nevertheless, none of these therapies is curative. Either alone or in combination, these treatment modalities have significant limitations in their ability to eradicate locally advanced prostate cancer. Younger patients with locally advanced prostate cancer still face a serious threat from progression to metastatic prostate cancer. Achieving excellent local control of prostate cancer may be very important in delaying progression of the disease.

New vessel formation is essential to cancer progression including prostate cancer. Weidner et al. (1993) showed a correlation between microvessel count and metastatic prostate cancer. The mean microvessel count for the metastatic group was 76.8 vessels per field, as compared to 39.2 for those without metastasis ($p < 0.0001$) (Weidner, 1993). This study appears to support the theory that the degree of angiogenesis is an important predictor of disease progression.

At least eight polypeptide molecules have been shown to stimulate angiogenesis. Fibroblast growth factors (FGF), basic FGF and acidic FGF, are two of the most potent endothelial mitogens. Several other FGF's have been identified including three oncogenes: kFGF from Kaposi's sarcoma, FGF-5 from bladder cancer, and hst from gastric cancer. BFGF levels are easily monitored in the urine of patients with rapid growing tumors (i.e. newborns with hemangiomas will have large quantities of bFGF, as well as patients with bladder cancer and renal carcinoma). Other possible regulators of angiogenesis include: angiogenin, transforming growth factor-alpha, transforming frowth factor-beta, tumor necrosis factor-alpha, platelet-derived endothelial cell growth factor, angiotropin, vascular endothelial growth factor, and low molecular weight non-peptide angiogenic factors (Folkman, 1993).

The inhibition of angiogenesis has been proposed as a potential means for selectively impairing tumor growth. Treatment with an angiogenesis inhibitor may reduce the extension of the tumor outside the capsule of the prostate and potentially eradicate small volumes of extra-prostatic disease.

Thalidomide is a sedative hypnotic agent that has been shown to alter adhesion molecule expression, suppress tumor necrosis factor- α (TNF-α), increase IL-10 production, downregulate IL-6, and inhibit basic fibroblast growth factor (bFGF)- and vascular endothelial growth factor (VEGF)- induced angiogenesis in the rabbit cornea micropocket assay as well as in a murine model of corneal vascularization.

VEGF or bFGF are two strong angiogenic growth factors implicated in prostate cancer progression in vivo.

Thalidomide has shown some evidence of clinical activity in patients with metastatic Androgen Independent Prostate Cancer (AI-PCa). Approximately 30% of 45 treated patients with overt metastatic AI- PCa had some "clinical benefit" without significant side effects [among them one individual had improvement in bony lesions (documented on bone scan over an 8 month period) that resulted in clinical improvement and another patient had a PSA decline of >50% that corresponded with symptomatic improvement and less pain medications. In addition, several individuals have had minor reductions of soft tissue masses as documented by CT scan] (NCI study, Figg et al, personal communication). The side effects have been relatively minor in this patient population: constipation, occasional sedation, depression and mild peripheral neuropathy in those receiving drug for greater than 6 months.

It is postulated that the efficacy of anti-angiogenic agents, such as thalidomide, will be seen in both the primary organ as well as the metastatic sites. However, angiogenesis is site-specific and the effects of different agents may be variable in different tissues – organs.

The safety of treatment with thalidomide at the doses proposed has been established in a pilot study conducted by our department in patients with advanced metastatic renal cell carcinoma.

The safety of pre-operative treatment with a different angiogenesis inhibitor (fumagillin analog) has been evaluated in a previous trial, although the results may not be necessarily comparable due to a different mechanism of action and much longer half-life of thalidomide compared to the fumagillin analog. Among the first 20 (out of the planned 25) patients who have completed therapy and undergone RRP so far, excessive bleeding was encountered in only one patient (thought to be unrelated to the study drug) and wound healing problem (fascia dehiscence) was encountered in 1 patient, both events within the range of the expected historical rates of 8% and 2%, respectively. Because of the different (much longer) half-life of thalidomide and the planned surgery within 2-3 days from end of treatment, we will be monitoring for excessive toxicity during the trial (excessive bleeding and/or wound dehiscence rates).

This pre-operative trial will:

a) assess the safety of treatment with thalidomide before radical prostatectomy,
b) screen for evidence of biologic activity (rate of PSA decline and tumor reduction with thalidomide), and
c) provide preliminary information concerning the effect of the treatment on tissue and serum markers of known angiogenic factors as well as the effect

of the treatment on the epithelial compartment (apoptosis / proliferation markers) that will help us design future combination therapies.

2.1 Analysis of risks and benefits of the study:

Potential risks of the study include development of side effects while on thalidomide treatment as well as the potential for increase morbidity at the time of prostatectomy because of the prior treatment with thalidomide.

Having a prostate and/or bone marrow biopsy may cause pain, redness, swelling, infection, and/or bleeding through in the stool and/or urine for a few days after the biopsy. In addition, with some biopsies, underlying structures can be damaged. Sometimes this structural damage may require further tests or even surgery to correct.

Blood draw may cause pain, redness, swelling and / or infection where the needle enters the body.

Diagnostic procedures like ECG, Chest x-ray, bone scan are not associated with risk to the patient. The use of intravenous contrast during a CT-scan evaluation can in a small number of patients cause allergic reaction (in patients with allergy to iodine) and could worse the kidney function in patients with compromised kidney function.

Potential benefits for the individual patient include: inhibition of neo-angiogenesis in the primary organ (prostate gland) as well as at sites of micrometastases (lymph nodes and / or bone) that could lead to down-staging at the time of the surgery and may reduce prostate cancer recurrence.

Potential benefits for prostate cancer research in general and subsequent patients diagnosed with prostate cancer may be derived from our ability to assess in vivo the effects of thalidomide in prostate and bone tissue as well as identify surrogate markers of anti-angiogenic activity which will be invaluable to the design of new effective therapies.

To address the potential risks while on study we take rigorous measures:

a) The most devastating event associated with thalidomide therapy is the teratogenicity. Patients are warned and counseled regarding this risk and are required to use adequate birth control during and for 2 months after participation in this study. Men are required to use a latex condom every time they have heterosexual intercourse during and for 8 weeks after stop taking thalidomide, even if they have had a

successful vasectomy.

b) Patients are also warned regarding other potential side effects of thalidomide (i.e.: somnolence, dizziness, hypotension, bradycardia, nausea, vomiting, fatigue, photosensitivity, low blood counts / infections, changes in apetite, increase risk of bleeding and decreased wound healing) and are monitored very closely during the study (see appendix A). Patients are reminded not to drive while they are taking part in the study.

c) Patients are counseled regarding potential risks of invasive procedures during the study (i.e.: bone marrow biopsy, prostate biopsy). Bone marrow biopsies are performed in our institution by highly trained personnel using adequate local anesthesia. TRUS/prostate biopsies are performed by highly trained physicians and physician assistants with minimal discomfort to the patients. Blood draw is performed in our institution by qualified phlebotomists with minimal risks to the patients. The total amount of blood drawn during the study (230 cc) is drawn in 5 different time points over a 4 month period of time, and is well below the maximum recommended amount to be drawn, either in one setting or over this specified period of time.

d) The primary clinic attending of the patient and our radiology department screen patients very carefully for possible iodine allergy prior to CT scan evaluation. Patients are not given intravenous contrast if they have known allergic reaction to iodine or are given medications to prevent the reaction. Patients are monitored during CT-scan evaluation by trained personnel and medical treatment is provided if necessary in the case of a newly developed allergic reaction. Patients are not given intravenous contrast if they have abnormal kidney function.

e) We also monitor patients very closely in the trial regarding potential increased morbidity at the time of the prostatectomy; there is a mandatory evaluation every 4 patients on the trial to assess for toxicity and efficacy before the trial can continue accrual. Very strict early stopping rules are in place (see section 8.0 statistical section of the protocol), even though our prior experience with another angiogenesis inhibitor (fumagillin analog) prior to prostatectomy did not show increased toxicity.

2.2 Ethical considerations

Gender and Minority Inclusion for Research Involving Human Subjects

There are no restrictions based on race or minority status except for important safeguards against administering thalidomide to patients who cannot comply with the safety requirements of the protocol (i.e. use adequate birth control during and for 2 months after participation in this study, even if they have had a successful vasectomy).

Women and / or Children are not included in the protocol since prostate cancer is a disease of adult men.

3.0 BACKGROUND DRUG INFORMATION

Thalidomide is a potent teratogen that causes dysmelia (stunted limb growth) in humans (Kruger et al, Figg et al 1999). Thalidomide was marketed as a sedative, but was withdrawn from the European market 30 years ago because of its teratogenic effects. The compound was later discovered to be extremely effective in lepromatous leprosy (and received FDA approval in 1998 for the treatment of leprosy (Bauer et al 1998a)) and is presently used as an experimental drug in the treatment of a variety of diseases with an autoimmune character, including recurrent aphthosis of nonviral and nonfungal origin in human immunodeficiency patients. Recently, in vitro data has suggested that thalidomide has antiangiogenic activity (D' Amato, et al). Figg and colleagues demonstrated that a metabolite of thalidomide was responsible for the antiangiogenesis properties (Bauer et al 1998b). Thalidomide's safety in non-pregnant humans was initially established in a study of graft versus host disease (GVHD) conducted at the Johns Hopkins University School of Medicine. Its known side effects (at dosages above that to be used in this trial) include sedation, constipation, and sensory peripheral neuropathy, occurring in 3% of subjects.

It has been postulated that limb defects seen with thalidomide were secondary to an inhibition of blood vessel growth in the developing fetal limb bud. The limb bud is unique in requiring a complex interaction within angiogenesis. Since angiogenesis is the formation of new blood vessels from sprouts of preexisting vessels, the limb bud would be a particularly vulnerable target to a teratogen that inhibited vascular endothelial growth. It was recently demonstrated that orally administered thalidomide is an inhibitor of angiogenesis when using the rabbit cornea micropocket assay (D' Amato, et al). Based on this in vivo animal model, it is suggested that thalidomide might be useful in the treatment of angiogenesis of solid tumors.

Thalidomide, a glutamic acid derivative, was first described in 1953 by the Swiss pharmaceutical company Ciba. Ciba discontinued research on the compound and a German company Chemie Grunenthal undertook development in 1954. It was later marketed as a sleeping pill, and was subsequently blamed for nearly 12,000 birth defects between the late 1950s and early 1960s.

Shortly after the withdrawal of thalidomide from the market, a pronounced effectiveness of the substance against inflammation associated with leprosy was noted. Despite its teratogenic potential, it has been used in the treatment of leprosy for more than 20 years. Additionally, thalidomide was reported to inhibit the graft versus host reactions following bone marrow transplantation. Recently, in vitro data has suggested that thalidomide has anti-angiogenic activity.

3.1 Physical, Chemical and Pharmaceutical Properties

Thalidomide (N-Phthalidoglutarimide; C13O4N2H10) is a racemate. The S(-)/l and R(+)/d forms represent derivatives of l- and d-glutamic acid, respectively (Simmons et al). The maximal solubility of racemic thalidomide in water is approximately 2 x 104 mol/L (45 to 60 mg/L) [Schumacher et al.]. The ultraviolet spectrum of thalidomide is characterized by an absorbance maximum at 300nm which is dependent on an intact phthalimide moiety All 4 amide bonds present in the molecule are susceptible to hydrolytic cleavage in vitro at pH values higher than 6 (Schumacher et al., Luzzio et al).

