**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0521**

# A PHASE III PROTOCOL OF ANDROGEN SUPPRESSION (AS) AND 3DCRT/IMRT VS AS AND 3DCRT/IMRT FOLLOWED BY CHEMOTHERAPY WITH DOCETAXEL AND PREDNISONE FOR LOCALIZED, HIGH-RISK PROSTATE CANCER

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The following Cooperative Groups have endorsed this trial: SWOG: Co-chair Mark Garzotto

**RTOG Headquarters**
**1-800-227-5463, ext. 4189**

**This study is supported by the NCI Cancer Trials Support Unit (CTSU). [1/24/07]**

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.

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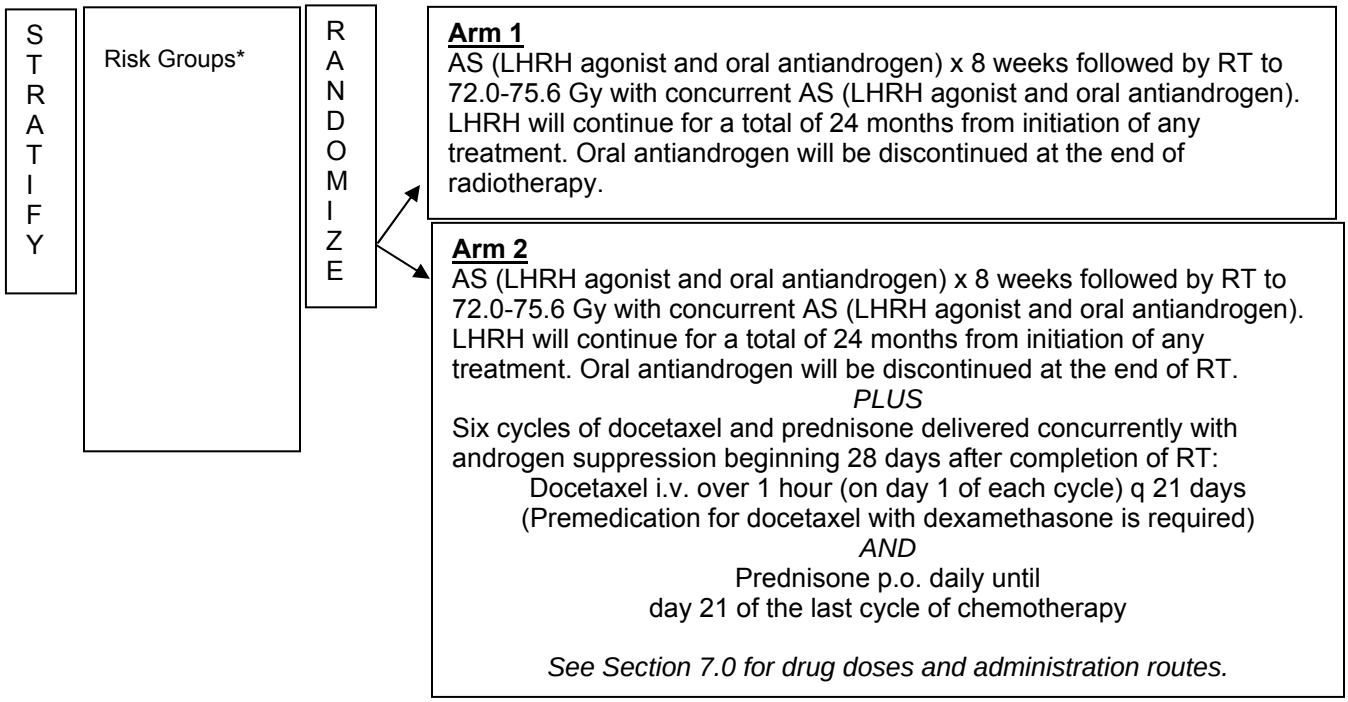
## SCHEMA




*Patients will be stratified by the following combinations:
1. Gleason ≥ 9, PSA ≤ 150, and any T-stage
2. Gleason 8, PSA < 20, and ≥ T2
3. Gleason 8, PSA ≥ 20-150, any T-stage
4. Gleason 7, PSA ≥ 20-150, any T-stage

**INSTITUTION MUST BE PRE-CREDENTIALED (See Section 5.0)**

**Patient Population**: (See Section 3.0 for Eligibility)
- Histologically confirmed prostate cancer with one of the following combinations:

| Gleason Score | | PSA | | T-Stage |
|---|---|---|---|---|
| ≥ 9 | *and* | ≤ 150 | *and* | Any |
| 8 | *and* | < 20 | *and* | ≥ T2 |
| 8 | *and* | ≥ 20-150 | *and* | Any |
| 7 | *and* | ≥ 20-150 | *and* | Any |

- Clinically negative lymph nodes as established by imaging (pelvic CT or pelvic MR), or pathologically negative by lymph node sampling or dissection.
- No prior radical prostatectomy or cryosurgery for prostate cancer.
- No prior pelvic radiation therapy or bilateral orchiectomy.
- No metastatic disease (M0).

**Required Sample Size: 600**

**RTOG Institution #** _____

**RTOG 0521** **ELIGIBILITY CHECKLIST** (12/8/05)(10/4/06)(04/27/07)(5/15/08)

**Case #** _____ (page 1 of 3)

_____(Y) 1. Is there histologically confirmed (within 180 days prior to registration) prostate cancer?

_____(Y) 2. Is there one of the following combination of factors?

| Gleason Score | | PSA | | T-Stage |
|---|---|---|---|---|
| ≥ 9 | *and* | ≤ 150 | *and* | Any |
| 8 | *and* | < 20 | *and* | ≥ T2 |
| 8 | *and* | ≥ 20-150 | *and* | Any |
| 7 | *and* | ≥ 20-150 | *and* | Any |

_____(Y) 3. Is the patient M0?

_____(Y/N) 4. Have clinically negative lymph nodes been established by imaging (pelvic CT, MR) or pathologically by sampling or dissection within 90 days prior to registration?
____(Y) If no, were equivocal or questionable lymph nodes ≤ 1.5 cm by imaging?

_____(Y) 5. Has the study entry PSA been done prior to start of any hormone therapy and within 180 days of registration?

_____(Y) 6. Were a history and physical done and weight obtained within 8 weeks prior to registration?

_____(Y) 7. Is Zubrod performance status 0-1?

_____(Y) 8. Are lab values as defined in 3.1.6, 3.1.7, and 3.1.8?

_____(Y/N) 9. Was a bone scan negative within 90 days prior to registration?
____(Y) If no, were plain films negative for metastasis?

_____(Y) 10. Was a medical oncology consultation done?

_____(N) 11. Has the patient had a prior radical prostatectomy, or cryosurgery for prostate cancer, or bilateral orchiectomy for any reason?

_____(N) 12. Was there prior pelvic RT?

_____(Y/N) 13. Has the patient received pharmacologic androgen ablation for prostate cancer?
____(N) If yes, were they started more than 50 days before registration?

_____(Y/N) 14. Has there been any prior invasive malignancy (except non-melanomatous skin cancer)?
____(Y) If yes, has the patient been disease free for a minimum of 3 years?

_____(N) 15. Has there been prior systemic chemotherapy for prostate cancer?

_____(N) 16. Has the patient had prior finasteride (in the past 60 days) and/or testosterone (in the past 90 days) before registration?

**(Continued on the next page)**

_____(N) 17. Has the study entry PSA been done during any of the following time frames?
- Within 10 days following prostate biopsy
- After initiation of hormone therapy
- Within 30 days of discontinuation of finasteride
- Within 90 days of discontinuation of dutasteride

_____(N) 18. Does the patient have any of the following severe, active co-morbidities?
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition (Note that HIV testing is not required for entry into this protocol)

_____(N) 19. Has the patient had a prior allergic reaction to the drugs involved in this protocol or to other drugs formulated with polysorbate 80?

_____(N) 20. Does the patient have existing peripheral neuropathy ≥ grade 2?

_____(Y) 21. If the patient is of child-producing potential, is he willing to consent to use effective contraception while on treatment and for at least 3 months afterwards?

**The following questions will be asked at Study Registration (10/4/06):**

Specify modality (3D vs. IMRT)

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)

_____ 5. Patient's Initials (First Middle Last)]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

**(Continued on the next page)**

**RTOG Institution #** _____

**RTOG 0521** **ELIGIBILITY CHECKLIST** (12/8/05)(10/4/06)(04/27/07)

**Case #** _____ (page 3 of 3)

_____ 12. Patient's Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Treatment Start Date (androgen suppression)

_____ 17. Medical Oncologist

_____(1/2/3/4)18. Risk group:
1. Gleason ≥ 9, PSA ≤ 150, and any T-stage
2. Gleason 8, PSA < 20, and ≥ T2
3. Gleason 8, PSA ≥ 20-150, any T-stage
4. Gleason 7, PSA ≥ 20-150, any T-stage

_____ 19. What is the Gleason score?

_____ 20. What is the PSA value?

_____ 21. What is the T-stage?

_____(Y/N) 22. Tissue kept for cancer research?

_____(Y/N) 23. Tissue kept for medical research?

_____(Y/N) 24. Allow contact for future research?

_____(Y/N) 25. Blood kept for cancer research? (06/20/07)

_____(Y/N) 26. Blood kept for medical research? (06/20/07)

_____(Y/N) 27. Blood kept for future research? (06/20/07)

_____ 28. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

## 1.0 INTRODUCTION

Prostate cancer is a common cause of cancer morbidity and mortality in the United States. In 2005, there will be an estimated 232,090 new cases of prostate cancer and 29,900 prostate cancer deaths in the United States.[1] As prostate cancer becomes more commonly diagnosed in this country, there has been increasing awareness of the clinical heterogeneity of the disease. Some patients present with metastatic disease, while there are subsets of patients whose disease is quite indolent and may be observed. Other subsets of patients may be treated with curative local therapies, such as radical prostatectomy, external beam radiation therapy, or interstitial radiotherapy.

In recent years, attention has been directed at identifying and defining subsets of patients who would benefit from adjuvant systemic treatment in addition to local therapy. RTOG 86-10 demonstrated an improvement in local control and progression-free survival (but not overall survival) in patients with large (>25 cc) prostate tumors treated with radiation therapy plus goserelin compared with radiation alone.[2] RTOG 85-31 examined adjuvant goserelin in a group of patients estimated to be at high risk for failure for prostate cancer.[3] In this trial, patients were randomized to adjuvant goserelin prior to radiation therapy versus radiotherapy alone with goserelin at relapse. There was statistically significant improvement in local recurrence, metastasis, disease-free survival, and overall survival in the patients who received adjuvant goserelin. In a European randomized study, Bolla et al.[4] demonstrated a local control and survival benefit for 3 years of androgen suppression plus radiation therapy versus radiation alone.

The findings of these and similar studies have resulted in enthusiasm and further testing of androgen suppression in adjunct to radiotherapy. The exact combination of hormonal agents, sequencing of hormonal therapy with radiation therapy, radiation therapy field sizes, appropriate subsets of patients in whom hormonal therapy will be acceptable, and duration of hormonal therapy have been and continue to be subjects of active investigations (RTOG 92-02, 94-08, 94-13, 99-10). RTOG 92-02, which completed accrual of over 1500 patients in 1995, randomized patients to a 4-month course of total androgen suppression (TAS) (goserelin plus flutamide) given for 2 months prior to and then concurrently with radiation therapy (70.2 Gy) versus 4 months of TAS plus radiation therapy followed by androgen suppression with goserelin alone for 2 years.[5] The standard arm of the current trial is similar to the experimental arm of that trial, based in part on the results of Bolla et al.,[4] which noted a survival advantage to prolonged androgen suppression. In RTOG 94-13, patients with intermediate- to high-risk prostate cancer were all treated with 4 months of TAS plus radiation therapy (70.2 Gy), with a double randomization: half of the patients were treated with TAS prior to and concurrent with radiation therapy, and half were treated with TAS after radiation therapy. In addition, half of the patients were treated to a pelvic field with a prostate boost volume, and half were treated to a small volume for the entire course of treatment. This trial has shown that the combination of pelvic irradiation and simultaneous androgen ablation is important in high-risk prostate cancer;[6] the use of pelvic irradiation and simultaneous androgen suppression will be used in all patients in the current trial. These trials are helping to answer questions regarding the optimal nature, duration, and sequence of anti-androgen therapy for prostate cancer. There is a realization, however, based on multiple studies of prognostic factors in prostate cancer, that there are subsets of patients who remain at high risk of failure and who may benefit from more aggressive treatment approaches, including cytotoxic chemotherapy.

There are high-risk subsets of prostate cancer patients with poor prognosis who can be identified for treatment failure after radiation therapy. In an analysis of 500 patients treated with radiation therapy alone for clinically localized prostate cancer, Pisansky et al.[7] noted that the factors of clinical tumor stage, Gleason score, and pretreatment PSA level were all independently associated with clinical or biochemical relapse risks. Using these factors they were able to separate patients into low-, intermediate-, and high-risk groups, with distinct relapse-free probabilities at 5 years after radiation therapy (92%, 67%, and 24%, respectively; $p < 0.0001$). Patients eligible for the current protocol will have similar pretreatment prognostic factors to those in the high-risk group identified by Pisansky et al. Other investigators have shown similar findings.[8-11]

Although treatment techniques, patient populations, and definitions of biochemical control may have varied between different institutions, there are remarkable consistencies in the findings that patients with elevated PSA at presentation, high Gleason score, and advanced T-stage have relatively poor prognosis compared with other patients. We believe that the results obtained with conventional treatment for these patients are sufficiently poor to justify the exploration of a more aggressive approach in an attempt to improve therapeutic results. Because of the importance of pretreatment prognostic factors in predicting for outcome in studies of prostate cancer patients, we believe that a randomized, controlled, phase III

study is the best way to determine if cytotoxic chemotherapy will add to the control rates that can be obtained with radiation therapy plus androgen suppression alone.