General: CAS registry No.50-35-1
Molecular formula = C13 H10 N2 O4
Molecular weight = 258.23 daltons

Non enzymatic cleavage of 1 or more of the amide bonds in the thalidomide molecule produces hydrolysis products which contain at least 1 carboxyl group (Schumacher et al.). They are thus more polar and can be expected to cross biological membranes less efficiently than the parent compound. Thalidomide constitutes a transport form for its hydrolysis products; the non polar parent compound enters cells or tissues and is converted to polar derivatives which have been shown to accumulate in erythrocytes and in the embryo (Fabro et al. 1967a).

3.2 Pre-clinical Experience

Thalidomide has recently been shown to inhibit angiogenesis (30-51% reduction in vascularization) induced by FGF in the rabbit cornea micropocket model. It appears the antiangiogenic activity in this model is the result of one of the epoxide active metabolites; thalidomide did not have activity in the chicken chorioallantoic membrane assay (a topical assay

compared with orally administered animal model).

Gordon et al. reported that rats were resistant to the teratogenic effects of thalidomide, but rabbits (as well as higher primates) were sensitive (Gordon et al). They speculated that differences were due to alterations in biotransformation between the species. Furthermore, they noted that after thalidomide treatment, 4- and 5-hydroxylated metabolites of thalidomide were recovered from the urine of rabbits, but not rats. The presence of phenolic derivatives of thalidomide suggests that the drug might undergo oxidative metabolism via an arene oxide intermediate. Arene oxides have been implicated as mutagens, cytotoxins, and teratogens. The intermediate metabolite is also most likely responsible for the antiangiogenic activity. Furthermore, Gordan et al. showed that inhibiting epoxide hydrolase results in enhanced teratogenicity. Likewise, Folkman and colleagues noted that inhibition of epoxide hydrolase results in enhanced antiangiogenic properties.

Bauer et al evaluated thalidomide in two in vitro angiogenesis models (rat aorta model and human endothelial cell culture) and demonstrated antiangiogenic activity in the presence of human liver microsomes (Bauer et al. 1998b). Furthermore, they reported that rodent microsomes failed to generate the active metabolite, but rabbits did.

3.2.1 Preclinical Pharmacology

The biochemical mechanism of the non sedative effects of thalidomide is unclear. Very little work has been done to understand the neurotoxic action or immunomodulatory effect of the compound on a molecular bases. Considering the possible combinations of hydrolysis, hydoxylation, and optical activity, there may be more than 50 metabolites of thalidomide in vivo.

Effects of thalidomide on the endocrine system have been consistently observed in both clinical trials and animal experiments. These actions may be due to an effect of the drug on the hypothalamus (Locker et al. 1971). In humans, a tendency to normalize hyperthyroid states has been noted. Iodine uptake by the thyroid gland was slightly decreased, and myxedema was occasionally observed. Increased urinary secretion of 17-hydroxycorticosteroids associated with hypoglycemia has been reported. Drug interactions with thalidomide have not been systematically studied. Thalidomide enhances the sedative activity of barbiturates, alcohol, chlorpromazine and reserpine, while its sedative action is antagonized by methylamphetamine and methylphenidate. Based on the clinical experience of the investigators at NCI

hypothyroidism has not been observed in patients with metastatic prostate cancer. To date, no significant drug interactions have been identified between thalidomide and cytochrome P450 enzyme inducers and inhibitors (Figg et al, personal communication).

3.2.2 Preclinical Toxicology

Thalidomide is a potent teratogen. In 1961, McBride and Lenz described the association between limb defects in babies and maternal thalidomide usage. Although humans are exquisitely sensitive to the teratogenic effects of thalidomide, experiments in rodents failed to reveal similar effects. Teratogenic effects could be experimentally reproduced by the administration of thalidomide to pregnant rabbits at an oral dose of 100-300 mg/kg/day. [Over the past 30 years the mechanism of thalidomide's teratogenicity has been extensively studied, but has remained unsolved (Stephens 1988)].

3.2.3 Pharmacokinetics and Drug Metabolism in Animals

Studies in experimental animals showed high concentrations of the drug in the gastrointestinal tract, liver and kidney, and lower concentrations in muscle, brain and adipose tissue. In pregnant animals, thalidomide is able to pass across the placental barrier (Fabro et al. 1967a; Nicholls 1966; Schumacher et al. 1965a, 1970).

In animals, the main pathway of degradation appears to be non-enzymatic hydrolytic cleavage (Fabro et al. 1967a; Schumacher et al. 1965a). Minor amounts of hydroxylated products have been detected in the urine of some species (Schumacher et al. 1965a). Hepatic metabolism of thalidomide probably involves enzymes of the cytochrome P450 family (Braun et al. 1986). Only the parent compound is enzymatically modified (Braun & Weinreb 1985; Schumacher et al. 1965a). Thalidomide itself does not cause enzyme induction (Brode 1968a), but possibly interferes with enzyme induction caused by other compounds (Brode 1968a).

3.3 Clinical Pharmacokinetics

The pharmacokinetics of thalidomide have not been clearly characterized in man (Piscitelli et al). Theoretically, greater than 12 different metabolites can be formed from thalidomide by hydrolysis and several others by alternative metabolic pathways (phenolic metabolites): however, the main transformation of thalidomide in the body may be by spontaneous chemical processes and not involve enzyme reactions. Thus, it seems probable that a minor proportion of the drug is enzymatically

hydroxylated.

Oral administration of thalidomide at 100 to 200 mg in humans results in maximal blood concentration of 0.9 to 1.5 μg/mL after 4 to 6 h (Chen et al.). Absorption and elimination half-lives calculated from data of 8 healthy subjects were 1.7 ± 1.05 and 8.7 ± 4.11 h, respectively; a lag time of 0.41 ± 0.17 h was observed in 6 individuals (Chen et al. 1989). Using a 1- compartment model, the authors calculated a volume of distribution of 120.64 ± 45.36 L, a total body clearance of 10.41 ± 2.04 L/h, and a renal clearance of 0.08 ± 0.03 L/h. Only 0.6 ± 0.22% of the administered dose was excreted as unchanged compound in the urine. The hydrolytic cleavage in serum (Chen et al.) is much slower than that in vitro at pH 7.4 (Schumacher et al. 1965b). This may be because thalidomide is highly bound to plasma proteins (Bakay & Nyhan 1968).

There is some controversy over the incidence of neurotoxicity associated with thalidomide. The incidence may be disease specific (patients with prurigo nodularis may have a higher incidence than patients with rheumatoid arthritis or some other disease). A group from Columbia reported treating 17 patients with arthritis with a dose of 400 to 600 mg per day of thalidomide (mean duration of therapy, 24.8 month, range 7-65 weeks). They found that 2 patients developed symptoms of peripheral sensory neuropathy that was reversed on discontinuation of therapy. Crawford reported that 25% of patients (n=60) receiving thalidomide for the management of chronic discoid lupus erythematosus developed neuropathies, and all patients (n=8) receiving it for nodular prurigo and aphthous stomatitis were found to have neuropathies. Sheehan reported the development of neurological complications in 2 of 5 patients receiving thalidomide for prurigo nodularis. Polyneuropathy persisted in one of those patients for greater than 12 months after the discontinuation of therapy. Aronson et al. reported the development of sensory peripheral neuropathies (onset 2 to 12 months into therapy) in 3 of 4 patients with prurigo nodularis that were receiving thalidomide (100 to 300 mg per day). Their in vitro work went on to show that thalidomide induced primary neuronal degeneration. Schroder et al. reported that there was a reduction in sheath thickness) and a decrease in conduction velocity in thalidomide treated New Zealand white rabbits as compared to controls.

Figg and colleagues have reported on the pharmacokinetics of thalidomide in patients with prostate cancer (Figg et al 1999). They observed a slight decrease in the clearance and an estimated terminal half-life daily dosing of 200 mg/d to be 7.1 hours. There was a linear relationship between dose and plasma concentration using does between 200 and 1200 mg/day.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Prostatic adenocarcinoma without evidence of regional or distant metastases, clinical stage T1c-T2c with Gleason score $\geq$ 7 on initial biopsy and PSA > 10 ng/dl or clinical stage T3.

4.1.2 Negative bone scan and CT abd/pelvis.

4.1.3 Life expectancy of at least 10 years.

4.1.4 Surgical candidate for radical prostatectomy and ECOG performance status of $\leq$ 2.

4.1.5 Patients must have no other concurrent malignancies (or within the past 5 years, with the exception of non-melanoma skin cancer or treated superficial transitional cell carcinoma of the bladder).

4.1.6 Peripheral granulocyte count $\geq$ 1,500/mm3, platelet count of $\geq$ 100,000/mm3 and Hb$\geq$ 10.0 gm/dl, adequate hepatic function with a bilirubin $\leq$ 1.5 mg % and SGPT $\leq$ 2.5x the upper limits of normal, and adequate renal function defined as serum creatinine $\leq$ 1.5 mg% or creatinine clearance > 40 ml/min.

4.1.7 Patients with biochemical hypothyroidism will have their thyroid hormone replaced concurrent with starting the study. Patients with clinical hypothyroidism should have their thyroid replaced prior to starting this study.

4.1.8 Informed consent indicating that patients are aware of the investigational nature of the study, in keeping with the policies of the institution. The only approved consent form is appended to this protocol.

4.1.9 Patients must be willing and able to travel to UT-MDACC for re-evaluation as necessary per protocol.

4.1.10 Patients should be counseled about the possibility that thalidomide may be present in the semen and must use a latex condom every time they have sexual intercourse with a woman during therapy and for 4 weeks after discontinuing thalidomide, even if they had a

successful vasectomy.

4.2 Exclusion criteria

4.2.1 Patients who have received any prior hormonal-, immuno-, radiation or chemo-therapy for prostate carcinoma are excluded from the trial. Prior herbal and/or homeopathic medication is allowed if discontinued at least 2 weeks prior to study entry. PC-SPES is considered hormonal therapy.

4.2.2 Patients with history of substantial non-iatrogenic bleeding diathesis and patients with macroscopic hematuria or active GI bleeding are not eligible.

4.2.3 Patients with uncontrolled cardiac, respiratory, hepatic, renal, neurologic or psychiatric disorder are excluded from the trial.

4.2.4 Patients with NCI grade 2 or greater peripheral neuropathy of any cause (clinically detectable), or receiving anti-convulsive medications are not eligible for this trial.

4.2.5 Patients who are receiving sedative/hypnotic agents which cannot be discontinued (if necessary) are not eligible for this study.

4.2.6 Patients positive for HIV are excluded from this trial.

5.0 TREATMENT PLAN:

All patients will be registered with the Data Management Office at 792-2926.

Patients will be treated as outpatients with thalidomide orally on a daily basis. The starting dose will be 200 mg/day (in the evening), and can be escalated by 200 mg/day every week to a maximum of 600 mg/day. One treatment cycle will be 42 days. The treatment cycle will be repeated for a maximum of 2 cycles (3 months) in patients who show stable or regressing disease (by DRE, TRUS, and/or PSA) after the first 6 weeks of treatment, and then patients will proceed to radical prostatectomy.