Until recently, the role of cytotoxic chemotherapy in prostate cancer has been limited to the treatment of patients with advanced disease refractory to treatment with androgen suppression.[12] However, clinical experience from other disease sites suggests that chemotherapy may be more effective if used earlier in the course of disease. When used in the adjuvant setting, the tumor burden may be lower and there is less chance for malignant cells to develop resistance to therapeutic agents. Chemotherapy may also be able to target hormonally resistant cells, complementing the ability of androgen suppression to target hormonally sensitive cells.

This study is designed to determine whether cytotoxic chemotherapy with docetaxel and prednisone, in addition to androgen suppression plus radiotherapy, will result in improved control and survival rates over those obtained with androgen suppression plus radiotherapy. In hormone-refractory prostate cancer, single-agent docetaxel given at three weekly intervals has been reported to produce a PSA response in 46% of patients and measurable soft tissue disease response in 28% of patients.[13,14]

Docetaxel has also been administered every 3 weeks in combination with estramustine in the treatment of hormone-refractory prostate cancer, resulting in a 45% to 74% PSA response (50% decrease in PSA).[15-17] However, this regimen has been associated with a significant incidence of thrombotic events, most likely due to estramustine. The Southwest Oncology Group (SWOG) recently tested the combination of docetaxel and estramustine versus mitoxantrone and prednisone in a large phase III study. The docetaxel and estramustine arm resulted in an increase in overall survival (17.5 months vs. 15.6 months), time to progression (6.3 months vs. 3.2 months), PSA decline of at least 50% (50% vs. 27%), and an increase in objective response rate (17% vs. 11%).[18]

A second large study has also been recently reported supporting docetaxel without estramustine. TAX 327 was a phase III multicenter comparison of docetaxel given weekly or every 3 weeks with prednisone versus mitoxantrone and prednisone in patients with hormone-refractory prostate cancer. Over 1,000 men were randomized on this study, producing results that were statistically significant for survival (18.9 months vs. 16.5 months) and PSA decline by at least 50% (45% vs. 32%) for patients treated with every-3-week docetaxel and prednisone. In addition, there were statistically significant reductions in pain (35% vs. 22%) and improvement in quality of life (22% vs. 13%).[19] Although the observed survival benefit is modest in terms of the number of months of life extension, the benefit in the adjuvant setting could be much more impressive.

Prostate cancers are heterogeneous collections of cells. Combination therapy with docetaxel and prednisone may help to kill hormone refractory prostate cancer cells early in the course of therapy. Treatment with hormonal agents, such as TAS, may kill hormone sensitive cells or make them sensitive to radiation-induced killing during the course of external beam radiation therapy. There are numerous examples in oncology literature of which agents that are found to have limited activity as single agents in advanced disease are found to have significant activity when used early in the course of therapy before treatment-resistant clonogens are selected out or induced by previous cytotoxic therapy.

The potential for increased toxicity with chemotherapy and radiation is of concern. Myelotoxicity is the major potentially life-threatening toxicity associated with the docetaxel and prednisone chemotherapy. We believe, however, that these interactions can be limited by treating patients sequentially, with chemotherapy following radiation rather than given concurrently. Nevertheless, the potential for added toxicity—hematologic and otherwise—will need to be carefully monitored, especially in view of the mild anemia that androgen suppression can produced.

Radiation therapy field sizes and doses will follow from previous RTOG trials. The total dose to the prostate will be 72.0-75.6 Gy, a modest increase in the lower and upper range to reflect the significant changes in practice and consistent with the range strategy allowed in RTOG 92-02. Higher doses have been used in RTOG 94-06; however, that trial is a conformal trial, with treatment volumes limited to the prostate, seminal vesicles, and immediate surrounding tissues only. Furthermore, it is a trial with limited institutional participation, with special institutional credentialing required. The patients to be enrolled in this study will have a significant risk of lymph node involvement,[20] so we do not believe that treatment of the prostate alone is indicated. Three dimensional conformal radiation therapy (3DCRT) or intensity

modulated radiation therapy (IMRT) will be required for patients treated on this trial. Institutions must be appropriately credentialed for participation in this trial using one of these two methods.

This trial follows upon the closure of RTOG 99-02, a trial examining a chemotherapy regimen employing paclitaxel, etoposide, and estramustine. The radiotherapy, eligibility, and hormonal therapy used in that trial are similar to this trial. RTOG 99-02 accrued nearly 400 patients but was closed early due to thromboembolic complications thought to be associated with estramustine. These complications occurred despite the use of therapeutic levels of warfarin. The current design has the advantage of eliminating estramustine from the regimen and thus should have a markedly reduced risk of thromboembolic problems.

Additionally, in order to obtain data that may help to validate a recent observation by D'Amico et al, [21] we will obtain all PSA values available in the year prior to diagnosis. Pretreatment PSA velocity, as defined by D'Amico, or other PSA constructs, such as pretreatment PSA doubling time, will then be analyzable for influence on predicting overall survival. As in D'Amico's study, some patients may only have a single PSA value in the year prediagnosis and may not be informative for pretreatment PSA velocity, but they will still be otherwise eligible for this trial.

**1.1 Single Nucleotide Polymorphisms (SNPs) and Normal Tissue Toxicity (04/27/07)**

RT produces its biological effects mainly through the generation of short lived but highly reactive DNA radicals that evolve into stable/long-lived DNA lesions such as DSBs[22] or through interactions with the plasma membrane,[23] leading to cell death. The total number of gene products currently known to be involved in determining cellular radiosensitivity is well over 100 and growing.[24] Several groups have reported analysis of genetic variants of individual candidate genes potentially implicated in normal tissue radiosensitivity.[25,26] A more powerful search approach, in the post-genome era, would be to screen patients for a large number of genes that could impact on radiosensitivity. Variations in the sequence of the human genome can comprise repeating sequences such as variable number of tandem repeats (VNTRs), short tandem repeats (STRs) and SNPs.[27] Although the human genome is ~99.9% identical among individuals, the ~0.1% variations (the vast majority of which are SNPs) tend to be heritable and stable.[28] It is postulated that these variations in the genome explain phenotypic differences between individuals and may also serve as a genetic blueprint for susceptibility to disease and cellular responses to pharmacologic agents.[29,30] SNP-types associated with a higher risk of radiation-induced normal tissue toxicity would comprise a predictive molecular signature of radiation injury, and would have broad applicability in patient selection for radical radiotherapy.

Several groups have reported preliminary results in their analysis of the association between candidate SNPs and late toxicity after RT for breast cancer.[31-36] An association between TGFB1 -509T and +869C alleles and fibrosis was found by Quarmby et al, while Andreassen et al found TGFB1 position -509 and codon 10 to be associated with fibrosis. The latter study also found associations between other DNA damage-related SNPs (SOD2 (codon 16), XRCC3 (codon 241), XRCC1 (codon 399)) and clinical late toxicity. Recently, in a different breast cancer patient cohort, Andreassen et al[35] found statistically significant associations between the TGFB1 codon 10 Pro allele (P=0.005) as well as the TGFB1 position -509 T allele (P=0.018) and increased risk of late breast fibrosis as indicated by breast appearance. The functional significance of either the TGFB1 codon 10 Pro allele or the TGFB1 position -509 T allele is currently unclear. However, recently Andreassen et al[37] failed to replicate these earlier associations in a study where DNA was obtained from formalin fixed paraffin embedded tissue samples in a different cohort of breast cancer patients. In order to avoid false positive associations, SNP-association studies should be validated in larger, well-defined cohorts of homogeneously treated patients.

The correlation of SNPs and pelvic normal tissue toxicity was reported by De Ruyck et al,[38,39] who examined SNPs in XRCC1, XRCC3, TGFB1 position -509, TGFB1 codon 10 and OGG1. Patients with three or more risk alleles in XRCC1 and XRCC3 had a significantly increased risk of developing late pelvic GI/GU toxicity (odds ratio 10.10, p = 0.001). Damaraju et al[40] analysed 53 SNPs in BRCA1, BRCA2, ESR1, XRCC1, XRCC2, XRCC3, NBS1, RAD51, RAD52, LIGIV, HAP1, ATM, BCL2, TGFβ-1, MSH6, XPD (ERCC2), XPF (ERCC4), GRL, CYP1A1, CYP2C19, CYP3A5, CYP2D6, CYP11B2, and CYP17 genes from a cohort of 83 men who had undergone 3-dimensional conformal RT for prostate cancer. Significant univariate associations with late rectal or bladder toxicity (grade 2+) were found for XRCC3 A>G 5' UTR NT 4541, LIGIV T>C Asp568Asp, MLH1 C>T, Val219Ile, CYP2D6*4 G>A splicing defect, mean rectal and bladder

dose, dose to 30% of rectum or bladder, and age <60 years. In a Cox multivariate analysis, significant associations with toxicity were found for LIGIV T>C, Asp568Asp; XPD G>A, Asp711Asp; CYP2D6*4 G>A, splicing defect; mean bladder dose >60 Gy, and dose to 30% of rectal volume >75 Gy. These data suggest an association between candidate SNPs and late pelvic radiation toxicity.

**1.2 Proposal for Banking of Buffy Coat Specimens for SNP Analysis**

In order to search for a genomic signature correlated with a higher propensity to normal tissue radiation damage, it is appropriate to propose a broad-based genetic (SNP) analysis for candidate genes. The working hypothesis is that toxicity (rectum and/or bladder in the case of pelvic sites; skin and subcutaneous tissue in the case of breast) will be correlated to a patient's genetic makeup measured as SNPs in a select group of candidate genes. The criteria for selecting SNPs should be based on published evidence for the various genes implicated or previously demonstrated to be involved in RT-induced tissue damage and repair pathways. Genomic DNA for SNP analysis can be most effectively isolated from buffy coat leukocytes using standard procedures. Banking of buffy coat leukocytes can be performed at any time in the patient's trajectory, whether before, during, or after treatment.

## 2.0 OBJECTIVES

### 2.1 Primary

To assess the relative efficacy of the combination of androgen suppression (AS) + radiotherapy (RT) followed by androgen suppression vs. AS + RT followed by docetaxel and prednisone chemotherapy + androgen suppression in a population of patients with clinically localized prostate cancer with unfavorable prognostic factors. The primary endpoint will be overall survival.

### 2.2 Secondary (04/27/07)

1. To assess the differences between the two treatment arms for:
- Biochemical control (freedom from PSA failure)
- Local control
- Freedom from distant metastases
- Disease-free survival
- Incidence of adverse events

2. In addition, the following will be assessed:
- Validity of PSA-defined endpoints as a surrogate for the primary objective
- The time interval between biochemical failure and distant metastases with respect to testosterone level

3. To collect paraffin-embedded tissue blocks, serum, plasma, and buffy coat cells for future translational research analyses.

## 3.0 PATIENT SELECTION

### 3.1 Conditions for Patient Eligibility (5/15/08)

**3.1.1** Histologically confirmed (within 180 days prior to registration) prostate cancer at high-risk for recurrence as determined by one of the following combinations:

| Gleason Score | | PSA | | T-Stage |
|---|---|---|---|---|
| ≥ 9 | *and* | ≤ 150 | *and* | Any |
| 8 | *and* | < 20 | *and* | ≥ T2 |
| 8 | *and* | ≥ 20-150 | *and* | Any |
| 7 | *and* | ≥ 20-150 | *and* | Any |

Histological diagnosis of index lesion for accrual must be performed within 180 days prior to registration. Patients may have had positive prostate cancer biopsies previously and undergone active surveillance. Dates and Gleason scores of previous positive biopsies, if any, must be available.

**3.1.2** Clinically negative lymph nodes as established by imaging (pelvic CT or pelvic MR), nodal sampling, or dissection within 90 days prior to registration.

**3.1.2.1** Patients with lymph nodes equivocal or questionable by imaging are eligible if the nodes are ≤ 1.5 cm.

**3.1.2.2** Patients with positive lymph nodes by capromab pendetide (ProstaScint) scans are eligible provided a corresponding lymph node identified by CT or MR imaging is ≤ 1.5 cm.

**3.1.3** No distant metastases, based upon the following minimum diagnostic work-up:

**3.1.3.1** History/physical examination (including weight) within 8 weeks prior to registration

**3.1.3.2** Bone scan within 90 days prior to registration. Equivocal bone scan findings are allowed if plain films are negative for metastasis.

**3.1.4** Zubrod performance status 0-1

**3.1.5** Age ≥ 18

**3.1.6** CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:

**3.1.6.1** Absolute neutrophil count (ANC) ≥ 1,800 cells/$mm^3$

**3.1.6.2** Platelets ≥ 100,000 cells/$mm^3$

**3.1.6.3** Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)

**3.1.7** Pretreatment serum PSA, obtained prior to any LHRH or antiandrogen therapy, within 180 days of randomization.

**3.1.8** ALT, AST, and total bilirubin within 1.5X institutional upper normal limits; and alkaline phosphatase within 2.5X institutional upper normal limits, obtained within 8 weeks prior to registration.

**3.1.9** Medical oncology consultation prior to registration.

**3.1.10** Prior 5-alpha reductase inhibitor (for example, finasteride) for prostatic hypertrophy is allowed if discontinued at least 60 days prior to registration.