Patients in this study will be allowed to receive up to 6-weeks supply of thalidomide at one time.

Follow-up evaluation by digital rectal exam and TRUS will be performed at 6 and 12 weeks of treatment. CT scan (tumor perfusion protocol) of the prostate will be performed before and after thalidomide treatment. Biopsy of the prostate tumor will be obtained (optional) at 6 weeks of the therapy.

Radical prostatectomy will be performed upon completion of the thalidomide treatment (+/- 3 days) provided the patient is not suffering any toxicity that necessitates delaying the surgery. Surgery will be delayed if there is any bleeding abnormality and/or until platelet count is $\geq$ 100,000 and coagulation profile (PT/PTT) is normal. If at the time of surgery a patient is found to have positive lymph nodes, prostatectomy will be abandoned, a repeat prostate biopsy will be performed at the time of the surgery, and the patient will be offered other treatment modalities (hormones, XRT).

Patients will be considered as showing evidence of biologic activity if they have: a) more than 25% reduction in the product of the bidimentional measurements of the intraprostatic lesion(s) by TRUS without PSA progression after 12 weeks of treatment, or b) stable intraprostatic lesion by TRUS at 12 weeks and $\geq$ than 50% reduction is serum PSA at 12 weeks.

"PSA progression" is defined as a more than 25% increase in serum PSA over the baseline value (pretreatment PSA).
Progression of measurable prostatic lesion by TRUS is considered a more than 25% increase in the product of perpendicular diameters of measurable lesion (s).

5.1 Dose Modifications

The dose of thalidomide may be reduced by 200 mg per day for toxicity (grade $\geq$ 3 toxicity that appears to be drug related or grade $\geq$ 2 peripheral neuropathy) which resolves to grade $\leq$ 1 with interruption of treatment within a 2 week period. If a patient requires an additional dose adjustment, then they will be removed from the study based on toxicity.

5.2 The investigational drug (Thalidomide) is kept by the U.T.-M.D. Anderson Cancer Center Pharmacy. Drug is dispensed by the Pharmacy and a drug dispense log is kept by the U.T.-M.D. Anderson Cancer Center Pharmacy.

Subject compliance will be assessed every clinic visit. Patients will be asked regarding pills taken (or missed) and about adherence to protocol requirements (with particular focus on the issue of birth control). A notation of the above will be made in the patient's chart from the clinic nurse / research nurse / clinical nurse specialist / advanced practice nurse or physician. Unused drug will be returned and disposed appropriately.

5.3 The IND for this drug application is 56,533. This IND is held by U.T.-MDACC.

6.0 PRETREATMENT EVALUATION (see also Appendix A)

6.1 Complete history and physical examination including performance status. Symptoms
and quality of life questionnaire.

6.2 Histologic examination of prostate biopsies.

6.3 PSA, PAP, CBC with diff, platelets, BUN, creatinine, glucose, alkaline phosphatase, total bilirubin, calcium, total protein, albumin, phosphorus, uric acid, SGPT, lactic dehydrogenase, sodium, potassium, chloride, bicarbonate, PT/PTT, TSH, T4, T3, urine analysis, urine creatinine, stool for occult blood, electrocardiogram, serum transferase level, bone marrow aspirate and biopsy, $\leq$ 14 days before starting thalidomide treatment.

6.4 HIV serology (HIV test results can be accepted if obtained within 6 months prior to study enrollment).

6.5 Radiologic studies including CXR, bone scan and CT abdomen/pelvis $\leq$ 4 weeks before starting thalidomide.

6.6 Step section TRUS with volume determination and 10 staging biopsies [2 each from the apex, mid-section, base, seminal vesicles and extracapsular area of the prostate].

6.7 Assignment of local extent of the disease using DRE / TRUS. Assignment of clinical
stage will be done by the urologist after completion of the above tests.

6.8 Assessment of intermediate endpoints (see section 1.3)

7.0 EVALUATION DURING STUDY (see also Appendix A)

7.1 On-Treatment Evaluation (Pre-radical prostatectomy)

7.1.1 Weekly during the 3-week dose escalation period: history, physical exam, assessment of toxicity, and performance status. Serum PSA, and soluble (serum and urine markers) will also be done. CBC, diff, platelets, BUN, creatinine, glucose, alkaline phosphatase, total bilirubin, calcium, albumin, total protein, SGPT, SGOT, lactic dehydrogenase, uric acid, phosphorus, sodium, potassium, chloride, bicarbonate, PT/PTT will be done only if clinically indicated.

Patients who develop AEs/SAEs will be followed for a minimum of 30 days post last day of Thalidomide intake or 30 days post surgery, whichever is longest.

7.1.2 At 6 weeks and 12 weeks: history, physical exam, DRE, TRUS, **optional** prostate biopsy (only at 6 weeks), assessment of toxicity, and performance status. Serum PSA, and soluble (serum and urine) markers, CBC, diff, platelets, BUN, creatinine, glucose, alkaline phosphatase, total bilirubin, calcium, albumin, total protein, SGPT, SGOT, lactic dehydrogenase, uric acid, phosphorus, sodium, potassium, chloride, bicarbonate, PT/PTT, serum transferase level, TSH, T4, T3, urine analysis, urine creatinine. CT scan of abdomen and pelvis and **optional** bone marrow biopsy to be done only preoperatively (at the end of treatment).

7.1.3 Immediately before surgery (within 24-48 hours, if surgery is not done within 2-3 days from completion of thalidomide treatment due to toxicity): CBC, diff., Platelets, BUN, creatinine, glucose, alkaline

phosphatase, total bilirubin, calcium, albumin, total protein, SGPT, lactic dehydrogenase, uric acid, phosphorus, sodium, potassium, chloride, bicarbonate, serum transferase level, PT/PTT, PSA, urine analysis, and urine creatinine.

7.1.4 Assessment of intermediate endpoints (as per section 1.3) if an **optional** prostate biopsy is obtained.

7.1.5 Approximately 46 teaspoons (230 cc) of blood will be collected during participation in the trial.

7.2 Post-Radical Prostatectomy Evaluation:

7.2.1 Assessment of intermediate endpoints (as per section 1.3).

7.2.2 PSA, quality of life assessment at 1, 3, 6 mos and q 6 mos thereafter x 5 years.

7.2.3 DRE of prostatic fossa at 3, 6 mos and q 6 mos thereafter x 5 years. (can be done by the patient's local urologist).

7.2.4 Urine analysis at 3 mos postoperatively.

7.2.5 Bone scan at yearly intervals beginning when an elevated (>0.3) PSA is detected, or earlier if clinically indicated. CT scan of abdomen/pelvis as clinically indicated.

7.2.6 TRUS guided biopsy of vesico-urethral anastomosis if an elevated PSA (>0.3) is detected.

7.3 Methodology for the assessment of the in vivo effect of therapy.

TRUS prostate tumor measurement and prostate biopsies will be obtained pre- treatment, at 6 weeks (biopsy optional at that time) and before the surgery.

Serum and urine samples will be obtained weekly x 3 weeks (during escalation phase of thalidomide), then at 6, 12 weeks, pre- and post-

operatively.

Serum PSA will be measured pre-therapy, at 6 and 12 weeks on therapy, 3 weeks post-RRP and every 3 months thereafter.

Bone marrow (BM) aspirate and biopsy will be obtained pre-treatment and post-treatment (optional) with thalidomide and the effect of the therapy on bone marrow endothelial cells will also be assessed.

We will look at the effects of therapy on:

- **Endothelial compartment:**

  - Prostate (cancer and normal gland) MVD will be assessed immunohistochemicaly by staining with anti-CD31 antibody (Weidner, 1995). Correlate with Gleason score and compare matched pre- and post-treatment samples.
  - Endothelial cell (EC) apoptosis in normal prostate, prostate cancer, bone marrow biopsy (by Dual fluorescent labeling technique in CD-31 positive cells [TUNEL])
  - Expression of bFGF, VEGF by PCa epithelium and prostatic stroma (by immunohistochemistry and / or in-situ hybridization (Greene 1997, Weidner 1995, Melnyk 1999).
  - Modulation of circulating endothelial markers (18-21) (serum: E-selectin and Thrombomodulin) by ELISA.
  - Modulation of serum: VEGF, TGFb1, IL-6 / Il-8, urine: bFGF levels and BM supernatant: VEGF, IL-6/IL-8 levels will be measured by ELISA (Ferrer 1997, Melnyk 1999, Hoosein 1995, Adler 1999, Drachenberg 1999).

- **Epithelial compartment:**

  - Tumor size (by TRUS)
  - PSA modulation on thalidomide therapy and freedom from biochemical relapse after surgery.
  - Apoptosis in prostate cancer cells (by TUNEL)
  - Proliferation index of PCa cells (by PCNA or Ki67)

We will assess whether expression of tissue or circulating pro-angiogenic molecules and cytokines: a) correlates with pathological findings at surgery (Gleason score, MVD changes, pathologically organ confined prostate cancer, rate of positive surgical margins and / or lymph node metastases) b) could serve as surrogate markers for anti-angiogenic activity in prostate cancer.

8.0 STATISTICAL CONSIDERATIONS

This is a phase II trial of neo-adjuvant thalidomide prior to radical retropubic prostatectomy (RRP) in patients with newly diagnosed locally advanced prostate cancer. The design of Thall, Simon and Estey (1995, Thall and Sung 1998) will be used. For the purpose of sample size determination and safety monitoring, patient success, S, is defined as stable disease (no increase in tumor mass) at 6 weeks, followed by $\geq$ 25% tumor shrinkage, compared to baseline mass or $\geq$ 50% decline in serum PSA (with no tumor progression) at 12 weeks. At 12 weeks, once S is evaluated, all patients will undergo RRP. The adverse event, A, pertains to surgery, and is defined as either excessive bleeding (> 5 units of blood required during the first 24 hours post surgery) or fascia dehiscence. A success probability of .20 or larger will be considered clinically promising, and a maximum adverse event rate of .10 is desired. Formally, denote the success probability by p_S, the adverse event rate by p_A, and assume the historical probabilities of the four possible combinations (No S, No A), (No S, A), (S, No A), (S, A) follow a Dirichlet prior with parameters (720,80,180,20), which implies historical (H) mean rates for $p_S(H)$ and $p_A(H)$ of 10% and 20% as noted above, with independence of the two events S and A. For the probabilities under the experimental regimen (E) studied in this trial, we assume a Dirichlet prior with the same mean but parameters that sum to 4. The two safety monitoring criterion will be to stop the trial if either $Pr[p_S (H) < p_S(E) \mid data] < .01$ or $Pr[p_A (H) < p_A(E) \mid data] > .95$. A maximum of n=40 patients will be treated which, if 8/40 (20%) successes are observed, will yield a 90% posterior credibility interval running from .11 to .31. Applying these monitoring criteria after each cohort of 4 patients has been treated and evaluated, the trial will be terminated if the observed [#successes]/[# patients evaluated] $\leq$ 0/16, 0/20, 0/24, 1/28, 1/32, or 2/36, or if the observed [#adverse events]/[# patients evaluated] $\geq$3/4, 4/8, 4/12, 5/16, 5/20, 6/24, 7/28, 7/32, or 8/36. The operating characteristics of this design are as follows:

True p_S p_A	Early Stopping Probability	Sample Size Quartiles
.20 .10	.11	40 40 40
.20 .20	.59	16 32 40
.20 .30	.93	12 12 20
.05 .10	.79	16 28 36

References:
Thall, PF, Simon, R and Estey, EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in Medicine* 14, 357-

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8.1 Statistical analysis of Quality of Life

The Quality of Life will be measured using the FACT-P questionnaires and will be analyzed as described previously (Esper 1997, Lee 1999). Descriptive statistics and composite scores are going to be calculated. Repeated measures analysis of variance (ANOVA) will be conducted.

9.0 CRITERIA FOR DISCONTINUING DRUG THERAPY

9.1 Progressive disease (> 25% increase of intraprostatic lesions by TRUS or > 25% increase of serum PSA compared to baseline) at 6 weeks.

9.2 Development of unacceptable toxicity defined as unpredictable, irreversible, or grade 4 non-hematologic toxicity.

9.3 Non-compliance by patient with protocol requirements.

9.4 Patient refusal.

10.0 STUDY CONDUCT / DATA AND PROTOCOL MANAGEMENT

10.1 Recruitment Process: Patients seen in the Genitourinary Medical Oncology clinic or the Urology clinic at MDACC with newly diagnosed prostate carcinoma who are candidates for this clinical trial will be identified by the respective attending physician who evaluates the patient and will be offered participation in this clinical trial. Other available treatment options (i.e.; surgery alone, radiation therapy alone or combination of radiation and hormonal therapy) are discussed with patient (as also stated in the consent form, page 4, section 6).

Informed Consent will be obtained according to the established Surveillance Committee Policies (see Office of Protocol Research PR manual, section 12.0 Informed Consents. The informed consent process will be performed according to the established Surveillance Committee policies (see Section 12.040 Research Informed Consent Process, OPR Manual) that emphasize the dialogue and face-to face interactions of the physician investigator and

the patient and research nurse prior to signing the informed consent document. It is specified that, as required also by our IRB, the consent form has to be signed in the presence of a witness for all patients in the trial. The witness may be a member of the research team, a family member or an independent party. The role of the witness is to ensure that the participant has been informed of all aspects of the trial and had an opportunity to have all questions answered prior to agreeing to participate in the trial.

10.2 Protocol compliance:

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

The attending physician and / or oncology research nurse must see each patient each week prior to each drug administration. All required interim and pretreatment data should be available and the physician must have made a designation as to toxicity grade and tumor response as required.

The storage and disposition of clinical data is to be performed according to the U.T.-M.D. Anderson Cancer Center's policies in compliance with Federal Guidelines and in accordance with the Federal-Wide Assurance (FWA 00000363) as provided to U.T.-M.D. Anderson Cancer Center IRB (IRB Identifier IRB00000121).

10.3 Adverse Event / Experience Reporting: In addition to the procedures required to report Adverse Experiences to the MDACC IRB as described in Appendix F of the protocol, "Adverse Events that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy Chief or Staff for Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165 **and** send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to U. S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Definition: Adverse Event

An adverse event temporally related to participation in the study should be documented whether or not considered to be related to the test article. This definition includes intercurrent illnesses and injuries, and exacerbations of preexisting conditions. Include the following in all IND safety reports:

Subject identification number and initials; associate investigator's name and name of MTF; subject's dated of birth, gender, and ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication(s) including dose, route and duration of treatment, and date of last dose.

Follow-up of Adverse Events / Serious Adverse Events: Patients who experience Adverse Events / Serious Adverse Events during the trial will be followed until resolution of the adverse event (if possible) or for a minimum of 30 days post last administration of study drug or 30 days postoperatively, whatever is longest.

Medical Monitor: Dr. Paul Mathew, M.D. will serve as Medical Monitor for this clinical trial. Dr. Mathew is a qualified physician that is not associated with this protocol. His background in genitourinary medical oncology allows him to provide medical care to subjects for conditions that may arise during the conduct of this study. Dr. Mathew will review all serious and unexpected adverse events (per ICH definitions) associated with the protocol and provide an unbiased written report of the event to USAMRMC (see address above) within 10 calendar days of the initial report, commenting on the outcome of the adverse event, relationship of the adverse event to the test article, and whether he concurs with the details of the report provided by the study investigator.

10.4 Data entry: Data must be entered into the Protocol Data Management System (PDMS). A brief explanation for required but missing data should be recorded as a comment.

10.5 Accuracy of data collection: The Study Chairman will be the final arbitrator of response or toxicity should a difference of opinion exist.

10.6 Reporting of non-compliance: The principal investigator's, department chairperson's, and division head's are responsible for reporting promptly to the Surveillance Committee via the Office of Protocol Research any serious or continuing non-compliance with the requirements of this Assurance or the determinations of the Surveillance Committee.

Reporting of non-compliance is performed according to institutional guidelines under the Federal-Wide Assurance (Identifier: FWA00000363) for HHS IRB Registration Identifier IRB00000121.

Protocol deviations will be reported to the HSRRB as well as the U.T.-M.D. Anderson Cancer Center IRB.

10.7 All amendments (that are not required for immediate patient safety) must be approved by the local IRB and the Human Subjects Research Review Board (HSRRB) prior to implementation.

10.8 The IND for this drug application is 56,533. This IND is held by UT MDACC.

10.9 Use of Samples

Samples will be used for evaluations related to this protocol alone.

Samples will be analyzed in the following laboratories:

a) Histology and Frozen Section Laboratories, Department of Pathology, Division of Pathology and Laboratory Medicine, University of Texas M D Anderson Cancer Center
b) Laboratory of Dr. David McConkey, Department of Cancer Biology, University of Texas M D Anderson Cancer Center
c) Research laboratory of Genitourinary Medical Oncology, Department of Genitourinary Medical Oncology, Division of Cancer Medicine, University of Texas M D Anderson Cancer Center.

Storage:
Specimens in their entirety will be processed and embedded in paraffin blocks. Blocks will be stored in a separate file designated for this protocol and accessible to appropriate personnel only. If there is occasion to freeze samples they will be snap frozen in OCT with liquid nitrogen and stored in a $-80^{\circ}C$ freezer until completion of the study.

Patient Confidentiality/Labeling:
All patient information will remain confidential. All data and records for this study will be kept according to the FDA regulations, (21 CFR SS 312.62(c), and according to GCP and HIPPA guidelines and the UT M. D. Anderson Cancer Center's policies. All samples will be labeled with a unique identifying code and will be entered in a database. A password-protected

database has already been developed for these samples. This database is the only place where there exists a cross-reference between this code and the MDACC medical record number. Any decoding of patient data will be performed solely for computer based analysis to correlate the relationship of investigational results with biological activity and/or clinical outcome.

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APPENDIX A
Evaluation Before and During Treatment

	Pre-Study	Q 1 Week On Escalation	At 6 Weeks	Pre-Prostatectomy	Post Prostatectomey
History, Physical, PS	X	X	X	X	as indicated
Quality of Life	X		X	X	1,3,6 mos and q 6 mos x 5 yrs
Toxicity	X	X	X	X	3 mos
DRE	X		X	X	3,6 mos and q 6 mos x 5 yrs
Step sect TRUS/Doppler	X		X	X	as indicated
Staging biopsies	X		X+		*
PSA	X		X	X	1, 3, 6 mos and q 6 mos x 5 yrs
PAP	X				as indicated
CBC, diff, Plat	X	[a]	X	X	as indicated
Chemical Survey[b]	X	[a]	X	X	as indicated
TSH, T4, T3	X		X		
Serum transferase level	X		X	X	
PT/PTT	X		X	X	as indicated
HIV test[c]	X				
Urine analysis/creatinine	X		X	X	3 mos
Electrocardiogram	X				
Bone Marrow Asp/Bx	X			X+	
Chest X-ray	X				
Bone Scan	X				X[d]
CT abdomen/pelvis	X			X	as indicated
Tumor neovascularity	X		X	X	X (at surgery)
Tissue Angiogenic Factors	X		X	X	X (at surgery)
Tissue Apoptosis Markers	X		X	X	X (at surgery)
Serum E-Selectin	X	X	X	X	X**
Serum Thrombomodulin	X	X	X	X	X**
Serum IL-6	X	X	X	X	X**
Serum VEGf	X	X	X	X	X**
Urine (bFGF/Creatinine)	X	X	X	X	X**
Entry info into PDMS	X		X	X	X

a If indicated
b BUN, creatinine, glucose, alk. phosphatase, total bilirubin, calcium, total protein, albumin, phosphorus, uric acid, SGPT, SGOT, Na, K, lactic dehydrogenase, chloride, bicarbonate, Mg
c HIV test results are acceptable if obtained within 6 months prior to study enrollment
d Yearly starting when elevated PSA is detected, or earlier if clinically indicated.
* TRUS guided biopsy of vesico-urethral anastomosis if PSA > 0.3
** On the fourth post-operative day (+/- 2 days)
+ Optional
++ Can be performed by the patient's treating urologist at home

Any studies necessary to completely evaluate malignant and concurrent non-malignant diseases and drug toxicity must be obtained and recorded at baseline and before each course as appropriate.

APPENDIX B
Performance Status Scales

Karnofsky Performance Scale (1)		Zubrod Performance Scale (2)	
Point	Description	Point	Description
100	Normal, no complaints, no evidence of disease	0	Normal activity; asymptomatic
90	Able to carry on normal activity; minor signs or symptoms of disease	1	Symptomatic; fully ambulatory
80	Normal activity with effort; some signs or symptoms of disease		
70	Cares for self, unable to carry on normal activity or to do active work	2	Symptomatic; in bed <50% of time
60	Requires occasional assistance but is able to care for most of his/her needs		
50	Requires considerable assistance and frequent medical care		
40	Disabled, requires special care and assistance	3	Symptomatic; in bed 50% of time; not bedridden
30	Severely disabled, hospitalization indication. Death not imminent		
20	Very sick, hospitalization indicated. Death not imminent	4	100% Bedridden
10	Moribund, fatal processes progressing rapidly		
0	Dead	5	Dead

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APPENDIX C

Symptom Improvement Questionnaire (Quality of Life)

Quality of Life Questionnaire (FACT-P)

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain.	0	1	2	3	4
GP5	I am bothered by side effects of treatment.	0	1	2	3	4
GP6	I feel ill.	0	1	2	3	4
GP7	I am forced to spend time in bed.	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends.	0	1	2	3	4
GS2	I get emotional support from my family.	0	1	2	3	4
GS3	I get support from my friends.	0	1	2	3	4
GS4	My family has accepted my illness.	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).	0	1	2	3	4
	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.					
GS7	I am satisfied with my sex life.	0	1	2	3	4