**3.1.11** Prior testosterone administration is allowed if last administered at least 90 days prior to registration.

**3.1.12** Prior pharmacologic androgen ablation for prostate cancer is allowed only if the onset of androgen ablation is ≤ 50 days prior to the date of registration.

**3.1.13** Patient must sign study specific informed consent prior to study entry.

**3.1.14** Men of child-producing potential must be willing to consent to use effective contraception while on treatment and for at least 3 months afterwards.

### 3.2 Conditions for Patient Ineligibility (10/4/06)

**3.2.1** PSA > 150

**3.2.2** Evidence of M1 metastatic disease

**3.2.3** Pathologically positive lymph nodes or nodes > 1.5 cm on imaging

**3.2.4** Prior radical prostatectomy, cryosurgery for prostate cancer, or bilateral orchiectomy for any reason

**3.2.5** Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the oral cavity or bladder are permissible)

**3.2.6** Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable. See Section 3.2.5.

**3.2.7** Prior radiotherapy, including brachytherapy, to the region of the study cancer that would result in overlap of radiation therapy fields

**3.2.8** Severe, active co-morbidity, defined as follows:

**3.2.8.1** Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

**3.2.8.2** Transmural myocardial infarction within the last 6 months

**3.2.8.3** Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

**3.2.8.4** Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

**3.2.9** Prior allergic reaction to the drugs involved in this protocol or to other drugs formulated with polysorbate 80.

**3.2.10** Existing peripheral neuropathy ≥ grade 2.

**3.2.11** Study entry PSA obtained during the following time frames: (1) 10-day period following prostate biopsy; (2) following initiation of hormonal therapy; (3) within 30 days after discontinuation of finasteride; (4) within 90 days after discontinuation of dutasteride.

## 4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

(In addition to the mandatory pre-entry testing for eligibility in Section 3.0)

**Note: The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient's eligibility for this study, please contact RTOG HQ immediately (215) 574-3189.**

### 4.1 Additional Mandatory Pretreatment Evaluations/Interventions

See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

**4.1.1** Testosterone assessment obtained within 8 weeks prior to randomization (unless patient has already received androgen ablation)

### 4.2 Strongly Recommended Pretreatment Evaluations (04/27/07)

Serum, plasma, buffy coat cells, and archival tissue (preferably in blocks; see Section 10.2) for banking: For patients who consent to this component of the study

## 5.0 REGISTRATION PROCEDURES

### 5.1 Pre-Registration Requirements FOR ALL INSTITUTIONS

**Patients MUST be treated with either 3DCRT or IMRT on this trial. Credentialing requirements for 3DCRT and IMRT are described below.**

**5.1.1** *3DCRT Credentialing*: All institutions that have been previously credentialed to submit protocol compliant cases to prior RTOG 3DCRT prostate trials (94-06, 0126) may register patients on this trial. All other institutions that have met the technology requirements and that have provided the baseline physics information described in the Quality Assurance Guidelines (see ATC website at http://atc.wustl.edu) may enter patients into this study.

**5.1.2** *IMRT Credentialing*: Institutions that have been credentialed for RTOG 0126 or other RTOG studies for IMRT may elect to treat patients with IMRT on RTOG 0521 using the guidelines outlined in Section 6.0. Only institutions that have met the technology requirements and that have provided the baseline physics information that is described in the IMRT Quality Assurance Guidelines (see ATC website at http://atc.wustl.edu) may enter patients into this study.

**5.1.2.1** Institutions or investigators anticipating the use of IMRT on this study must have completed an IMRT Facility Questionnaire. A copy of the IMRT Facility Questionnaire may be obtained at the Image-Guided Therapy Center (ITC) link via the ATC website at http://atc.wustl.edu. The IMRT Facility Questionnaire requests information regarding the training and experience of the IMRT team; IMRT treatment planning and treatment equipment; and in-house QA procedures. In addition, all institutions must successfully complete an IMRT "dry-run" or benchmark case with the ITC. An IMRT phantom or benchmark study with the RPC (see ATC website at http://atc.wustl.edu) must also be successfully completed if the institution has not previously met this credentialing requirement on another RTOG IMRT study.

### 5.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS (5/15/08)

**5.2.1** Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form. Canadian institutions must also complete the *"Request for Clinical Medication by Fax"* form included in the "Health Canada study approval broadcast." The form must be faxed to RTOG Headquarters at 215-574-0300 prior to registering the first patient. Headquarters will fax the completed form to Sanofi-Aventis once all regulatory documents are received. Please allow one week prior to registering your first case to receive your shipment.

### 5.3 Pre-Registration Requirement for Shipment of Taxotere (docetaxel) [11/15/06] (04/27/07)(5/15/08)

All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **After receipt of written approval of submitted LOI forms from RTOG Headquarters, International institutions** must submit the SASF and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).This must be done prior to registration of the institution's first case.

**Note: Canadian institutions** must use the Canadian SASF, which can be accessed in the Canadian Information Section on the RTOG web site, at http://www.rtog.org/members/CanadaInfo/0521/0521drug request.html. The Canadian SASF must be submitted to RTOG Headquarters with documentation of IRB approval (Fax 215-574-0300).

This must be done prior to registration of the institution's first case. Institutions should allow adequate time (7-10 days) to process the form before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment.

### 5.4 Registration (5/15/08)

Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters at (215) 574-3191.

## 6.0 RADIATION THERAPY NOTE: INTENSITY MODULATED RT (IMRT) IS ALLOWED (5/15/08)

**Sample nodal volumes are available from the Pelvic Lymph Node Volumes for Prostate Cancer Atlas on the RTOG web site:**

**http://www.rtog.org/atlases/PelvicLymphNodeProstateAtlas/main.html**

### 6.1 Treatment Arms

Radiation therapy (RT) will be delivered on both arms to 72.0-75.6 Gy, using either conformal or IMRT treatment. RT will begin 8 weeks following the initiation of hormone administration.

### 6.2 3DCRT Treatment (See Section 6.3 for IMRT Treatment)

#### 6.2.1 *Physical Factors*

Megavoltage equipment is required with photon energies of ≥ 6 MV (≥ 10 MV is preferred). The minimum source-to-axis (SAD) distance will be 100 cm. Any treatment technique (field

arrangement) capable of producing the required dose distribution will be acceptable, with the following exceptions: (1) Perineal boost will not be permitted, and (2) AP/PA technique will not be permitted except for photon energies ≥ 24 MV photons. Typical field arrangements will be four-field technique for the regional lymphatic volume, and 4 - 6 field technique for the prostate boost volume.

**6.2.2** *Target Volumes (Note: CT for treatment planning is required)*

**6.2.2.1** Regional Lymphatics Target Volumes (see Section 6.3.1 for optional IMRT to pelvic lymph nodes)

A four field technique using digitally reconstructed radiographs for portal definition is allowed for the pelvic component of radiation therapy. In this case, explicit nodal target volumes need not be defined. The superior border of the regional lymphatic volume will be between the bottom of the SI joints (minimum allowed superior border) and the L5-S1 interspace. Lateral borders will be at least 1 cm lateral to the pelvic brim. Inferior borders will be generally near the inferior border of the ischial tuberosity. If a urethrogram is used, the border should be set at least 1.5 cm below the apex of the urethrogram.

In the lateral fields, care should be made to adequately cover the internal and external iliac lymph nodes below the SI joints (usual posterior border at approximately S2-3, but CT planning is helpful) and to include the posterior extension of the seminal vesicles.

**6.2.2.2** Prostate Boost Target Volume

GTV = Prostate**
CTV = Prostate + *proximal* BSV*
PTV = CTV + 0.5-1.5 cm

*BSV = bilateral seminal vesicles. The proximal seminal vesicle is defined as the portion from its origin with the prostate and extending 1.0 cm superiorly.

**GTV=Prostate and entire BSV, if cT3b disease present

**6.2.2.3** Films

One set of approved portal films/images of each treatment field and simulation films will be submitted for review per Section 12.2.

**6.2.3** *Doses*

46.8 Gy will be given to the regional lymphatics followed by a 25.2-28.8 Gy boost to the prostate, to bring the total dose to the prostate to 72.0-75.6 Gy. Daily prescription doses will be 1.8 Gy per day, 5 days per week x 8-8.5 weeks.

The dose will be prescribed to the minimum target dose (i.e., to the highest isodose line, which encompasses the planning target volume).

Regional lymphatics will receive a dose of 46.8 Gy.

Prostate PTV will receive a boost of 25.2-28.8 Gy to bring the total dose to 72.0-75.6 Gy.

If seminal vesicles are clinically or radiographically involved with tumor (T3b disease, Appendix III), the boost PTV will be the prostate and BSV + 1.0-1.5 cm.

**6.2.4** *Critical Normal Structures*

Portions of the bladder will receive the same dose as the regional lymphatics. The base of the bladder will be included in the prostate boost planning target volume and will receive the same dose as the prostate. Every effort should be made to keep the bladder distended.

Doses to the entire rectum should be minimized. Portions of the anterior rectal wall will, by necessity, receive the same dose as the prostate.

**6.2.5** *Compliance Criteria*

| Assessment | Per Protocol | Variation, Acceptable | Deviation, Unacceptable |
|---|---|---|---|
| Field Borders | Within 1 cm of protocol definition | > 1 to 2 cm of protocol definition | > 2 cm of protocol definition |
| Total Dose | Within < 5% of protocol specified dose | > 5 to 10% of protocol specified dose | > 10% of protocol specified dose |
| Fractionation | Within 0.05 Gy of specified 1.8 Gy daily fraction size | > 0.05 Gy to 0.10 Gy of 1.8 Gy | > 0.10 Gy of 1.8 Gy |
| Elapsed Days During Radiotherapy | 1 to 7 break days | 8 to 14 days | > 14 days |

## 6.3 IMRT Treatment

Institutions that have been credentialed for RTOG 0126 or other RTOG studies for IMRT may elect to treat patients with IMRT on RTOG 0521 using the guidelines outlined below. If institutions have not previously been credentialed specifically for IMRT by the Radiological Physics Center (RPC), patients should be treated using the non-IMRT guidelines. If institutions not previously credentialed for RTOG IMRT studies would like to become IMRT credentialed, they may fill out the IMRT Facility Questionnaire via the ATC website at http://atc.wustl.edu and proceed with the process to become IMRT credentialed through the Image Guided Therapy Center (ITC), including an IMRT phantom study with the RPC.

IMRT may be used in this trial. There are two IMRT scenarios. First, IMRT may be used for the prostate boost (after conformal RT to the pelvis as in Section 6.2.2.1). Second, IMRT may be used for the pelvic lymph nodes as well as the prostate, but in this scenario there must be two separate IMRT plans: one for the larger pelvic field and one for the prostate boost.

**6.3.1** *Pelvic LN IMRT* **(5/15/08)**

Target Volumes (see 6.3.5 for further details)

GTV = Prostate** and pelvic LN (obturator, internal iliac, external iliac). The superior extent of the LN GTV will be between the bottom of the SI joints and the L5-S1 interspace. Presacral LN should also be included, with the inferior border no lower than S3. The inferior extent of the external iliac LN GTV is at the superior border of the femoral head.

Sample nodal volumes are available from the RTOG Web site (Pelvic Lymph Node Volumes for Prostate Cancer Atlas; http://www.rtog.org/PelvicLymphNodeProstateAtlas/main.html).

CTV = Prostate + *proximal* BSV* + pelvic LN
PTV = CTV + 0.5-1.0 cm

*BSV = bilateral seminal vesicles. The proximal seminal vesicle is defined as the portion from its origin with the prostate and extending 1.0 cm superiorly.
**GTV=Prostate and entire BSV, if cT3b disease present

*Dose Specification* **(04/27/07)(5/15/08)**

The prescription dose is the minimum dose to ≥95% of the PTV (defined above). The maximum dose to a volume of no more than 3% of the PTV should not exceed the prescription dose by more than 7% (inhomogeneity ≤7%) and will be scored as no variation: ≤7%; minor variation: >7 to ≤10%; major variation: >10%.

Prescription dose to the PTV shall be according to the following dose schema delivered in 1.8 Gy minimum dose fractions. All fields treated once daily, 5 fractions per week to a prescription dose of 46.8 Gy No more than 5% of the PTV and <3% of the CTV may receive less than 46.8 Gy.

| Dose Goal (Prescription) | Minimum PTV dose (encompassing ≥95% of PTV) | Minimum CTV dose (encompassing ≥97% of CTV) | Maximum PTV dose to <3% of PTV[1] (No variation) | Maximum PTV dose to <5% of PTV[1] (Minor variation) | Maximum PTV dose to <7% of PTV[1] (Major variation) |
|---|---|---|---|---|---|
| | 46.8 Gy | 46.8 Gy | 50.1 Gy | 51.5 Gy | >51.5 Gy |

[1] The maximum dose must not be within an "Organ at Risk" such as the Rectum, Bladder, or Penile Bulb

**6.3.2 For Prostate only IMRT (after IMRT or 3DCRT to the pelvis)**

*Target Volumes (see 6.3.5 for further details)*

GTV = Prostate**

CTV = Prostate + *proximal* BSV*

PTV = CTV + 0.5-1.0 cm

*BSV = bilateral seminal vesicles. The proximal seminal vesicle is defined as the portion from its origin with the prostate and extending 1.0 cm superiorly.