FACT-P (Version 4) (Appendix C, continued)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad.	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.	0	1	2	3	4
GE4	I feel nervous.	0	1	2	3	4
GE5	I worry about dying.	0	1	2	3	4
GE6	I worry that my condition will get worse.	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.	0	1	2	3	4
GF3	I am able to enjoy life.	0	1	2	3	4
GF4	I have accepted my illness.	0	1	2	3	4
GF5	I am sleeping well.	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.	0	1	2	3	4
GF7	I am content with the quality of my life right now.	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.	0	1	2	3	4
C6	I have a good appetite.	0	1	2	3	4
P1	I have aches and pains that bother me.	0	1	2	3	4
P2	I have certain areas of my body where I experience significant pain.	0	1	2	3	4
P3	My pain keeps me from doing things I want to do...	0	1	2	3	4
P4	I am satisfied with my present comfort level.	0	1	2	3	4
P5	I am able to feel like a man.	0	1	2	3	4
P6	I have trouble moving my bowels.	0	1	2	3	4
F7	I have difficulty urinating.	0	1	2	3	4
BL2	I urinate more frequently than usual.	0	1	2	3	4
P8	My problems with urinating limit my activities.	0	1	2	3	4
BL5	I am able to have and maintain an erection.	0	1	2	3	4

APPENDIX D
Staging Nomenclature

Primary Tumor, Clinical (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 prostate capsule**
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumor invades the seminal vesicles

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 one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

***Note:* Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

Regional Lymph Nodes (N) (include: Pelvic NOS, Hypogastric, Obturator, Iliac, Sacral)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metsastasis in regional lymph node(s)

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)

STAGE GROUPING

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2-4
	T1b-T2	N0	M0	any G
Stage III	T3	N0	M0	any G
Stage IV	T4	N0	M0	any G
	Any T	N1	M0/M1	any G

APPENDIX E

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COMMON TOXICITY CRITERIA (CTC)

Adverse Event	Grade 0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever <38°C (<100.4°F)	urticaria, drug fever ≥38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					

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Adverse Event	Grade 0	1	2	3	4
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing - Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or ≤25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges:					
children (≤18 years)	*90% cellularity average*				
younger adults (19-59)	60 - 70% cellularity average				
older adults (≥60 years)	50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	<LLN - 500/mm^3	200 - <500/mm^3	50 - <200/mm^3	<50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	<LLN - 10.0 g/dL <LLN - 100 g/L <LLN - 6.2 mmol/L	8.0 - <10.0 g/dL 80 - <100 g/L 4.9 - <6.2 mmol/L	6.5 - <8.0 g/dL 65 - <80 g/L 4.0 - <4.9 mmol/L	<6.5 g/dL <65 g/L <4.0 mmol/L
For leukemia studies or bone marrow infiltrative/ myelophthisic processes, if specified in the protocol	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hemoglobin.					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Leukocytes (total WBC)	WNL	<LLN - 3.0 x 10^9/L <LLN - 3000/mm^3	≥2.0 - <3.0 x 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	<1.0 x 10^9/L <1000/mm^3
For BMT studies, if specified in the protocol.	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol.		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9/L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3	-
For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol.		*≥75 - <100%LLN*	*≥50 - <75%LLN*	*≥25 - <50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9/L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3
For BMT studies, if specified in the protocol.	WNL	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9/L ≥100 - <500/mm^3	<0.1 x 10^9/L <100/mm^3
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	<LLN - 75.0 x 10^9/L <LLN - 75,000/mm^3	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥10.0 - <50.0 x 10^9/L ≥10,000 - <50,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
For BMT studies, if specified in the protocol.	WNL	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9/L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9/L ≥10,000 - <20,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT studies, if specified in the protocol.	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Transfusion: pRBCs	none	-	-	yes	-
For BMT studies, if specified in the protocol	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
For pediatric BMT studies, if specified in the protocol	*none*	*≤15 mL/kg in 24 hours elective or planned*	*>15 - ≤30mL/kg in 24 hours elective or planned*	*>30mL/kg in 24 hours*	*hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin*
Also consider Hemoglobin.					
Blood/Bone Marrow - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-
Note: Grade palpitations only in the absence of a documented arrhythmia.					
Prolonged QTc interval (QTc>0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-

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Adverse Event	Grade 0	1	2	3	4
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia - Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T - wave flattening or changes	asymptomatic, ST - and T - wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥10% but <20% of baseline value; shortening fraction ≥24% but <30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥20% of baseline value; <24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥0.03 - <0.05 ng/mL	≥0.05 - <0.1 ng/mL	≥0.1 - <0.2 ng/mL	≥0.2 ng/mL
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mm Hg (diastolic) or to >150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by >20 mm Hg (diastolic) or to >150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis

**Note: For pediatric patients, use age and sex appropriate normal values >95th percentile ULN.*

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting).					
Notes: Angina or MI is graded as Cardiac-ischemia/infarction in the CARDIOVASCULAR (GENERAL) category.					
For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	with physiologic consequences	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Notes: Injection site reaction is graded in the DERMATOLOGY/SKIN category.					
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Adverse Event	Grade 0	1	2	3	4
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also consider Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg
Partial thromboplastin time (PTT)	WNL	>ULN - ≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Phlebitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	>ULN - ≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT studies, if specified in the protocol.	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin, Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia) Note: See Appendix III for performance status scales.	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling

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Adverse Event	Grade 0	1	2	3	4
Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10^9/L)	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	>40.0°C (>104.0°F) for <24hrs	>40.0°C (>104.0°F) for >24hrs
Also consider Allergic reaction/hypersensitivity.					
Note: The temperature measurements listed above are oral or tympanic.					
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain	<5%	5 - <10%	10 - <20%	≥20%	-
Also consider Ascites, Edema, Pleural effusion (non-malignant).					
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure
Also consider Ascites, Edema, Pleural effusion (non-malignant).					
Weight loss	<5%	5 - <10%	10 - <20%	≥20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
Constitutional Symptoms - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Also consider Allergic reaction/hypersensitivity.					
Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					
Rash/dermatitis associated with high-dose chemotherapy or BMT studies	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol	None	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity.					
Note: Stevens-Johnson syndrome is graded separately as Erythema multiforme in the DERMATOLOGY/SKIN category.					

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Adverse Event	Grade 0	1	2	3	4
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound-infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fasciitis
Wound-non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia, Hypokalemia.					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis), Hypotension.					
Diarrhea patients without colostomy:	none	increase of <4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	None	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
For pediatric BMT studies, if specified in the protocol.		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If the adverse event is radiation-related, grade either under Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation.					
Dysphagia-esophageal related to radiation Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula-esophageal.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	Dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Dysphagia-pharyngeal related to radiation Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula-pharyngeal.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Fistula-esophageal	none	-	-	present	requiring surgery
Fistula-intestinal	none	-	-	present	requiring surgery

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Fistula-pharyngeal	none	-	-	present	requiring surgery
Fistula-rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Notes: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Notes: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia-esophageal related to radiation or Dysphagia-pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Amylase is graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					

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Adverse Event	Grade 0	1	2	3	4
Proctitis	none	increased stool frequency, occasional blood-streaked stools or rectal discomfort (including hemorrhoids) not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain due to radiation.					
Notes: Fistula is graded separately as Fistula-rectal/anal.					
Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva; may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
For BMT studies, if specified in the protocol	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Adverse Event	Grade 0	1	2	3	4
HEMORRHAGE					
Notes: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (<50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider Platelets, Transfusion: pRBCs, and Transfusion: platelets in addition to grading severity by grading the site or type of bleeding. If the site or type of Hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS Hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage-Other (Specify site, _____). Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, Hemorrhage - Other (Specify site, _____). Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery Note: Expected blood loss at the time of surgery is not graded as an adverse event.	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring <2 pads per day	requiring ≥2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage - Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin	WNL	>ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol	normal	≥2 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
GGT (γ - Glutamyl transpeptidase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for treatment related adverse event including Veno-Occlusive Disease.					
Hypoalbuminemia	WNL	<LLN - 3 g/dL	≥2 - <3 g/dL	<2 g/dL	-
Liver dysfunction/ failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hepatic - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)

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Adverse Event	Grade 0	1	2	3	4
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C) Also consider Neutrophils Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L) Also consider Neutrophils Notes: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This adverse event criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia Also consider Neutrophils	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
Infection/Febrile Neutropenia - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH <normal, but ≥7.3	-	pH <7.3	pH <7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH >normal, but ≤7.5	-	pH >7.5	pH >7.5 with life-threatening physiologic consequences
Amylase	WNL	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	<LLN - 16 mEq/dL	11 - 15 mEq/dL	8 - 10 mEq/dL	<8 mEq/dL

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
CPK (creatine phosphokinase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5 x ULN	>5 - 10 x ULN	>10 x ULN
Hypercalcemia	WNL	>ULN - 11.5 mg/dL >ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dL >2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dL >3.1 - 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Hypercholesterolemia	WNL	>ULN - 300 mg/dL >ULN - 7.75 mmol/L	>300 - 400 mg/dL >7.75 - 10.34 mmol/L	>400 - 500 mg/dL >10.34 - 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Hyperglycemia	WNL	>ULN - 160 mg/dL >ULN - 8.9 mmol/L	>160 - 250 mg/dL >8.9 - 13.9 mmol/L	>250 - 500 mg/dL >13.9 - 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis
Hyperkalemia	WNL	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypermagnesemia	WNL	>ULN - 3.0 mg/dL >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL >1.23 - 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L
Hypernatremia	WNL	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10 x ULN	>10 x ULN
Hyperuricemia	WNL	>ULN - ≤10 mg/dL ≤0.59 mmol/L without physiologic consequences	-	>ULN - ≤10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Hyperkalemia.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dL <LLN - 2.0 mmol/L	7.0 - <8.0 mg/dL 1.75 - <2.0 mmol/L	6.0 - <7.0 mg/dL 1.5 - <1.75 mmol/L	<6.0 mg/dL <1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dL <LLN - 3.0 mmol/L	40 - <55 mg/dL 2.2 - <3.0 mmol/L	30 - <40 mg/dL 1.7 - <2.2 mmol/L	<30 mg/dL <1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dL <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dL 0.4 - <0.5 mmol/L	0.7 - <0.9 mg/dL 0.3 - <0.4 mmol/L	<0.7 mg/dL <0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dL <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dL ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dL ≥0.3 - <0.6 mmol/L	<1.0 mg/dL <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	>ULN - 1.5 x ULN	>1.5 -2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Metabolic/Laboratory - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

Adverse Event	Grade 0	1	2	3	4
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia [tenderness or pain in muscles] is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline >2 SD*	*inability to work/frank mental retardation*

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This adverse event is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability (children <3 years of age)	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	none	mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum	moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum	severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Mood alteration-anxiety, agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy-cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy-motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus	absent	present	-	-	-
Also consider Vision-double vision					
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.					

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Adverse Event	Grade 0	1	2	3	4
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision-blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-

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Adverse Event	Grade 0	1	2	3	4
Vision-night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision-photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual - Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flare is graded in the SYNDROME category.					
Pain - Other (Specify, _____)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation

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	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Carbon monoxide diffusion capacity (DL_{CO})	≥90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme-Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Notes: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Adverse Event	Grade 0	1	2	3	4
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmodic	severe symptoms requiring narcotic	-
Creatinine	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or <0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or >3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and dip stick reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase >2 x normal but <hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	requiring frequent in/out catheterization (≥4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture

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Adverse Event	Grade 0	1	2	3	4
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy - Other (Specify type, _____) excludes metastasis from initial primary	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Feminization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	oligospermia (low sperm count)	azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function - Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					

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Adverse Event	Grade 0	1	2	3	4
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) is graded in the COAGULATION category.					
Tumor flare	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Also consider Hypercalcemia.					
Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.					
Tumor lysis syndrome	absent	-	-	present	-
Also consider Hyperkalemia, Creatinine.					
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded in the RENAL/GENITOURINARY category.					
Syndromes - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

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Appendix I

Adverse Event Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

Adverse Event:	Date of Treatment:		Course Number:
Date of onset:			Grade at onset:
Date of first change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Did adverse event resolve? If so, date of resolution of adverse event:	Yes_____	No_____	
Date of last observation (if prior to recovery):			
Reason(s) observations stopped (if prior to recovery):			
Was patient retreated?	Yes_____	No_____	
If yes, was treatment delayed for recovery?	Yes_____	No_____	
Date of next treatment?			
Dose reduced for next treatment?	Yes_____	No_____	

Additional Comments:

_____

_____

If module is being activated for new adverse event not currently in CTC, please provide definitions for adverse event grading:

Grade 0 = _____

Grade 1 = _____

Grade 2 = _____

Grade 3 = _____

Grade 4 = _____

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Appendix II

Infection Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

1. Use the Common Toxicity Criteria definitions to grade the severity of the infection.
2. Specify type of infection from the following (CHOOSE ONE):

   BACTERIAL FUNGAL PROTOZOAL VIRAL UNKNOWN
3. Specify site of infection from the following (CHOOSE ALL THAT APPLY):

   BLOOD CULTURE POSITIVE
   BONE INFECTION
   CATHETER (intravenous)
   CATHETER (intravenous), tunnel infection
   CENTRAL NERVOUS SYSTEM INFECTION
   EAR INFECTION
   EYE INFECTION
   GASTROINTESTINAL INFECTION
   ORAL INFECTION
   PNEUMONIA
   SKIN INFECTION
   UPPER RESPIRATORY INFECTION
   URINARY TRACT INFECTION
   VAGINAL INFECTION
   INFECTION, not otherwise specified (Specify site, _____)
4. Specify organism, if known: _____.
5. Prophylactic antibiotic, antifungal, or antiviral therapy administration

   Yes_____ No_____

   If prophylaxis was given prior to infection, please specify below:

   Antibiotic prophylaxis _____

   Antifungal prophylaxis _____

   Antiviral prophylaxis _____

   Other prophylaxis _____

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Appendix III

Performance Status Scales/Scores

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

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Appendix IV

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 mL)	Necrosis/contracted bladder (capacity <100 mL)/severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus- Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%; creatinine 1.5 - 2.0 mg%; creatinine clearance >75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea >36 - 60 mg%; creatinine clearance >50 - 74%	Severe albuminuria; severe hypertension; persistent anemia (<10 g%); severe renal failure; urea >60 mg%; creatinine >4 mg%; creatinine clearance <50%	Malignant hypertension; uremic coma/urea >100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis

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Appendix IV (continued)

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for adverse event occurring greater than 90 days after radiation therapy.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O_2/assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis
Radiation - Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

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Appendix V

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used if specified by the protocol. These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Bilirubin associated with graft versus host disease for BMT studies.	normal	≥2 - <3 mg/100 mL	≥3 - <6 mg/100 mL	≥6 - <15 mg/100 mL	≥15 mg/100 mL
Diarrhea associated with graft versus host disease (GVHD) for BMT studies.	none	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
Diarrhea for pediatric BMT studies.		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Hepatic enlargement	absent	-	-	present	-
Leukocytes (total WBC) for BMT studies.	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9/L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	<0.5 x 10^9/L <500/mm^3
Leukocytes (total WBC) for pediatric BMT studies (using age, race and sex normal values).		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia for pediatric BMT studies (using age, race and sex normal values).	mm^3	*≥75-<100%LLN*	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC) for BMT studies.	WNL	≥1.0 - <1.5 x 10^9/L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9/L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9/L ≥100 - <500/mm^3	<0.1 x 10^9/L <100/mm^3
Platelets for BMT studies.	WNL	≥50.0 - <75.0 x 10^9/L ≥50,000 - <75,000/mm^3	≥20.0 - <50.0 x 10^9/L ≥20,000 - <50,000/mm^3	≥10.0 - <20.0 x 10^9/L ≥10,000 - <20,000/mm^3	<10.0 x 10^9/L <10,000/mm^3
Rash/dermatitis associated with high-dose chemotherapy or BMT studies.	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies.	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation

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Appendix V (Continued)

BMT-Specific Adverse Events

Summary of BMT-Specific Adverse Events that may be used **if specified by the protocol.** These differ from the standard CTC and may be more relevant to the transplant setting. They are listed here for the convenience of investigators writing transplant protocols. They are also included in the CTC document.

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Stomatitis/pharyngitis (oral/pharyngeal mucositis) for BMT studies.	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Transfusion: Platelets for BMT studies.	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Transfusion: pRBCs for BMT studies.	none	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Transfusion: pRBCs for pediatric BMT studies.	*none*	*≤15mL/kg in 24 hours elective or planned*	*>15 - ≤30mL/kg in 24 hours elective or planned*	*>30mL/kg in 24 hours*	*hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin*
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) for BMT studies.	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascites	≥10% or fluid retention resulting in pulmonary failure

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Appendix VI

BMT Complex/Multicomponent Events

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Note: The grading of Complex/Multicomponent Events in bone marrow transplant will be defined in the protocol. The grading scale must use the CTC criteria for grading the specific component events (adverse events).					
Failure to engraft	absent	mild	moderate	severe	life-threatening
Also consider Hemoglobin, Neutrophils/granulocytes (ANC/AGC), Neutrophils/granulocytes (ANC/AGC) for BMT studies, if specified in the protocol, Platelets, Platelets for BMT studies, if specified in the protocol					
Graft versus host disease	absent	mild	moderate	severe	life-threatening
Also consider Fatigue, Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol					
Stem cell infusion complications	absent	mild	moderate	severe	life-threatening
Also consider Allergic reaction/hypersensitivity, Conduction abnormality/Atrioventricular heart block, Nodal/junctional arrhythmia/dysrhythmia, Prolonged QTc interval (QTc >0.48 seconds), Sinus bradycardia, Sinus tachycardia, Supraventricular arrhythmias (SVT/atrial fibrillation/flutter), Vasovagal episode, Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia), Cardiovascular/Arrhythmia - Other (Specify, _____), Hypertension, Hypotension, Fever (in the absence of neutropenia, where neutropenia is defined as AGC $<1.0 \times 10^9$/L), Rigors/chills, Sweating (diaphoresis), Rash/desquamation, Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Urticaria (hives, welts, wheals), Diarrhea for patients without colostomy, Diarrhea for patients with colostomy, Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Diarrhea for pediatric BMT studies, if specified in the protocol, Nausea, Vomiting, Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hemoptysis, Alkaline phosphatase, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, GGT, SGOT (AST), SGPT (ALT), Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC $<1.0 \times 10^9$/L), Infection without neutropenia, Hyperkalemia, Hypernatremia, Hypokalemia, Depressed level of consciousness, Seizures, Abdominal pain, Headache, Creatinine, Hemoglobinuria					
Veno-Occlusive Disease (VOD)	absent	mild	moderate	severe	life-threatening
Also consider Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol, Bilirubin, Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol, Depressed level of consciousness, Hepatic pain, Renal failure, Hepatic enlargement					

IRB Approval
Date: 7/3/2002

APPENDIX F

Guidelines for Filing Reports of Adverse Experiences at M. D. Anderson Cancer Center

21 CFR 312.32

Serious Adverse Experience (SAE) –Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected Adverse Drug Experience - Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

MDA Policy and Procedure for reporting of adverse experiences (Includes both commercial and investigational drugs):

- All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study regimen. If an expected or anticipated event is documented in the protocol, then it does not have to be reported as an SAE. (Example: Expected Grade 4 mylosuppression needs only to be reported as part of the study results)

- All events falling under the definition of serious adverse event that are not listed in the protocol as being expected or anticipated, and occurring within 30 days following the last treatment date, must be reported to the sponsor within the specified time frame stated in the protocol.

- All deaths with possible, probable or definite attribution to the study drug, device, or intervention must have a written report submitted to the Institutional Review Board (IRB) via OPR within one working day (24 hours) of knowledge of the event.

- All serious adverse events other than that stated above must have a written report submitted to the Institutional Review Board (IRB) via OPR within 5 working days of knowledge of the event.

- If necessary, the sponsor is then required to notify the Food and Drug Administration (FDA) within 7 calendar days.

- All unexpected adverse experiences that are classified as Grade 4 must be reported by following the guidelines listed above.

- Known reactions classified as Grades 1-3 do not need to be reported. However, these toxicities should be submitted as part of the study results.

Adverse Experience Reporting Forms:

Attached is the MDACC severe adverse event reporting form. This form should be utilized if MDACC is the sponsor, the study is a non-sponsored study, or the sponsor does not provide an appropriate reporting form.

If the study sponsor requires a protocol specific SAE form to be completed, then that form may be use for IRB submission as long as the MDACC protocol number and patient medical record number is written at the top of the front page.

External Adverse Experiences / Safety Reports

All external adverse events/safety reports received from the sponsor should be submitted to the IRB through the Office of Protocol Research. The "External Adverse Event Report" can be located under section 1 of the OPR Forms Manual, and should be utilized as the cover sheet for this submission.