**GTV=Prostate and entire BSV, if cT3b disease present.

*Dose Specification* **(5/15/08)**

The prescription dose is the minimum dose to ≥95% of the PTV *(defined above).* The maximum dose *to a volume of no more than 3% of the PTV* should not exceed the prescription dose by more than 7% (inhomogeneity ≤7%) and will be scored as no variation: ≤7%; minor variation: >7 to ≤10%; major variation: >10%.

Prescription dose to the PTV shall be according to the following dose schema delivered in 1.8 Gy minimum dose fractions. All fields treated once daily, 5 fractions per week. 25.2-28.8 Gy for the IMRT Boost. No more than 5% of the PTV and <3% of the CTV may receive less than 25.2 Gy.

| Dose Goal (Prescription) | Minimum PTV dose (encompassing ≥95% of PTV) | Minimum CTV dose (encompassing ≥97% of CTV) | Maximum PTV dose to ≤3% of PTV[1] (No variation) | Maximum PTV dose to ≤5% of PTV[1] (Minor variation) | Maximum PTV dose to ≤7% of PTV[1] (Major variation) |
|---|---|---|---|---|---|
| | 25.2 Gy | 25.2 Gy | 30.1 Gy | 31.7 Gy | >31.7 Gy |

[1] The maximum dose must not be within an "Organ at Risk" such as the Rectum, Bladder, or Penile Bulb

**6.3.3** *External Beam Equipment*

Megavoltage equipment is required with effective photon energies ≥6 MV. Credentialing requirements and QA guidelines for institutions planning to participate in this study using IMRT can be found on the ATC web site, http://atc.wustl.edu.

**6.3.4** *Treatment Planning Imaging and Localization Requirements*

An urethrogram is recommended, but not required, to establish the most inferior portion of the prostate. Use of radio-opaque seeds within the prostate are optional as a localization aid.

For IMRT, a treatment planning CT scan will be required to define tumor, clinical, and planning target volumes and the critical structures (see Section 6.3.5.5). The treatment planning CT will be acquired with the patient in the same position and with immobilization device and conditions as will be utilized for treatment. That is, if treatment is planned with a full bladder, the simulation CT should be performed with a full bladder. The rectum should be empty. Standard institutional immobilization techniques are allowed. The CT scan of the pelvis should start at or above the iliac crest down to the perineum. All tissues to be irradiated must be included in CT scan. CT scan thickness should be ≤0.5 cm through the region that contains the target volumes. The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm.

The GTV, CTV, and PTV (see Section 6.3.5), and normal tissues must be outlined on all CT slices in which the structures exist.

**6.3.5** *Volume Definitions*

**6.3.5.1** The Gross Tumor Volume *(GTV)* is defined by the physician as all known disease as defined by the planning CT, urethrogram, and clinical information. Prostate dimensions should be defined as visualized on CT scan. The GTV will include the entire BSV, if cT3b disease is present.

**6.3.5.2** The Clinical Target Volumes *(CTV)* **(5/15/08)** are the GTV plus areas considered to contain microscopic disease, delineated by the treating physician, and is defined as follows:

CTV is the GTV (*prostate*) plus the proximal bilateral seminal vesicles (unless cT3b; see Section 6.3.2). Only the first 1.0 centimeter of seminal vesicle tissue adjacent to the prostate shall be included in the clinical target volume. This 1.0 cm of seminal vesicles refers to both radial (in plane) and superior (out of plane) extent. If both prostate and seminal vesicle are visualized in the same CT slice, this seminal vesicle tissue will contribute to the 1.0 cm of tissue.

IV contrast is optional at the time of treatment planning, CT but may assist in the definition of the nodal target volumes. A 0.7 –1.0 cm margin around the iliac vessels that respects anatomic limits will encompass the majority of lymphatic tissue at risk. The $CTV_{nodes}$ should not extend outside the true pelvis, into the pelvic musculature nor into adjacent identifiable organs, such as the bladder, rectum or other bowel. Extension of CTV into adjacent bone may be carved out. The $CTV_{nodes}$ should include the common iliac vessels below S1 and the internal and external iliac vessels inferiorly. Note that the inferior extent of the external iliac LN is at the superior border of the femoral head. The internal iliac vessels should be contoured inferiorly to the level of the seminal vesicles and posteriorly to the same border as the prostate and seminal vesicles. For patients with the superior border of LN volumes above the bottom of the sacroiliac joints, presacral lymph nodes should be treated, but the inferior border should not extend below S3.

Sample nodal volumes are available from the RTOG Web site Pelvic Lymph Node Volumes for Prostate Cancer Atlas
**http://www.rtog.org/atlases/PelvicLymphNodeProstateAtlas/main.html**

**6.3.5.3** The Planning Target Volume *(PTV)* will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A minimum of 5 mm around the CTV is required to define each respective PTV.
It is advised that extreme bladder or rectal filling not be present at the time of the planning CT scan. A distended bladder or rectum can introduce a systematic error that may increase the probability of missing the CTV.

**6.3.5.4** The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

**6.3.5.5** Critical Normal Structures
The normal tissue volume to be contoured will include bladder, rectum, bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, and the rectum from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints. Large and small bowel in the pelvis below the L4-5 interspace need to be contoured in the event that IMRT is used. The tissue within the skin and outside all other critical normal structures and PTVs is designated as unspecified tissue. See the ITC web site to view examples of target and normal tissue contours.

The following table summarizes the naming of organs.

| Standard Name | Description |
|---|---|
| **BLADDER** | Bladder |
| **CTV** | Clinical Target Volume |
| **FEMUR_LT** | Left Femur |
| **FEMUR_RT** | Right Femur |
| **GTV** | Gross Tumor Volume (Prostate) |

| | |
|---|---|
| **PENILE_BULB** | Penile Bulb |
| **PTV** | Planning Target Volume |
| **RECTUM** | Rectum |
| **SKIN** | External patient contour |
| **SEM_VES** | Seminal Vesicles |
| **PELVIC LN PTV** | Regional Lymph Nodes + 0.5-1.0 cm |

### 6.4 RT Quality Assurance Reviews

The Radiation Oncology Co-Chair, Seth Rosenthal, MD, will perform an RT Quality Assurance Review after ITC has received complete digital data for the first 25 cases enrolled. Dr. Rosenthal will perform a subsequent review after ITC has received complete digital data for the next 25 cases enrolled. The final cases will be reviewed within 3 months after the study has reached target accrual or as soon as ITC has received complete digital data for all cases enrolled, whichever occurs first. These reviews will be ongoing and reviewed via remote review tool. For further information about digital data submission logistics, see Section 12.2.1.

### 6.5 Radiation Toxicity

Adverse effects include: skin reactions; hair loss in treatment area; transitory tiredness; infertility; impotence that could be permanent; urethral scar tissue; small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, rectal bleeding, hematochezia, and bowel incontinence; bladder complications including urinary frequency, dysuria, hematuria, urinary tract infections, and urinary incontinence; injuries to the rectum, bowel, or urinary system that could result in colostomy or other major surgical procedures.

### 6.6 Radiation Adverse Event Reporting (10/4/06)

See Section 7.10 for specific adverse event reporting instructions.

## 7.0 DRUG THERAPY

**Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.**

### 7.1 Treatment (10/4/06) (04/27/07)

**Androgen suppression must begin within 6 weeks after registration**

**7.1.1** Schedule

**7.1.1.1** *Arm 1*

Patients will receive androgen suppression (AS) (LHRH agonist and oral antiandrogen).
Oral antiandrogen will be discontinued at the end of radiation therapy.
LHRH agonist will continue for 24 months from initiation.

Radiation therapy will begin 8 weeks after the initiation of hormone treatment and will be given as specified in Section 6.0. For patients who have started hormone therapy as specified in Section 3.1.12, time to radiation therapy will be counted from the start date of either the LHRH agonist or antiandrogen (or both).

**7.1.1.2** *Arm 2*

Patients will receive androgen suppression (AS) (LHRH agonist and oral antiandrogen).
Oral antiandrogen will be discontinued at the end of radiation therapy.
LHRH agonist will continue for 24 months from initiation.

Radiation therapy will begin 8 weeks after the initiation of hormone treatment and will be given as specified in Section 6.0. For patients who have started hormone therapy as specified in Section 3.1.12, time to radiation therapy will be counted from the start date of either the LHRH agonist or antiandrogen (or both).

Patients will also receive six cycles of docetaxel and prednisone chemotherapy concurrently with LHRH agonist beginning 28 days* after the completion of radiation therapy:

Docetaxel 75 mg/m$^2$ i.v. over 1 hour (on day 1 of each cycle) q 21 days
(Premedication for docetaxel with dexamethasone is required)
*AND*
Prednisone 10 mg orally per day

until day 21 of the last cycle of chemotherapy

*Note: Chemotherapy may begin up to two days early on Day 26 or up to 5 days late at Day 33.

**Caution:** Docetaxel is a moderate to significant inhibitor of the CYP3A4 enzyme. There are many prescribed medications, over the counter agents, food, alternative therapies, and herbal products that are inducers or inhibitors of CYP34A and that, if taken concomitantly with docetaxel, may significantly alter the patient's metabolizing of docetaxel. Patients should discontinue use of potential inducers or inhibitors of CYP34A at least 14 days prior to administration of docetaxel and throughout docetaxel administration. Sites should refer to the most current package insert for information concerning inducers and inhibitors of CYP34A.

Prednisone may be tapered in an individualized manner in accordance with the instructions of the medical oncologist.

**7.2 LHRH agonists (such as leuprolide, goserelin, buserelin, triptorelin) (10/4/06)**

For further information, consult the package inserts.

**7.2.1** Description: LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA (or by Health Canada for Canadian institutions) can be used in this study.

**7.2.2** Supply: Commercially available. (NOTE: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries outside of the United States.)

**7.2.3** Storage: LHRH analogs should be stored as directed by the commercial supplier.

**7.2.4** Administration: LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer's instructions should be followed.

**7.2.5** Toxicity: Consult the package insert for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances have occurred. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, and muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely allergic generalized rash and difficulty breathing.

**7.3 Eulexin (flutamide) (10/4/06) (04/27/07)**

For further information, consult the package insert.

**7.3.1** Description: Flutamide is a substituted anilide. It is a fine, light, yellow powder, insoluble in water but soluble in common organic solvents such as aromatic or halogenated hydrocarbons. Its concentration in plasma can be determined by gas chromatography. Flutamide is a nonsteroidal antiandrogen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

**7.3.2** Supply: Commercially available.

**7.3.3** Storage: Flutamide should be stored at temperatures ranging from 20-30 °C (36 °-86 °F) and protected from excessive moisture.

**7.3.4** Administration: The drug is administered orally at a dose of 250 mg (two 125-mg capsules) three times a day for a total daily dose of 750 mg. Flutamide will begin 8 weeks prior to radiotherapy and continue throughout radiotherapy. If the patient has already started LHRH therapy without flutamide or bicalutamide, flutamide or bicalutamide should be initiated after study entry and terminated on the last day of radiotherapy. Radiotherapy should begin 8 weeks after start of

LHRH therapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. See Section 7.3.6. Flutamide will be terminated on the last day of radiotherapy or on day 112, whichever occurs first. During radiotherapy interruptions, flutamide will be continued.

**7.3.5** Toxicity: Consult the package insert for comprehensive toxicity information. The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2 to 8 months. There have been post-marketing reports of hospitalization, and, rarely, death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide. Other side effects include impotence and loss of libido, fatigue, and rarely photosensitivity.

**7.3.6** Dose Modifications: If gastrointestinal disturbances *(*cramps, diarrhea) occur prior to initiation of radiotherapy, flutamide will be withheld until the side effects subside; the drug will then be reintroduced at a dose of 250 mg/day and increased (at 3-day intervals) to 500 mg/day and then to 750 mg/day as tolerated. If gastrointestinal disturbances occur after administration of radiotherapy, it might be difficult to identify their cause. However, if severity of diarrhea exceeds the level commonly observed during pelvic irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued. ALT will be measured pretreatment, then monthly during oral antiandrogen therapy. If ALT increases ≥ 2 x upper institutional limit of normal, flutamide must be discontinued.

## 7.4 Casodex (bicalutamide) (10/4/06) 04/27/07)

For further information, consult the package insert.

**7.4.1** Description: Bicalutamide is a nonsteroidal antiandrogen, which has no androgenic or progestational properties. The chemical name is propanamide, N-[4-cyano-3(trifluoromethyl)phenyl]- 3- [(4-fluorophenyl)sulphonyl]- 2- hydroxy- 2- methyl, (+,-). Bicalutamide is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or R-enantiomer. Bicalutamide has a long half-life compatible with once-daily dosing. Bicalutamide is well tolerated and has good response rates in phase II trials (Kennealey and Furr, 1991, Tyrrell 1994).

**7.4.2** Supply: Commercially available.

**7.4.3** Storage: Bicalutamide should be stored in a dry place at room temperature between 68°-77°F.

**7.4.4** Administration: Bicalutamide is administered orally at a dose of one 50 mg tablet per day. Bicalutamide will begin 8 weeks prior to radiotherapy and continue throughout radiotherapy. If the patient has already started LHRH therapy without bicalutamide or flutamide, bicalutamide or flutamide should be initiated after study entry and terminated on the last day of radiotherapy. Radiotherapy should begin 8 weeks after start of LHRH therapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. Bicalutamide will be terminated on the last day of radiotherapy or on day 112, whichever comes first. During radiotherapy interruptions, bicalutamide will be continued.