APPENDIX G
Surgical Dictation Card

I. Intraoperative

a) Lymph node dissection

1. Appearance
Nonsuspicious
Suspicious
Grossly Positive-Frozen Section (+/-)

2. Difficulty
Standard
More Difficult
Very Difficult

3. Complication of lymph node dissection (yes-list/no)

b) Prostatectomy

1. Campbell's technique or Retrograde (or combination)

2. Nervesparing (yes/no)

3. Apical dissection
Standard
More Difficult
Very Difficult

4. Dissection along rectum
Standard
More Difficult
Very Difficult

5. Seminal vesicle dissection
Standard
More Difficult
Very Difficult

6. Bladder neck sparing (yes/no)

7. Tumor grossly confined (yes/no)

8. Urethral length
Shorter than usual
Average
Long

9. Number of sutures
   ≤ 4
   5-6
   ≥ 7

10. Difficulty of anastomosis
    Standard
    More difficult
    Very difficult

11. Complications (yes/no)

12. Estimate of inteaoperative blood loss (list)

13. Need for any transfusion (yes/no)
    (a) Autologous (predeposited only #units)
    (b) Homologous (bank # units)

14. Operative time (Incision to skin closed)

II. Post-operative

1. # PRBC units transfused during the first 24 hours
2. Urinary leak (yes/no)
3. Bladder spasms
4. Length of hospitalization

III. Follow-up

1. Superficial wound dehiscence
2. Fascia dehiscence
3. Days with drainage
4. Infection (yes/no)

APPENDIX H

Onstudy Dictation for Pre-Op Thalidomide

1. P/S Stated

2. Pathology

3. Clinical Stage (Urologist's)

4. Statement of "Meets Survival Requirements and Has No Contraindications for Surgery"

5. Pertinent Interpretation of Staging
(i.e. abnormality reported on bone scan is not consistent to define metastasis)

6. Patient states "Will use latex condom when having sexual intercourse"

7. Signed Written Informed Consent: Date: _____ Time: _____

8. "Patient meets eligibility criteria for protocol ID00-089"

9. "Planned start date is _____"

Appendix I

Key Personnel for ID00-089, MDA IND 56,533

Areas of Responsibilities and Telephone Contact Information

Personnel (Name/Degrees)	Responsibilities/Department	Tel./Fax/Pager
Danai Daliani, M.D.	***Study Chair***, Principal Investigator, Project Leader Department: GU Oncology	Tel: (713) 792-2830 Fax: (713) 745-1625 Pgr: (713) 404-2717 e-mail: ddaliani@mdanderson.org
Paul Mathew, M.D.	***Medical Monitor*** Department: GU Oncology	Tel: : (713) 792-2830 Fax: (713) 745-1625 Pgr: (713) 404-0652 e-mail: pmathew@mdanderson.org
Pauline Dieringer, R.N.	***Research Nurse.*** Under the supervision of the Study Chair and in coordination with collaborating physicians provides: Liaison with patients; scheduling patient visits for all phases of the clinical trial; liaison with the Clinical Care Coordinator. Participates in obtaining informed consents; tracking of all clinical specimens & experimental therapeutics; obtain clearance from insurance companies; arrange tests to determine eligibility and review all clinical test results; liaison with patient's physicians off-site; posting of data in patient charts, summaries and supervises posting of data in PDMS by the data manager. Supervises the data manager. . Department: GU Oncology	Tel: 713-792-2830 Fax: 713-745-2900 Pager: 713-404-3109 e-mail: pdiering@mdanderson.org
Cherie A. Perez, B.S., R.N.	***Research Nurse Supervisor.*** Overall coordination of Research Nurse services for the department. ***Effective 1/16/00.*** Department: GU Oncology	Tel: 713-792-2830 Fax: 713-745-2900 Pager: 713-404-6649 e-mail: caperez@mdanderson.org
Marla Johnson	***Coordinator Clinical Research Programs.*** Overall supervision of data collection and management for clinical research protocols. Review and implementation of CRFs. Review of clinical protocols for compliance with GCPs Department: GU Oncology	Tel: 713-792-2830 Fax: 713-745-1625 Pager: e-mail: mjohnson@mdanderson.org

Darlene Montgomery	***Data Manager.*** Liasion with the research and clinic nurse. Responsible for data collection and entry in to PDMS Department: GU Oncology	Tel: 713-792-2830 Fax: 713-745-2900 Pager: e-mail:
Mary Abioye, MA PBT ASC	***Technician. Phlebotomist*** Department: GU Oncology	Tel: 713-792-2830 Fax: 713-792-2075 Pager: 713-404-3744 e-mail: mabioye@mdanderson.org
Margaret A. Armstrong **Program Coordinator**	***Regulatory Affairs.*** Review of documentation & regulatory affairs issues; liaison with MDACC OPR/ORA; provides support to the Study Chair's admininistrative assistant in the area of regulator affairs and documentation. Department: GU Oncology	Tel: 713-792-2830 Fax: 713-745-1625 Pager: 713-404-5060 e-mail: marmstro@mdanderson.org
Linda Hicks	***Administrative Assistant to Study Chair.*** Preparation of documents & correspondence. Department: GU Oncology	Tel: 713-792-2830 Fax: 713-745-0827 Pager: e-mail: lhicks@mdanderson.org
Victor H. Pang, B.S., R.Ph.	***Investigational Pharmacist II*** Department: Pharmacy (B01.4415). Receiving of investigational new drugs. Entry of experimental drug data into the data management system.	Tel: 713-792-2848 Fax: 713-794-4990 Pager: 713-404-2909 e-mail:
Mark A Kramer, M.S., R.Ph.	***Supervisor, Investigational Drugs*** Department: Pharmacy (B01.4415). Receiving of investigational new drugs. Entry of experimental drug data into the data management system.	Tel: 713-792-2848 Fax: 713-794-4990 Pager: 713-404-2967 e-mail:

The University of Texas
M.D. ANDERSON CANCER CENTER

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

PROTOCOL TITLE: "A Tolerance and Efficacy Trial of Preoperative Thalidomide Treatment Followed by Radical Retropubic Prostatectomy (RRP) in Select Patients with Locally Advanced Prostate Cancer"

1. _____ _____
Participant's Name I.D. Number

You are being asked to take part in this clinical research study at The University of Texas M. D. Anderson Cancer Center (hereinafter referred to as "UTMDACC" or "the institution"). This research study is strictly voluntary. This consent form explains why we are performing this research study and what your role will be if you choose to participate. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to participate in the study. This study complies with all laws and regulations that apply.

You are being asked to take part in this study because you have prostate cancer.

DESCRIPTION OF RESEARCH

2. PURPOSE OF STUDY

Treatment: The goal of this clinical research study is to find out whether it is safe to treat patients diagnosed with locally advanced prostate cancer with the drug Thalidomide before removing the tumor (radical retropubic prostatectomy).

Researchers also want to learn if Thalidomide can shrink or slow the growth of the prostate cancer before the surgery.

Optional Procedures: Patients will be asked to get a repeat prostate tissue sample at the end of the treatment. The sample will be used to learn more about the effects of Thalidomide on prostate cancer and the blood vessels that feed the tumor.

Patients will also be asked to give a bone marrow sample at the end of the treatment. This sample will be used to learn more about the effects of Thalidomide on the bone marrow and on the blood vessels in the bone.

3. DESCRIPTION OF RESEARCH:

Treatment: Before treatment starts, all patients will have a complete exam including blood , urine and stool tests. About 5 tablespoons of blood will be drawn for the blood tests. A chest x-ray will be done. A bone scan, CT scan of the abdomen and pelvis, and bone marrow biopsy will be done to rule out the possibility of spread of the cancer. Patients will have an EKG to check their heart function. Patients will have a transrectal ultrasound with biopsies of the prostate tumor. A rectal exam will be performed. Patients will fill out a questionnaire about their disease and how it affects their lives. It will take about 15 minutes to complete the questionnaire.

The initial evaluations will require approximately 6 hours.

Patients will take Thalidomide by mouth every day. Thalidomide will be given by mouth starting at 200 mg per day. If the patient tolerates the drug well the dose of thalidomide will be increased every week by 200 mg per day until the maximum dose of 600 mg per day. It is recommended that patients take the entire dose at night, but if they prefer they can divide the dose throughout the day. During the dose adjustment phase (the first 3 weeks of the study), patients will have a physical exam and blood tests (about 3 tablespoons each) each week.

The blood tests are done to make sure the blood counts and kidney and liver function remain normal as the dose of the drug is increased. Some of this blood will also be used to see if any blood vessel changes in the blood can be detected.

After the first three weekly visits, patients will be examined in the clinic and will have repeat blood, urine, and stool tests at 6 and 12 weeks from the start of the treatment. These tests will also be done at the end of Thalidomide treatment. Approximately 7.7 oz. of blood will be collected during your participation in the trial over a 4-month period of time (including the optional research blood test).

The transrectal ultrasound of the prostate will be repeated at 6 weeks from the beginning of the treatment and right before surgery to measure the size of the prostate

and the size of the tumor. If you agree to have an optional prostate biopsy at 6 weeks from the beginning of the treatment that biopsy will be obtained at the time of your repeat transrectal ultrasound of the prostate.

A repeat CT scan of the abdomen and pelvis will also be done before surgery.

Subsequent clinic visits will require approximately 1 hour.

After surgery, patients will be watched closely to track how well or whether the cancer has been stopped. Patients will need to return to M. D. Anderson at 1 and 3 months after surgery. After the first 3 months, patients will need to have an urologist examine them every 6 months for 5 years. During these visits, patients will have a physical exam, digital rectal exam and blood tests (about 1 tablespoon of blood will be drawn to measure the serum PSA to detect whether there is any cancer recurrence or not).

The exam after the first 3 months can be done either at M. D. Anderson Cancer Center or by the patient's local urologist who will forward the information. Patients will also be given a questionnaire to answer in writing. Questions will concern the quality of their lives after this treatment. It will take about 15 minutes to complete the questionnaire. CT scans, bone scans, and transrectal ultrasound will be done as needed.

Treatment can be terminated if the patient withdraws consent, or if the patient does not comply with the specific requirements of the study. Treatment can also be terminated if the physician believes that it is not safe to continue therapy and / or if there is evidence of progression of the cancer.

Patients' records will be kept according to the Federal guidelines that protect patient confidentiality.

Quality of Life questionnaires are labeled only with the patient's initials and a number that identifies whether they are the first, second, third, etc. patient on this trial.

Data will be maintained and handled according to FDA regulations and HIPPA. Tissue samples collected during this trial will be used for the research outlined in this clinical trial. Tissue samples are stored and filed under a protocol accession number to avoid the possibility of laboratory personnel to "link" the patient to the tissue samples. Any decoding of patient data will be performed solely for computer based analysis to correlate the relationship of investigational results with clinical outcome.

This is an investigational study. While the FDA has approved Thalidomide, its use in this study as a drug for the treatment of prostate cancer is investigational. Free

medications and procedures include: the administration of thalidomide pills, the cost of the optional prostate ultrasound and biopsy, the cost of the optional bone marrow biopsy, as well as the cost for the optional blood tests.

If you are injured because of your participation in this research study, you will be provided medical care for research related injuries at no cost to you. Medical care will be provided only for research related injuries. You will not receive any money for your injury; you will only receive medical care. This does not mean that you are giving up any legal rights that you may have. You may contact Danai Daliani, M.D. at 1515 Holcombe Boulevard, Houston, Texas 77030 at (713) 792-2830 if you have questions. All other costs (clinic visits, standard blood tests, standard radiographic tests, surgery costs and pathology costs) will be the responsibility of the patient/patient's insurance.

About 40 patients will take part in the study. All will be enrolled at M. D. Anderson Cancer Center. This protocol is partially funded by a research grant from the sponsor, Celgene, Inc., and the Department of Defense (DOD).

Optional Procedures (Prostate Biopsy and Bone Marrow Biopsy): Patients who agree will have a repeat prostate biopsy after 6 weeks of treatment. This will be done at the time of the scheduled re-evaluation, of the prostate tumor by transrectal ultrasound. Patients who agree will also have a bone marrow sample taken at the end of the treatment. This means that a small piece of bone will be removed with a needle from the pelvic bone, after the area has been numbed. Patients do not have to consent to these optional procedures in order to receive treatment.

4. RISKS, SIDE EFFECTS AND DISCOMFORTS TO PARTICIPANTS

Treatment: Thalidomide may cause nausea and/or vomiting. It may cause fatigue, sensitivity to the sun, skin changes, and/or nail changes. It may cause a decreased appetite and/or altered senses of taste and/or smell.

Thalidomide may also prevent the patient's body from making new blood cells. This means that while the patient takes it, there is more of a chance of getting an infection, including pneumonia. The patient may need a blood transfusion and/or antibiotics.

Thalidomide may cause low blood pressure, slow heart rate and dizziness. Thalidomide may cause patients to feel sleepy. Because of this, patients will be reminded not to drive while they are taking part in the study during the 12 weeks they are taking thalidomide.

Thalidomide may cause constipation, swelling, numbness, and tingling. It may also cause damage to nerves and pain in the hands/feet. Upon discontinuation of the drug, patients may have trouble sleeping.

Some patients who took Thalidomide for a disease besides cancer (HIV infection) and who had many other problems became very badly confused. This confusion remained even after the patients stopped taking the drug. It is not known whether the Thalidomide caused the confusion.

Some patients who took thalidomide for other types of cancer (i.e. kidney cancer) and at double the dose than the dose used in this study did develop some difficulty concentrating while reading or watching TV. This difficulty concentrating was reversible (disappeared) after the patients stopped taking the drug.

Thalidomide may cause bigger appetite, lower sex drive, headache, and/or fever. The drug may cause dry mouth, dry skin, itching, and/or rash. It may affect thyroid function.

Thalidomide may cause wounds such as cuts or bruises not to heal as fast as they normally would. Patients treated with Thalidomide may have a higher risk for bleeding and/or delayed wound healing during surgery or during the prostate biopsy. If a patient has low blood counts (white cells or platelets) the risks associated with these procedures can be higher.

The risks and side effect of prostate removal surgery will be explained in a separate consent.

Diagnostic procedures like ECG, Chest x-ray, bone scan are not associated with risk to the patient.

Blood draw may cause pain, redness, swelling and / or infection where the needle enters the body.

The transrectal ultrasound of the prostate may cause some discomfort or pain to the patient. If a prostate biopsy is obtained at the same time of the transrectal ultrasound of the prostate, there may also be a risk for infection, bleeding from the bladder and/or rectum, or both. In some rare circumstances patients may have to stay in the hospital for the treatment of these complications.

Giving dye through the vein during a CT-scan evaluation can in a small number of patients cause allergic reaction (in patients with allergy to iodine) and could worsen the

kidney function in patients with abnormal kidney function. Patients are asked before the CT-scan evaluation if they have allergies to iodine. Patients are not given intravenous contrast if they have known allergic reaction to iodine or are given medications to prevent the reaction. Patients are monitored during CT-scan evaluation by trained personnel and medical treatment is provided if necessary in the case of a newly developed allergic reaction. Patients are not given intravenous contrast if they have abnormal kidney function.

This clinical research study may involve unpredictable risks to the participant.

4a) Participants must practice birth control during the study if they are sexually active. There could be unknown risks to an unborn child.

The use of Thalidomide by pregnant women has been shown to cause birth defects. There is an extremely high risk that a deformed infant will result if pregnancy occurs while this drug is being taken in any amount even for a short time. Women who are pregnant or who may become pregnant should not handle Thalidomide. If women handle the pills, Thalidomide can be absorbed through their skin and cause serious birth defects. All patients must use adequate birth control during and for 8 weeks after participation in this study.

Men must completely avoid sexual intercourse or use a latex condom EVERY TIME they have sexual intercourse while they are taking Thalomid™ (Thalidomide) and for 8 weeks after they stop taking the drug, even if they have had a successful vasectomy.

Optional Procedures (Prostate Biopsy and Bone Marrow Biopsy): Having a prostate and/or bone marrow biopsy taken may cause pain, redness, swelling, infection, and/or bleeding through in the stool and/or urine for a few days after the biopsy. In addition, with some biopsies, underlying structures can be damaged. Sometimes this structural damage may require further tests or even surgery to correct.

5. POTENTIAL BENEFITS

Treatment: Thalidomide may shrink or slow the growth of the prostate tumor. The chance of surgery being successful may be increased. The chance of the cancer coming back may be lowered. There may be no benefit at all for patients in the study.

Patient's initials: _____

Witness' s initials: _____

Optional Procedures (Prostate Biopsy and Bone Marrow Biopsy): There are no benefits for the patient taking part in the optional procedures. Future patients may benefit from what is learned. This information will help physicians to learn more about the use of the drug in cancer treatment.

6. **ALTERNATE PROCEDURES OR TREATMENTS:** Patients may choose not to take part in this study. Patients may have their prostate removed surgically without Thalidomide treatment before surgery. Patients may have radiotherapy with or without hormonal treatment. Patients may choose to receive other experimental drugs, if available. Patients may choose not to have treatment for cancer at all. In all cases, patients will receive care for symptoms and pain.

Optional Procedures (Prostate Biopsy and Bone Marrow Biopsy): Treatment with the study drug may be given without receiving the optional biopsies.

I understand that the following statements about this study are true:

7. According to the institutional conflict of interest policy, the principal investigator of this study and my primary physician cannot have a financial interest in any aspect of this research. However, in instances of medical emergency, it is possible that I may be cared for by a physician and/or administrator who has some form of financial interest in the sponsor of this study.

8. If I want to receive updated information regarding the financial interests of any physician and/or administrator at UTMDACC who has cared for me, I may call the Conflict of Interest Coordinator at (713) 792-3220. Upon request, I will be given access to information disclosing the identity of all physicians and/or administrators who have a financial interest in the sponsor of this study.

9. My participation is voluntary.

10. I may ask any questions I have about this study, including financial considerations, of my treating physician. I may contact the principal investigator for this study Dr. Danai Daliani at (713) 792-2830 or the Chairman of the institution's Surveillance Committee at (713) 792-2933 with any questions that have to do with this study.

11. I may withdraw at any time without any penalty or loss of benefits. I should first discuss leaving the study with my physician. Should I withdraw from this study, I may still be treated at UTMDACC.

Patient's initials: _____

Witness' s initials: _____

12. I understand that the study may be changed or stopped at any time by my doctor, the principal investigator, the study sponsor, or the Surveillance Committee of UTMDACC.

13. I will be informed of any new information that might affect my willingness to continue participating in the study.

14. The institution will take appropriate steps to keep my personal information private. However, there is no guarantee of absolute privacy. The Food and Drug Administration ("FDA"),Celgene and respresentatives of the U.S. Army Medical Research and Materiel Command might review my record to collect data or to see that the research is being done safely and correctly. Under certain circumstances, the FDA could be required to reveal the names of participants.

15. If I suffer injury as a direct result of participation in this study, the institution will provide reasonable medical care. I understand that I will not receive reimbursement of expenses or financial compensation from the institution, the sponsor, or the manufacturer Celgene for this injury. I may contact the Chairman of UTMDACC's Surveillance Committee at 713-792-2933 with questions about study related injuries.

16. Unless otherwise stated in this consent form, all of the costs linked with this study, which are not covered by other payers (HMO, health insurance company, etc.), will be my responsibility.

17. I recognize that there are no plans to provide any compensation to me for any patents or discoveries that may result from my participation in this research.

BIRTH CONTROL

I understand that I must practice birth control. Female participants should not breast-feed while on study. If I become pregnant, or suspect that I am pregnant, I must notify my physician immediately. Getting pregnant may result in removal from participation in this study.

CONSENT FOR MEN:

INIT: _____ 1. I understand that I must not take THALOMID™ (Thalidomide) if I cannot avoid unprotected sex with a woman, even if I have had a successful vasectomy.

INIT: _____ 2. I understand that severe birth defects or death to an unborn baby have occurred when women took Thalidomide during pregnancy.

INIT: _____ 3. I have been told by my doctor that I must NEVER have unprotected sex with a woman (during the period I am taking thalidomide and for 8 weeks after I stop the drug) because it is not known if the drug is present in semen or sperm. My doctor has explained that men must completely avoid heterosexual intercourse or men must use a latex condom EVERY TIME they have sexual intercourse with a female partner while they are taking THALOMID™ (Thalidomide), and for 8 weeks after they stop taking the drug, even if they have had a successful vasectomy.

INIT: _____ 4. I also know that I must inform my doctor immediately if I have unprotected sex with a woman; or if I think FOR ANY REASON, that my sexual partner may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

INIT: _____ 5. I understand that THALOMID™ (Thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even women who has symptoms similar to mine. It must be kept out of reach of children and should never be given to women who are able to have children.

INIT: _____ 6. I understand that THALOMID™ (Thalidomide) can cause side effects including nerve damage (numbness, tingling or pain in the hands or feet that may not be reversible) and drowsiness. (If I become drowsy, I will not operate heavy machinery or drive a car. Also, I will avoid alcohol and other medicines not prescribed by my doctor). If I develop a red itchy rash I will contact my doctor immediately. If I feel dizzy, I will sit upright for a few minutes before standing up from a lying or sitting position. I understand all of the other possible side effects explained to me by my doctor. I know

that I cannot donate blood while taking THALOMID™ (Thalidomide).

INIT: _____ 7. My doctor has answered any questions I have asked.

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID™ (Thalidomide). I now authorize my doctor to begin my treatment with THALOMID™ (Thalidomide).

Authorization for Use and Disclosure of Protected Health Information

A. During the course of this study, the research team at UTMDACC will be collecting information about you that they may share with the FDA and/or Celgene. This information may include your treatment schedule and the results of any tests, therapies, or procedures that you undergo for this study. The purpose of collecting and sharing this information is to learn about how the treatment affects your disease and any side effects you experience as a result of your treatment.

Your doctor and the research team may share study information with certain individuals. These individuals may include representatives of the FDA and/or the above listed sponsor, clinical study monitors who verify the accuracy of the information, individuals with medical backgrounds who determine the effect that the treatment has on your disease, and/or individuals who put all the study information together in report form. The UTMDACC research team may provide this information to the FDA and/or the above listed sponsor at any time. There is no expiration date for the use of this information as stated in this authorization.

B. You may withdraw your authorization to share this information at any time in writing. More information on how to do this can be found in the UTMDACC Notice of Privacy Practices (NPP). You may contact the Office of Protocol Research at 713-792-2933 with questions about how to find the NPP.

C. If you refuse to provide your authorization to disclose this protected health information, you will not be able to participate in the research project.

D. I understand that my personal health information will be protected according to state and federal law. However, there is no guarantee that my information will remain confidential, and may be re-disclosed at some point.

CONSENT/AUTHORIZATION FOR TREATMENT AND OPTIONAL PROCEDURES
(Mark choice with an "X")

I agree to ____ or not to ____ have a prostate biopsy taken for optional studies.

Participant's initials _____.

I agree to ____ or not to ____ have a bone marrow biopsy taken for optional studies.

Participant's initials _____.

Having read and understood the above, and having had the chance to ask questions about this study and reflect and consult with others, I give _____ permission to enroll me on this study. I have been given a copy of this consent.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____ _____
WITNESS OTHER THAN PHYSICIAN OR INVESTIGATOR DATE

_____ _____
SIGNATURE OF PERSON RESPONSIBLE & RELATIONSHIP DATE

Participants Address: _____

_____

I have discussed this clinical research study with the participant and/or his or her authorized representative, using a language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
SIGNATURE OF STUDY DOCTOR OR PERSON OBTAINING CONSENT DATE

TRANSLATOR

I have translated the above informed consent into _____ for this participant.
(Name of Language)

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

Patient's initials: _____

Witness' s initials: _____