**7.4.5** Toxicity: Consult the package insert for comprehensive toxicity information. In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with bicalutamide during pregnancy. Although offspring from male animals dosed with bicalutamide did not show any birth defects, patients enrolled in this trial are advised not to cause pregnancy nor donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised. The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. When bicalutamide 50 mg was given in combination with an LHRH analog, the LHRH analog adverse event profile predominated with a high incidence of hot flashes (53%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%). Other side effects include impotence and loss of libido, fatigue, and rarely photosensitivity and diarrhea.

**7.4.6** Dose Modifications*:* Bicalutamide should be discontinued in instances of chemical liver toxicity. ALT will be measured pretreatment and then monthly during antiandrogen therapy. If the ALT rises ≥ 2 x the institutional upper limit of normal, bicalutamide must discontinued.

## 7.5 Taxotere (docetaxel) (10/4/06)

For further information, consult the package insert.

**7.5.1** Description: Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the needles of the European Yew tree. The chemical name is (2R, 3S)-N-carboxy-3-phenylisoserine, N-tert butyl ester, 13-ester with 5β-20-epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax -11 -en-9-one 4-acetate 2-benzoate trihydrate. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. Its effect is due to disruption of the microtubular network in cells that is required for mitotic and interphase cellular functions. After intravenous injection, it has a terminal half-life of 11.1 hours. It is metabolized in the liver, and metabolites and small amounts of unchanged drug are excreted through both the feces (75%) and urine (6%).

**7.5.2** **Supply (11/15/06) (5/15/08)**

**U.S. institutions** must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) and fax the form to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **International institutions** (non-Canadian institutions that submitted an approved LOI) must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300).

**Note**: **Canadian institutions** must use the Canadian SASF, which can be accessed in the Canadian Information Section on the RTOG web site, at http://www.rtog.org/members/CanadaInfo/0521/0521drug_request.html. The Canadian SASF must be submitted to RTOG Headquarters with documentation of IRB approval (Fax 215-574-0300).

This must be done prior to registration of the institution's first case. Institutions should allow adequate time (7-10 days) to process the form before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment.

The SASF for U.S. and International institutions for this study is available on the RTOG web site, http://www.rtog.org, next to the protocol.

**7.5.2.1** **U.S.: (7/28/09)** Docetaxel is being supplied free of charge to patients entered into this trial in U.S institutions. The drug will be distributed by a vendor, Biologics, Inc., under contract to RTOG.

The investigator, or a responsible party designated by the investigator must maintain a careful record of the inventory and disposition of all drug received using the 0521 Drug Accountability Record Form (DARF). The Study Agent Shipment Form must be submitted electronically to <<RTOGDRUG@acr-arrs.org>> as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case.

*For those institutions with cases already registered:*

The Taxotere supply will not be shipped by Biologics until the patient has been registered and Biologics has received the drug shipment form. Biologics generally ships drug Monday through Thursdays. **Biologics does not ship drug prior to weekends or holidays.** RTOG will notify Biologics to initiate each of these shipments. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date. At the close of the study, unused, unopened non-expired drug marked clearly with the institution number of the site returning the agent and the quantity being returned should be returned to Biologics. All other drug can be destroyed or disposed of at the site according to institutional policy. The equivalent of a faxed or mailed memo or email from the responsible party to Biologics specifying this was done with the institution number and quantity destroyed included will be required. In a case where drug expires and requires replacing, the drug can be destroyed on site and reordered through the normal reorder procedure noting the re-supply is to replace the destroyed expired drug.

Additional questions about supply and delivery should be directed to:

Karl Buer, Clinical Trial Project Manager
Biologics, Inc.
120 Weston Oaks Court
Cary, NC 27513-2256

**7.5.2.2** **Canada:** Docetaxel is being supplied free of charge to Canadian institutions.
*Distribution:* Canadian institutions must complete the *"Request for Clinical Medication by Fax"* form included in the Health Canada study approval broadcast. The form must be faxed to RTOG Headquarters at 215-574-0300 prior to registering the first patient. Headquarters will fax the completed form to Sanofi-Aventis once all regulatory documents are received. Please allow one week prior to registering your first case to receive your shipment. Sanofi-Aventis will ship medication and shipping documents via Purolator courier to the site pharmacist. The site pharmacist will need to confirm receipt of the medication shipment by signing and dating one copy of the shipping documents and returning it to Sanofi-Aventis in the pre-addressed and postage paid envelope provided with the shipment.
*Re-supply:* To receive docetaxel re-supply, complete the *"Request for Clinical Medication"* form included in each drug shipment and fax it to Sanofi-Aventis as per the instructions on the form.
*Destruction:* All docetaxel vials must be destroyed at the site, at a locally authorized facility for this type of product. Supporting documents such as facility's certification and documentation of the method of destruction will have to be collected. The investigator is responsible for maintaining documentation describing the amount of investigational product provided by Sanofi-Aventis, as well as the amount of product that is dispensed and destroyed. Discrepancies in product accountability must be explained and documented.

**7.5.3** Storage and Stability: Docetaxel powder should be stored between 2º and 25ºC (36 and 77ºF). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

**7.5.4** Administration: Dosage per schedules in Section 7.1.1. Docetaxel is administered through an intravenous infusion over 1 hour. Preparation is per the docetaxel package insert. Docetaxel is an irritant; treating investigators should follow their institutional protocol for management of extravasations.

**7.5.5** Toxicity: Consult the package insert for comprehensive toxicity information.
*Hematologic*: Neutropenia (virtually in 100% of patients given 100 mg/m$^2$) leukopenia, thrombocytopenia, anemia, febrile neutropenia
*GI*: Nausea and vomiting, diarrhea, stomatitis, abdominal pain, constipation, ulcer, esophagitis, GI hemorrhage, intestinal obstruction, ileus, loss of appetite, taste changes.
*Heart*: Fluid retention (even with premedication), hypotension, atrial fibrillation, DVT ECG abnormalities, thrombophlebitis, pulmonary embolism, heart failure syncope, tachycardia, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, hypertension (rare), hypotension (rare).
*GU*: Blood in urine (rare).
*Respiratory*: Dyspnea, acute pulmonary edema, ARDS
*Dermatologic*: Reversible cutaneous reactions characterized by a rash, including localized eruptions on the hands, feet, arms, face, or thorax, and usually associated with pruritus; hives; nail changes, alopecia
*Hypersensitivity*: Flushing, localized skin reactions, severe hypersensitivity reactions characterized by hypotension, bronchospasm, or generalized rash/erythema
*Musculoskeletal*: Myalgia, arthralgia, muscle cramps, muscle weakness.
*Neurologic*: Paresthesia, dysesthesia, pain in patients with anthracycline-resistant breast cancer; distal extremity weakness
*Reactions at infusion site*: Hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, mild swelling of the vein
*Miscellaneous*: Septic death, nonseptic death infections, fever in absence of infections, asthenia, diffuse pain, chest pain, renal insufficiency, confusion, sweating, chills, headache, weight gain, dizziness, depression, seizures, swelling in arms and legs, glaucoma and/or cataracts, decreased vision, vision changes, eye irritation, conjunctivitis, excessive lacrimation, slow wound healing, risk of developing leukemia requiring treatment (rare).

**7.5.6** Dose Modifications

**7.5.6.1** *Hematologic toxicities*: Dosage modification for docetaxel is based on docetaxel treatment day granulocyte and platelet counts. Treatment day counts may be obtained on the day before or day of treatment. Dose modification is for the next cycle and all subsequent cycles. Docetaxel must

not be administered until granulocyte count is ≥ 1,500 cell/mm$^3$ and platelet count ≥100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below If toxicity does not resolve by Day 21 of cycle or within 21 days of toxicity, discontinue protocol chemotherapy.

**% Calculated Dose**

| | | **Platelet Count** | | | |
|---|---|---|---|---|---|
| | | > 150K | 100-149K | 75-99K | < 75K |
| **ANC (x 1000)** | ≥ 1.5 | 100% | 100% | 75% | 50% |
| | 1.0 - 1.499 | 75% | 75% | 75% | 50% |
| | < 1.0 | 50% | 50% | 50% | 50% |

**7.5.6.2** *Elevated liver function tests*: Docetaxel should generally not be given to patients with bilirubin > upper limit of normal (ULN) or to patients with AST (SGOT) and/or ALT (SGPT) >1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia but do not have an increased incidence of toxic death. Bilirubin, AST (SGOT) or ALT (SGPT), and alkaline phosphatase values should be obtained prior to each cycle of docetaxel therapy and reviewed by the treating physician. Both AST and ALT should be drawn. The more abnormal of the two values (AST or ALT) should be used in determining the dose.

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

*****Hold until recovered, maximum 21 days, and then re-treat at a reduced dose (reduce docetaxel dose by 25%) for all subsequent cycles in that patient. For reduced dose noted in above chart, use a docetaxel dose reduction of 25%.

**7.5.6.3** *Neuropathy*: The docetaxel dose should be reduced by 25% for grade 2 neuropathy, without treatment delay. Treatment should be discontinued for grade 3/4 neuropathy.

**7.5.6.4** *Stomatitis:* If any grade stomatitis is present on day 1 of any cycle, treatment should be withheld until stomatitis has completely resolved. If grade 3/4 stomatitis occurs at any time, the dose of docetaxel should be reduced by 25% for subsequent cycles.

**7.5.6.5** *Hypersensitivity reactions:* There are no dose reductions for hypersensitivity reactions.

MANAGEMENT OF ACUTE HYPERSENSITIVITY

| Severity of Symptoms | Treatment Guidelines |
|---|---|
| **Mild** symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash | ▪ Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient.<br>▪ Then, complete docetaxel infusion at the initial planned rate. |
| **Moderate** symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg | ▪ Interrupt docetaxel infusion.<br>▪ Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms.<br>▪ Resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the patient, Docetaxel infusion should be resumed at a slower rate, then increased incrementally to the |

| | |
|---|---|
| | initial planned rate (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the initial planned rate).<br>▪ Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate (e.g., infuse at an 8- hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, and finally, administer at the initial planned rate). |
| **Severe** symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80 mm Hg, angioedema | ▪ Immediately discontinue docetaxel infusion<br>▪ Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms<br>▪ The same treatment guidelines outlined under moderate symptoms (i.e., the third and fourth bullets) should be followed. |
| **Anaphylaxis** (NCI grade 4 reaction) | ▪ NO FURTHER STUDY DRUG THERAPY |

**7.5.6.6** *Fluid retention:* There are no dose reductions for fluid retention.
Patients developing new-onset edema, progression of existing edema, or another sign of fluid retention (e.g., 2-pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below.

- Triamterene/hydrochlorothiazide one capsule po qd up to tid.
- Furosemide 40 mg po daily if edema progresses despite triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
- If after a 2-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response, and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

**7.5.6.7** *Other non-hematologic toxicities:* For other grade 3 and 4 toxicities, treatment should be withheld until the toxicity resolves to grade 1 or less, then restarted (if medically appropriate) with a 25% dose reduction.

**7.6 Prednisone (10/4/06) (04/27/07)**
For further information, consult the package insert.

**7.6.1** Description: Corticosteroid, naturally occurring; glucocorticoid-type; short-acting; t1/2: 80-118 min

**7.6.2** Supply: Commercially available.

**7.6.3** Storage: Store at room temperature.

**7.6.4** Administration: Dosage per schedules in Section 7.1.1

**7.6.5** Toxicity Consult the package insert for comprehensive toxicity information.
*Heart*: Sodium retention, fluid retention, CHF in susceptible patients, hypertension, myocardial rupture following recent myocardial infarction
*Musculoskeletal*: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rupture
*GI*: Fluid and electrolyte disturbance, potassium loss, hypokalemic alkalosis, negative nitrogen balance due to protein catabolism, peptic ulcer with possible perforation and hemorrhage, perforation of the

small and large bowel (particularly in patients with inflammatory bowel disease), pancreatitis, abdominal distention, ulcerative esophagitis
*Dermatologic*: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, increased sweating, may suppress reactions to skin tests, other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic edema
*Neurologic*: Convulsions, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, vertigo, headache, psychic disturbances
*Hormonal*: Development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics; hirsutism
*Ophthalmic*: Posterior sub capsular cataracts, increased intraocular pressure, glaucoma, exophthalmos
*Hypersensitivity*: Thromboembolism, weight gain, increased appetite, nausea, malaise.

**7.6.6** Dose Modifications: There are no dose modifications for prednisone but tapering post-chemotherapy completion is at the discretion of the treating oncologist.

### 7.7 Dexamethasone (10/4/06)

For further information, consult the package insert.

**7.7.1** Description: Corticosteroid, naturally occurring; glucocorticoid-type.

**7.7.2** Supply: Commercially available.

**7.7.3** Storage*:* Store at room temperature.

**7.7.4** Administration: To reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reaction, premedication with dexamethasone per institutional standard is required for all patients receiving docetaxel therapy. .

**7.7.5** Toxicity Consult the package insert for comprehensive toxicity information.
*Heart*: Hypertension
*Musculoskeletal*: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis
*GI*: Weight gain, increase in appetite
*Dermatologic*: Impaired wound healing
*Neurologic*: Mood changes, difficulty sleeping
*Hormonal*: Addison's disease; increased blood sugar content, possibly resulting in diabetes
*Ophthalmic*: Cataracts, glaucoma
*Other:* Increased risk of infection

**7.7.6** Dose Modifications: There are no dose modifications for dexamethasone

### 7.8 Criteria for Removal From Protocol Chemotherapy (10/4/06)

- Progression of disease;
- Unacceptable toxicity (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form;
- Toxicities identified in Section 7.5.5 that do not resolve by day 21 of cycle or within 21 days of toxicity;
- A delay in chemotherapy > 16 weeks;
- The patient may withdraw from study treatment at any time for any reason and still be followed per protocol. The institution must notify RTOG Headquarters Data Management about this in writing and follow the guidelines set forth in the RTOG procedure manual.

### 7.9 Modality Review (04/27/07)

The Medical Oncology Co-Chair, Oliver Sartor, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **per protocol**; **variation, acceptable**; **deviation unacceptable**; **not evaluable for chemotherapy review,** or, **incomplete chemotherapy**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Sartor will perform a Quality Assurance Review after complete data for the first 50 cases enrolled have been received at RTOG Headquarters. Dr. Sartor will perform the next review after complete data for the next 50 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received at RTOG Headquarters, whichever occurs first.

## 7.10 Adverse Events (5/15/08) (7/28/09) (8/18/10)

**Beginning October 1, 2010**, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for reporting of all adverse events. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

**In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF).** In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

### 7.10.1 Adverse Events (AEs)

**Definition of an AE**: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.11 also must be reported via AdEERS.**

**NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.**

### 7.10.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

**Definition of an SAE:** Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

**All supporting source documentation indicated as being provided in the Additional Information**

**Section of the AdEERS Report must be properly labeled with the study/case numbers and the Date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS.** Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

**SAE reporting is safety related and separate and in addition to the Data Management reporting requirements** as outlined in the previous AE reporting section. **Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

### 7.10.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

| RTOG Headquarters |
|---|
| AML/MDS Report |
| 1818 Market Street, Suite 1600 |
| Philadelphia, PA 19103 |

## 7.11 AdEERS Expedited Reporting Requirements (5/15/08)

CTEP defines routine AE reporting requirements for phase 1 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate Case report form (see Section 12.1).

**Phase 3 Trials** Utilizing a Commercially Available Agent: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Agent

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

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

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

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

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

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

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.**

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

## 8.0 SURGERY

### 8.1 Prostate Rebiopsy

**8.1.1** A biopsy will be performed for all patients with evidence of biochemical failure (protocol defined) or growth of a palpable abnormality.

**8.1.2** Biopsies are strongly recommended for patients with evidence of distant failure to assist in accurately determining the "true" local control rate. In the absence of a biopsy, such patients will be considered local failures if their exam is abnormal. If their exam is normal or if they are post orchiectomy they will be censored at the last point in time they were considered locally controlled and considered "not evaluable" for further assessment of local control.

## 9.0 OTHER THERAPY

### 9.1 Permitted Supportive Therapy

**9.1.1** Antiemetics: Please refer to current ASCO guidelines for antiemetic regimens regarding the use of docetaxel.

### 9.2 Non-Permitted Supportive Therapy

**9.2.1** Aprepitant

## 10.0 TISSUE/SPECIMEN SUBMISSION (04/27/07) (5/15/08) (7/28/09)

### 10.1 General Information

The RTOG Biospecimen Resource at the University of San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue will be submitted to the RTOG tissue bank for the purpose of tissue banking for biomarker studies (highly recommended but not required).

Biomarker studies are being done on all RTOG prostatic cancer protocols using the original diagnostic material. The emphasis has been on proliferation markers (e.g., DNA-ploidy, Ki-67), apoptotic pathway markers (e.g., p53, MDM2, bcl-2, bax, p16), and angiogenesis markers (e.g., COX-2, VEGF). These markers have shown promise in predicting prostate cancer patient outcome after definitive radiotherapy. A final decision on which markers will be studied awaits the results of completed RTOG prostate cancer trials that have reached maturity (e.g., 86-10, 92-02, 94-13). The trial described here will not be ready for biomarker analysis for several years, with the exception of the Abeta analysis, which will be conducted in conjunction with cognitive outcomes. The goal is to measure approximately 5-10 biomarkers using the archived pathologic material.

Because genomic DNA for SNP analysis can be most effectively isolated from buffy coat leukocytes, these specimens will also be banked.

**10.2 Specimen Collection for Tissue Banking for Biomarker Studies: Strongly Recommended**
**For patients who have consented to participate in the tissue/blood component of the study (See Appendices VI and VII).**

**10.2.1** Sites may submit the following specimens:

**10.2.1.1** A paraffin-embedded tissue block of the tumor (preferred). If tumor heterogeneity is observed, the submission of multiple blocks, including tissue from the area having the highest Gleason score, is desirable. If the block cannot be obtained, the tissue to be submitted depends upon specimen type and must be submitted as follows:

- **If the specimen is a prostate needle core biopsy and the block cannot be obtained**, then submit 10-15 unstained slides (please use charged or "Plus" slides) from the block of the tumor.
- **If the specimen is a TURP and the block cannot be obtained**, then either a 2-mm diameter core of tumor tissue, punched from the tissue block containing tumor using a skin punch (preferred) and submitted in a plastic tube labeled with the surgical pathology number (see Appendix VI for punch kit instructions), **OR** 10-15 unstained slides (please use charged or "Plus" slides) from the block of the tumor.
- Tissue block, punch, or unstained slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

- A Pathology Report documenting that the submitted paraffin tissue block specimen contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

**10.2.1.2** Serum, plasma, and buffy coat cells

See Appendix VII for the blood collection kits and instructions. See Section 10.2.1.3 for Specimen Collection Summary.

The following must be provided in order for the case to be evaluable for the Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, and buffy coat cells; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included.

**10.2.1.3** Specimen Collection Summary

| **Specimens for Tissue Banking** | | | |
|---|---|---|---|
| **Specimens taken from patient:** | **Specimens collected when:** | **Submitted as:** | **Shipped:** |
| A paraffin-embedded tissue block (preferred) of the primary tumor taken before initiation of treatment; **or** if needle core biopsy: 10-15 unstained slides; **or** if TURP: a 2 mm diameter core of tissue, punched from the tissue block with a skin punch *or* 10-15 unstained slides | From pretreatment biopsy | Paraffin-embedded tissue block or 10-15 unstained slides (on "plus" slides) | Block or unstained slides shipped ambient |
| 5-10 mL of whole blood in red-top tube and centrifuge for serum | Pretreatment | Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials | Serum sent frozen on dry ice via overnight carrier |

| | | | |
|---|---|---|---|
| 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for plasma | Pretreatment | Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials | Plasma sent frozen on dry ice via overnight carrier |
| 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat | Pretreatment | Frozen buffy coat samples in 1 mL cryovials | Buffy coat sent frozen on dry ice via overnight carrier |
| 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat | Week 4 of RT treatment | Frozen buffy coat samples in 1 mL cryovials | Buffy coat sent frozen on dry ice via overnight carrier |
| 5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat | *Next follow-up treatment visit | Frozen buffy coat samples in 1 mL cryovials | Buffy coat sent frozen on dry ice via overnight carrier |

*For patients enrolled on study prior to Amendment 3 (protocol Version Date April 27, 2007) and who have signed the consent form for blood banking.

**10.2.2** Submit materials for Tissue Banking:

**U. S. Postal Service Mailing Address: <u>For Non-Frozen Specimens Only</u>**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**Campus Box 1800**
**San Francisco, CA 94143-1800**

**Courier Address (FedEx, UPS, etc.): <u>For Frozen Specimens</u>**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**1657 Scott Street, Room 223**
**San Francisco, CA 94115**

**Questions: 415-476-RTOG (7864)/Fax 415-476-5271**
**rtog@ucsf.edu**

## 10.3 Reimbursement

RTOG will reimburse submitting institutions $300 per specimen for buffy coat cells, serum, and plasma; $200 per case for a block of material; and $100 per case for 10-15 slides. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

## 10.4 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

**10.4.1** Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

**10.4.2** Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

## 11.0 PATIENT ASSESSMENTS

### 11.1 Study Parameters (04/27/07) (5/15/08)

| Parameters | Pre-Study Entry | During Androgen Suppression | At the Completion of Radiotherapy | Prior to Chemotherapy (post RT) | During Chemotherapy | Follow-Up |
|---|---|---|---|---|---|---|
| H&P | X | | | X | | X |
| Weight & Performance Status | X | | X | X | X[a] | X[d] |
| CBC, Platelets | X | | | X | X[a] | |
| Chemistry | X[b] | X[b] | | X[g] | X[g] | |
| Testosterone | X | | | X | | X[h] |
| PSA | X | | | X[d] | | X[d] |
| Bone Scan | X | | | | | X[c] |
| Pelvic CT or other lymph node assessment | X | | | | | |
| Toxicity Assessment | | X[d] | X | X | X | X[d] |
| Prostate Biopsy | X[e] | | | | | X[f] |

a. CBC and platelets* on days 8, 15 and 21; weight and performance status every 3 weeks during chemotherapy. *Note: Institutions should follow their own standard procedures regarding the frequency of obtaining these assessments.
b. Serum ALT, AST, alkaline phosphatase, and bilirubin at baseline and every month during oral antiandrogen therapy.
c. As clinically indicated (see Section 11.2.3) and every 6 months after PSA progression.
d. 4 months and 7 months from the initiation of androgen suppression, then every 3 months x 4 (until the end of year 2), then every 6 months for 3 years, then annually.
e. Must include Gleason score, number of cores obtained, and number of positive cores.
f. A biopsy will be performed for all patients with evidence of biochemical failure or growth of a palpable abnormality (see Section 8.0).
g. Serum ALT, AST, alkaline phosphatase, and bilirubin on day 1 of each cycle of chemotherapy.
h. Testosterone with PSA frequency (see note d), until it reaches institutional normal range or salvage hormone therapy is started.

### 11.2 Follow-Up Schedule

**11.2.1** At the end of RT (4 months), at 7 months, then every 3 months (until the end of year 2).

**11.2.2** Every 6 months for 3 years, then annually for the remainder of the patient's life.

**11.2.3** A bone scan will be performed on any patient with complaints of bone pain that cannot be attributed to any intercurrent disease. Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease. See 11.1 for bone scan interval after PSA progression.

### 11.3 Measurement of Effect

**11.3.1** All PSA levels done during a follow-up interval will be recorded on the data forms.

**11.3.2** After study entry, disease activity evaluations will be made and recorded using the following criteria:

**11.3.2.2** Clinical Complete Response: A clinical complete response will be declared if there is a complete resolution of all palpable abnormalities. *Note*: patients with non-palpable lesions will not be considered in this category.

**11.3.2.3** Progressive Disease: This rating will be assigned when there is clinical evidence in the prostate gland of disease progression or recurrence measured by a 25% or greater increase in the product of the two largest perpendicular diameters of the prostate.

### 11.4 Other Response Parameters

**11.4.1** *Freedom from Biochemical (PSA) Failure*: The time to PSA failure will be measured from the date of randomization to the date of a rise by 2 ng/ml or more above the nadir PSA. Nadir PSA

is defined as the lowest PSA value after randomization and before the call date PSA. That is, the time of failure will be the date of the first PSA that is 2 ng/ml or more above the lowest prior post-randomization PSA value.

**11.4.2** *Time to Local Progression*: The time to progression will be measured from the date of randomization to the date of documented local progression. Patients who have a normal exam and no evidence of having a PSA failure will be considered controlled locally. Patients with a residual abnormality or a PSA failure shall undergo biopsy to distinguish between local and distant failures. If their exam is normal or if they are post orchiectomy, they will be censored at the last point in time they were considered locally controlled and considered "not evaluable" for further assessment of local control.

**11.4.3** *Time to Distant Failure*: The time to distant failure will be measured from the date of randomization to the date of documented metastatic disease. Patients with evidence of PSA failure but a negative biopsy will be considered to have experienced only a distant failure.

**11.4.4** *Disease-Free Survival*: The progression-free survival will be measured from the date of randomization to the date of documentation of progression or until the date of death. This endpoint includes all measures of disease including physical exam, PSA, bone scans and biopsies.

**11.4.5** *Survival*: The survival time will be measured from the date of randomization to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death. Post-mortem examination will be carried out when feasible and a copy of the final autopsy report should be sent to RTOG.

## 12.0 DATA COLLECTION

**Data should be submitted to:**

**RTOG Headquarters**
**1818 Market Street, Suite 1600**
**Philadelphia, PA 19103**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

### 12.1 Summary of Data Submission (10/4/06)

| Item | Due |
|---|---|
| Demographic Form **(A5)** | Within 2 weeks of registration |
| Initial Evaluation Form **(I1)** | Within 2 weeks of registration |
| Pathology Report **(P1)** | Within 2 weeks of registration |
| Slides/Blocks **(P2)** | Within 2 weeks of registration |
| Treatment Form **(TF)**<br>Adverse Event Form **(AE)**<br>If corresponding **TF** indicates an adverse event | After each cycle of chemotherapy and 30 days post-chemotherapy |
| Initial Follow-Up Form **(F0)**<br>Adverse Event Form **(AE)**<br>If corresponding **FO** indicates an adverse event | 4 months from initiation of hormone therapy (with T1 form) |
| Interim Follow-Up Form **(FS)**<br>Adverse Event Form **(AE)**<br>If corresponding **FS** indicates an adverse event | 8 months after initiation of hormone therapy, then every 3 months (until the end of year 2) |
| Follow-Up Form **(F1)**<br>Adverse Event Form **(AE)**<br>If corresponding **F1** indicates an adverse event | Beginning year 3: every 6 months x 3 years, then annually |

## 12.2 Summary of Dosimetry Data Submission for 3DCRT and IMRT (5/15/08)

***Submit to ITC; see Section 12.2.1***

| Item | Due |
|---|---|
| **Preliminary Dosimetry Information**<br>▪ Digital Data Submission Form **(DDSI)**<br>▪ CT data, critical normal structures, all GTV, CTV, and PTV contours<br>▪ Simulation films and/or digital film images for all initial treatment fields and orthogonal set up pair<br>▪ First day port films (or digital images) of all initial treatment fields and orthogonal set up pair<br>▪ Digital beam geometry for initial and boost beam sets<br>▪ Doses for initial and boost sets of concurrent treated beams<br>▪ Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan<br>▪ Hard copy color isodose distributions for total dose plan as described in QA guidelines | Within 1 week of start of RT |

| Item | Due |
|---|---|
| **Final Dosimetry Information**<br>▪ Radiotherapy Form **(T1) [copy to HQ and ITC]**<br>▪ Adverse Event Form (AE) if **T1** indicates an adverse event<br>▪ Daily Treatment Record **(T5) [copy to HQ]**<br>▪ Simulation films and/or digital film images (or digital images) of all boost treatment fields and orthogonal set up pair<br>▪ First day port films of all boost treatment fields and orthogonal set up pair<br>▪ Modified digital patient data as required through consultation with Image Guided Therapy QA Center | Within 1 week of RT end |

**12.2.1** *Digital Data Submission to ITC*

Digital data submission may be accomplished using magnetic tape or the Internet.

For network submission: The FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

**itc@castor.wustl.edu**

For tape submission: Please contact the ITC about acceptable tape types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)**
**ATTN: Roxana Haynes**
**4511 Forest Park, Suite 200**
**St. Louis, MO 63108**
**314-747-5415**
**FAX 314-747-5423**

## 13.0 STATISTICAL CONSIDERATIONS (10/4/06) (04/27/07)

### 13.1 Study Endpoints

**13.1.1** *Primary Endpoint*

- Overall survival:

**13.1.2** *Secondary Endpoints*

- Biochemical control (freedom from PSA failure)
- Local control
- Freedom from distant metastases
- Disease-free survival
- Incidence of adverse events
- The time interval between biochemical failure and distant metastases with respect to testosterone level
- Validity of PSA-defined endpoints as a surrogate for overall survival
- To collect paraffin-embedded tissue block, serum, plasma, and buffy coat cells for future translational research analyses

### 13.2 Sample Size

**13.2.1** *Stratification and Randomization*: Patients will be stratified before randomization according to risk group (see Schema). The risk group is the combination of Gleason score, PSA, and tumor stage. The treatment allocation scheme described by Zelen [41] will be used because it balances patient factors other than institution. Patients will be randomized to androgen suppression (AS) (LHRH agonist and oral antiandrogen) + radiation therapy (RT) (72.0-75.6 Gy) with concurrent AS (LHRH agonist and oral antiandrogen) [Arm 1] or to AS (LHRH agonist and oral antiandrogen) + RT (72.0-75.6 Gy) with concurrent AS (LHRH agonist and oral antiandrogen) followed by chemotherapy with docetaxel and prednisone [Arm 2]. AS and RT will be given and delivered identically both to patients in Arm 1 and Arm 2.

**13.2.2** *Sample Size Derivation*: The sample size calculations will address the specific primary hypothesis that the overall survival rate of Arm 2 is higher than that of Arm 1. Assume an exponential survival distribution for each arm and define $\lambda_1$ is the hazard rate for Arm 1 and $\lambda_2$ is the hazard rate for Arm 2. ($H_A$: $\lambda_1 > \lambda_2$ ). The clinical experience from RTOG 9202 with a similar patient group showed a 4-year overall survival rate of 86% in patients treated with 2 years of androgen deprivation following RT and concurrent hormones. Based on the result of RTOG 9202, we assume the control arm (i.e., Arm 1, patients treated with AS and RT alone) will have a 4-year overall survival rate of 86%, which translates to a yearly hazard rate of 0.0377.

The study is designed to show an absolute improvement of 7% in the 4-year overall survival rate (i.e., a 4-year overall survival rate of 93%), which translates to a yearly hazard rate of 0.018 in Arm 2). Assuming an exponential distribution for overall survival and using a group sequential design for early rejection of either the null or alternative hypotheses, four interim analyses and a final analysis are planned based on alpha and beta spending function boundaries that were chosen to be conservative to stop early for efficacy and aggressive to stop early for futility; 78 deaths are required to detect a 51% relative reduction in the yearly death rate with 90% statistical

power using a one-side log-rank test at the 0.05 significance level. Using the projected hazard rate for the control arm, a total sample size of 486 cases accrued uniformly over 5 years with an additional 4 years of follow-up will be required. Guarding against an ineligibility and dropout rate overall of 10%, **the final targeted accrual for this study will be 600 patients**.

**13.2.3** *Power Calculations for Secondary Endpoints*

**13.2.3.1** Biochemical control: The clinical experience from RTOG 9202 showed a 4-year biochemical control rate as first failure of 72% in patients treated with 2 years of androgen deprivation following RT and concurrent hormones. Based on RTOG 9202, we project a 42.9% relative reduction in the yearly biochemical failure rate (or a hazard ratio of 1.75) for patients in Arm 2. This translates to a 4-year biochemical control rate as first failure of 72% (a hazard rate of 0.082) in Arm 1 and 82% (a hazard rate of 0.047) in Arm 2. With 486 analyzable patients, we would have at least 96% statistical power of detecting at least a 42.9% relative reduction in the yearly biochemical failure rate using a one-sided log-rank test at the 0.05 significance level for patients in Arm 2.

**13.2.3.2** Local control: The clinical experience from RTOG 9202 showed a 4-year local control rate as first failure of 96.9% in patients treated with 2 years of androgen deprivation following RT and concurrent hormones. Based on this result, we project a 4-year local control rate as first failure of 96.9% (a hazard ratio of 0.00787) in Arm 1 and 98.4% (a hazard rate of 0.00393) in Arm 2. With 486 analyzable patients, we would have 40% statistical power of detecting a 50% relative reduction in the yearly local failure rate (or a hazard ratio of 2.0) using a one-sided log-rank test at the 0.05 significance level for patients in Arm 2.

**13.2.3.3** Freedom from distant metastases: The clinical experience from RTOG 9202 showed a 4-year freedom from distant metastases rate as first failure of 98.3% in patients treated with 2 years of androgen deprivation following RT and concurrent hormones. Based on this result, we project a 4-year distant metastases rate as first failure of 98.3% (a hazard rate of 0.00428) in Arm 1 and 99.1% (a hazard rate of 0.00214) in Arm 2. With 486 analyzable patients, we would have 27% statistical power of detecting a 50% relative reduction in the yearly distant metastases rate (or a hazard ratio of 2.0) using a one-sided log-rank test at the 0.05 significance level for patients in Arm 2.

**13.2.3.4** Disease-free survival: The clinical experience from RTOG 9202 showed a 4-year disease-free survival rate of 51.0% in patients treated with 2 years of androgen deprivation following RT and concurrent hormones. Based on this result, we project a 4-year disease-free survival rate as first failure of 51.0% (a hazard rate of 0.168) in Arm 1 and 63.9% (a hazard rate of 0.112) in Arm 2. With 486 analyzable patients, we would have at least 95% statistical power of detecting at least a 33.3% (or a hazard rate of 1.5) relative reduction in the yearly disease progression rate using a one-sided log-rank test at the 0.05 significance level for patients in Arm 2.

## 13.3 Patient Accrual

Based on patient accrual in previous RTOG randomized prostate studies, there will be relatively few entries during the initial 6 months while institutions are obtaining IRB approval. The RTOG Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually following this anticipated quiet period. The patient accrual is projected to be about 11 cases per month based on RTOG 9902. We expect to complete the accrual in 5 years. The total duration of the study is expected to be 9 years from the time the first patient is entered to the final analysis. If at 24 months after study activation the average monthly accrual between months 18 and 24 is less than 4 patients per month, the study statistician will recommend terminating the study to the RTOG DMC.

## 13.4 Analysis Plan

**All eligible patients randomized will be included in comparison of treatment arms (intent-to-treat analysis).**

**13.4.1** *Primary endpoint*: The primary endpoint is overall survival. The time of failure for overall survival will be measured from the date of randomization to the date of documented death due to any cause. The overall survival function will be estimated by the Kaplan-Meier method.[42]. We want to test whether or not the overall survival rate in Arm 2 ($\lambda_{o,2}$) is higher than that of Arm 1 ($\lambda_{o,1}$). The null and alternative hypotheses are:

$$H_0: \lambda_{o,1} \leq \lambda_{o,2} \text{ vs. } H_A: \lambda_{o,1} > \lambda_{o,2}$$

We will use the log-rank test [43,44] with a significance level of 0.05 at the final analysis to test this hypothesis. In addition, the Cox regression model[45] will be used to compare the treatment differences. Both adjusted and unadjusted hazard ratios and the respective 95% confidence interval will be computed. PSA, clinical stage, Gleason score, race, and age (as appropriate) will be adjusted for in this analysis.

**13.4.2** Secondary endpoints

**13.4.2.1** *Biochemical and local control and freedom from distant metastases:* The time of failure for secondary endpoints (such as biochemical control, local control, and freedom from distant metastases) will be measured from the date of randomization to the date of the event of interest. Specifically, time to biochemical failure is measured as the time to PSA failure measured from the date of randomization to the date of a rise by 2 ng/ml or more above the nadir PSA .In the presence of multiple endpoints of failure, the time to the first failure of any type would be the most clinically relevant endpoint to the treatment outcome and the first failure will affect subsequent endpoints. Therefore, if a patient experiences a competing event prior to the event of interest, the patient will be censored at the date of first occurrence of the competing event. The time-to-event function of these secondary endpoints will be estimated using the Kaplan-Meier method.[42] The cause-specific log-rank test,[46] which considers the presence of competing events, will be used to test whether the survival rates of each secondary endpoint in Arm 2 ($\lambda_{s,2}$) is higher than that of Arm 1 ($\lambda_{s,1}$). The null and alternative hypotheses will be tested for each secondary endpoint (biochemical control, local control, and freedom from distant metastases) with a significance level of 0.05.

$$H_0: \lambda_{s,1} \leq \lambda_{s,2} \text{ vs. } H_A: \lambda_{s,1} > \lambda_{s,2}$$

In addition, the Cox regression model [26] will be used to compare the treatment differences. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. Risk group defined as the combination of PSA, clinical stage, and Gleason score, race, and age (as appropriate) will be adjusted for in this analysis.

**13.4.2.2** *Disease-free survival:* The time of failure of disease-free survival will be measured from the date of randomization to the date of first failure (i.e., biochemical failure, local failure, distant metastases, or death due to any cause). The disease-free survival function will be estimated by the Kaplan-Meier method. We want to test whether or not the disease-free survival rate in Arm 2 ($\lambda_{D,2}$) is higher than that of Arm 1 ($\lambda_{D,1}$). The null and alternative hypotheses will be

$$H_0: \lambda_{D,1} \leq \lambda_{D,,2,} \text{ vs. } H_A: \lambda_{D,1} > \lambda_{D\,2,}$$

We will use the log-rank test with a significance level of 0.05 to test this hypothesis. In addition, the Cox regression model will be used to compare the treatment differences. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. Risk group defined as the combination of PSA, clinical stage, and Gleason score, race, and age (as appropriate) will be adjusted for in this analysis.

**13.4.2.3** *Incidence of adverse events:* Time to adverse events will be measured from the time that protocol treatment started (i.e., the start of hormones, RT, or chemotherapy) to the time of the worst severity of the adverse event. Adverse events are scored according to the Common Toxicity Criteria Adverse Event (CTCAE) version 3.0. The distribution of time to adverse events (observed severities of adverse events over time) will be estimated using the Kaplan-Meier method.[42] We want to test whether or not there is a difference in the adverse event rates between Arm 1 ($\lambda_{A,1}$) and Arm 2 ($\lambda_{A,2}$). The null and alternative hypotheses will be tested using the two-sided log-rank test with a significance level of 0.05 .

$$H_0: \lambda_{A,1} = \lambda_{A,2} \text{ vs. } H_A: \lambda_{A,1} \neq \lambda_{A,2}$$

**13.4.2.4** *The time interval between biochemical and distant failure:* A subgroup analysis of the time interval between biochemical failure and distant failure with respect to testosterone level will be done using the Cox proportional hazards model.[45] The Cox regression model will be used to compare the treatment differences. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. PSA, clinical stage, Gleason score, race, and age (as appropriate) will be adjusted for in this analysis between Arm 1 and Arm 2.

**13.4.2.5** *Validity of PSA-defined endpoints as a surrogate for overall survival*: Two definitions of biochemical failure will be evaluated in the context of this trial for the suitability as a surrogate endpoint for overall survival. Biochemical failure will be defined as: (i) protocol definition of a rise by 2 ng/ml or more above the nadir PSA (see Section 11.4.1) and (ii) a PSA doubling time of < 12 months.[47] These definitions will be tested as possible surrogate endpoint for overall

survival using Prentice's operational criteria.[48] The following list shows Prentice's operational criteria:

**Prentice's Operational Criteria**

Criterion 1: Treatment is prognostic for true endpoint
Criterion 2: Treatment is prognostic for surrogate endpoint
Criterion 3: Surrogate is prognostic for true endpoint
Criterion 4: The full effect of the treatment on the true endpoint is explained by the surrogate

If met, these criteria are sufficient to conclude that either one or both of the biochemical failure definitions are potential surrogate endpoints but might only be applicable to this study's patient population and treatment; i.e., biochemical failure is a surrogate endpoint for overall survival in patients with high-risk prostate cancer treated with AS plus RT followed by chemotherapy with a mechanism of action similar to docetaxel and prednisone. Regardless of whether the trial is negative (treatment is not prognostic for overall survival) or biochemical failure is not shown to be a surrogate endpoint in this study (Prentice's criteria are not met), the data from this study can be considered for inclusion in an appropriate meta-analysis of other prostate cancer clinical trials with a similar class of treatments and patient population.

Prentice's criteria will be tested using the Cox proportional hazards model.[45] Relative risks and 95% confidence intervals will be calculated for each criterion. For the Cox regression models, the time to overall survival will be measured from the date of randomization to the date of death due to any cause. The two definitions of biochemical failure will each be modeled as a time-dependent covariate to assess if it is prognostic for overall survival (criterion 3) and if the full effect of treatment on overall survival can be explained by the biochemical failure endpoint (criterion 4). In addition, actuarial estimates for overall survival will be calculated using the Kaplan-Meier method. This analysis will be completed if the study shows either efficacy or futility of the experimental treatment (i.e., AS and RT followed by chemotherapy with docetaxel and prednisone). Finally, the results from this analysis should be validated with an independent dataset if available.

**13.4.3** Significance Testing for Early Termination and Reporting of Efficacy and Futility

Four interim treatment comparisons will be performed for efficacy and futility of the experimental treatment. The alpha and beta spending function boundaries were user-specified. The alpha-spending function boundaries were chosen to be more conservative in rejecting the null hypothesis too early and to resemble the Lan-DeMets spending function with O'Brien-Fleming properties.[49] The beta-spending function boundaries were chosen to be more aggressive in rejecting the alternative hypothesis early. These boundaries closely resemble the Gamma spending function with a –1 parameter as described by Hwang, Shig, and DeCani.[50] At each planned interim analysis, we will test the following hypothesis for the primary endpoint with the nominal significance level, as shown in Table 1.

$$\text{Hypothesis: } H_0: \lambda_{o,1} \le \lambda_{o,2} \text{ vs. } H_A: \lambda_{o,1} > \lambda_{o,2}$$

where $\boldsymbol{\lambda_{o,1}}$ and $\boldsymbol{\lambda_{o,2}}$ are the overall survival rate for Arm 1 and Arm 2, respectively.

At each planned interim analysis, the p-value from the log-rank test assessing treatment efficacy or futility with respect to overall survival will be compared with the nominal significance level ($\boldsymbol{\alpha_n}$). The boundary for early stopping for either efficacy or futility will be computed based on the observed number of deaths according to the user-specified spending functions as described above. If the computed p-value is less than or equal to the nominal significance level boundary ($\boldsymbol{\alpha_{n1}}$), then we will stop the trial and conclude that the overall survival rate of Arm 2 is higher than that of Arm 1 (reject the null hypothesis, $H_0$). If the p-value is greater than or equal to the nominal significance level boundary ($\boldsymbol{\alpha_{n2}}$), then we will stop the trial and conclude that the overall survival rate of Arm 2 may not be higher than that of Arm 1 (reject alternative hypothesis, $H_A$), Otherwise, we will continue the trial.

**Table 1. Nominal Significance Levels ($\alpha_n$) for the Interim Analysis**

| Time for Analysis | Nominal Significance Levels | |
|---|---|---|
| Number of Deaths | Reject $H_0$ if p-value ≤ $\alpha_{n1}$ | Reject $H_A$ if p-value is ≥ $\alpha_{n2}$ |
| 31 | 0.0001 | 0.6039 |
| 43 | 0.001 | 0.4457 |
| 59 | 0.0098 | 0.1947 |
| 67 | 0.0296 | 0.1194 |

The responsible statistician will recommend to the RTOG DMC that the randomization be discontinued, if applicable, and the study be considered for early publication. Before making such a recommendation, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study are also taken into consideration with the p-value. The RTOG DMC will then make a recommendation about the trial to the RTOG group chair.

**13.4.4** Monitoring Schedule for Grade 4+ Adverse Events in Arm 2

Based on our experience in RTOG 9902, we estimated approximately 21% of the men who receive at least some of the chemotherapy regimen experienced a grade 4+ adverse event. For this study, a 20% rate of any grade 4+ adverse event ($p_t$) according to the CTCAE version 3.0 within 6 months of randomization is considered acceptable. A rate of 40% is considered unacceptable. The null hypothesis is that the chemotherapy with docetaxel is not tolerable versus the alternative hypothesis that the chemotherapy regimen is tolerable. The following hypothesis will be tested using Fleming's Multiple Testing Procedure,[51] with a significance level of 0.05 and *90% statistical power*.

$$H_0: p_t \geq 0.4 \text{ vs. } H_A: p_t \leq 0.2$$

We need **48 analyzable patients** (i.e., eligible patients with initial baseline information who had at least some of the chemotherapy with docetaxel and prednisone) from Arm 2 to ensure that the chemotherapy with docetaxel and prednisone is tolerable. We are more concerned with a false negative decision (i.e., failing to detect the increase in toxicity if it exists) than we are with a false positive decision (i.e., deciding the new regimen is more toxic, when in fact it is not). The stopping and continuation rules in Table 2 will be applied in three stages to the first eligible and analyzable 48 cases randomized to Arm 2 who received at least some chemotherapy. If at any stage, we stop and reject the alternative hypothesis and claim that the grade 4+ adverse event (any) rate may be greater than or equal to 40%, we will temporarily close the study to accrual, gather the relevant source data on the cases with a grade 4+ adverse event (any), prepare a statistical report summarizing the adverse event findings, and present the report to the radiation and medical oncology study chairs for review.

**Table 2 Stopping and Continuation Rules**

(The number of patients who have the grade 4+ adverse events in Arm 2)

| Number of Analyzable * Patients | **Stop and reject** $H_A$ **:** $p_t$ ≤ 0.2 | **Continue** |
|---|---|---|
| 16 | ≥ 7 | < 7 |
| 32 | ≥ 10 | < 10 |
| 48 | ≥ 13 | N/A |

*Analyzable patients is defined as eligible patients with baseline information who received some chemotherapy with docetaxel and prednisone.

The study chairs will review all CRFs and source documentation on the analyzed cases with grade 4+ adverse events and the statistical report summarizing the findings as soon as possible. Following the study chairs' review of data, a conference call will be scheduled with the study chairs, statistician, and RTOG group chair to discuss the findings and make a recommendation about the study. Once a recommendation is made, the responsible statistician will present the statistical report along with the recommendation to the RTOG Data Monitoring Committee (DMC)

for the Committee's consideration. The RTOG DMC will then make a recommendation about the course of action and future of the study. If at the first or second stage either of the stopping rules are not met, we will continue accrual and monitoring for grade 4+ adverse events (any type). If we continue until the last stage, we will either conclude "tolerability" or not.

**13.4.5** Interim Report to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of the adverse event by treatment arm. The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, overall survival, or secondary endpoints.

**13.4.6** Reporting the Initial Treatment Analysis

The primary hypothesis of this study is to determine if there is a clinically meaningful improvement in overall survival of patients in Arm 2 compared to that of patients in Arm 1. The analysis reporting the treatment results will be carried out after 78 deaths have been observed unless the criteria for early stopping are met. The overall survival difference between the control arm and the experimental arm will be tested using the log-rank test at a significance level of 0.05 given that the four interim analyses are carried out as described above. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; safety treatments; treatment compliance; and observed results with respect to the primary and secondary endpoints. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis (intent-to-treat analysis). In addition, exploratory analyses of treatment comparisons of overall survival, disease-free survival, biochemical control, local control, and freedom from distant metastases will be tested using the Cox proportional hazard model that includes age, race, and the stratification factors (PSA, combined Gleason score, and tumor stage). Also, where feasible, treatment comparisons with respect to overall survival, disease-free survival, biochemical control, local control, and freedom from distant metastases will be compared within each ethnic category..

**13.4.7** Inclusion of Minorities **(5/15/08)**

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of men will be examined in the interim analyses. Based on accrual statistics from RTOG 9202 and 9413 as shown in Table 3, Table 4 lists projected accrual by race/ethnicity.

**Table 3. Distribution of Race (African American vs. Non-African American) and Treatment Arm in RTOG 9413 and 9202**

| Study | Treatment Arms* | n | African American | Non-African American |
|---|---|---|---|---|
| 9413 | | | | |
| *Radiation Field* | WP RT | 641 | 153 (24%) | 488 (76%) |
| | PO RT | 638 | 176 (28%) | 462 (72%) |
| | | | | |
| *Hormone Timing* | NHT | 635 | 159 (25%) | 476 (75%) |
| | AHT | 644 | 170 (26%) | 474 (74%) |
| | | | | |
| 9202 | STAD | 761 | 92 (12%) | 669 (88%) |
| | LTAD | 753 | 105 (14%) | 648 (86%) |

*Treatment arms for RTOG 9413: WP RT = Whole Pelvis RT (Radiation Therapy) + Boost and TAS (Total Androgen Suppression); PO RT = Prostate Only RT and TAS; NHT = Neoadjuvant TAS and RT; and AHT = Adjuvant TAS and RT.

* Treatment arms for RTOG 9202: STAD = Short-term TAS (4 months) and RT; and LTAD = Long-term TAS (28 months) and RT.

**Table 4. Projected Distribution of Gender and Minorities**

| | **Gender** | | |
|---|---|---|---|
| **Ethnic Category** | **Females** | **Males** | **Total** |
| Hispanic or Latino | N/A | 18 | 18 |
| Not Hispanic or Latino | N/A | 582 | 582 |
| **Ethnic Category: Total of all subjects*** | N/A | 600 | 600 |
| | **Gender** | | |
| **Racial Category** | **Females** | **Males** | **Total** |
| American Indian or Alaskan Native | N/A | 1 | 1 |
| Asian | N/A | 3 | 3 |
| Black or African American | N/A | 102 | 102 |
| Native Hawaiian or other Pacific Islander | N/A | 2 | 2 |
| White | N/A | 492 | 492 |
| **Racial Category: Total of all subjects*** | | 600 | 600 |

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## APPENDIX I (10/4/06) (11/14/06) (04/27/07) (5/15/08)

## RTOG 0521

## A PHASE III PROTOCOL OF ANDROGEN SUPPRESSION (AS) AND 3DCRT/IMRT VS AS AND 3DCRT/IMRT FOLLOWED BY CHEMOTHERAPY WITH DOCETAXEL AND PREDNISONE FOR LOCALIZED, HIGH-RISK PROSTATE CANCER

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

**You are being asked to take part in this study because you have a prostate cancer that is at a high risk of spreading outside of the prostate.**

### Why is this study being done?

The main purpose of this study is to try to find out whether adding chemotherapy to the standard treatment for your stage of prostate cancer is more effective than the standard treatment by itself. The kind of treatment that most physicians would consider standard for this stage of prostate cancer combines radiation therapy and hormones. In this study all patients will receive both of these. In addition, half the patients will also receive chemotherapy drugs for about 4-5 months. It is hoped that chemotherapy will be found to provide additional benefit, but chemotherapy has significant side effects. The use of chemotherapy is experimental in prostate cancer; it needs to be tested to determine if it is beneficial and to find out more about the side effects of the two different treatments.

### How many people will take part in the study?

About 600 people will take part in this study.

### What will happen if I take part in this research study?

**Before you begin the study …**

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

- Bone scan
- CT or MR scan of the pelvis
- Blood tests (PSA, testosterone, liver tests, blood count):
  About 2 teaspoons of blood will be drawn from a vein or, if you have one, a catheter

**During the study …**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Blood tests (PSA and testosterone):
  About 2 teaspoons of blood will be drawn from a vein or, if you have one, a catheter. Your PSA will be measured at 4 and 7 months after you begin hormone therapy, and your testosterone level will be measured at 4 months after you begin hormone therapy.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Blood tests (Liver enzyme testing and blood counts):
  About 2 teaspoons of blood will be drawn from a vein or, if you have one, a catheter. Your liver enzymes will be measured on the first day of each docetaxel cycle. Your blood counts will be measured before you begin treatment with docetaxel and then every week while you are receiving docetaxel.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

**If you are in group 1 (often called "Arm A") …**
Eight weeks before starting your radiation treatments, you will receive commercial hormone treatments. These hormone treatments will consist of an LHRH agonist and daily Eulexin (flutamide) capsules or Casodex (bicalutamide) tablets. These medicines block the production and effectiveness of the male hormone testosterone. If you are given flutamide, you will take six (6) capsules by mouth every day for 2 months. If you are given bicalutamide, you will take one (1) tablet by mouth every day for 2 months. It is important that you take bicalutamide at the same time each day. After the 2 months are up, you will have radiation to your pelvis and prostate once a day, 5 days a week, for almost 8 weeks. The hormones and flutamide/bicalutamide will be given on the same schedule during radiation as before radiation began.

Once radiation is completed, you will stop taking the flutamide or bicalutamide. Hormone treatment with the LHRH agonist will be continued for about 20 more months (for a total of 24 months of therapy).

**If you are in group 2 (often called "Arm B")…** (10/4/06)
You will be given the exact same treatment described for group 1. Then beginning 28 days after radiation ends, you will receive two chemotherapy drugs: docetaxel (Taxotere) and prednisone. The first day you will be given docetaxel through a needle in a vein in your arm for one hour. You will be also be given a drug called dexamethasone before docetaxel to try to prevent some of the side effects of docetaxel. Docetaxel will be repeated every 3 weeks (21 days) for a total of 6 times. In addition,

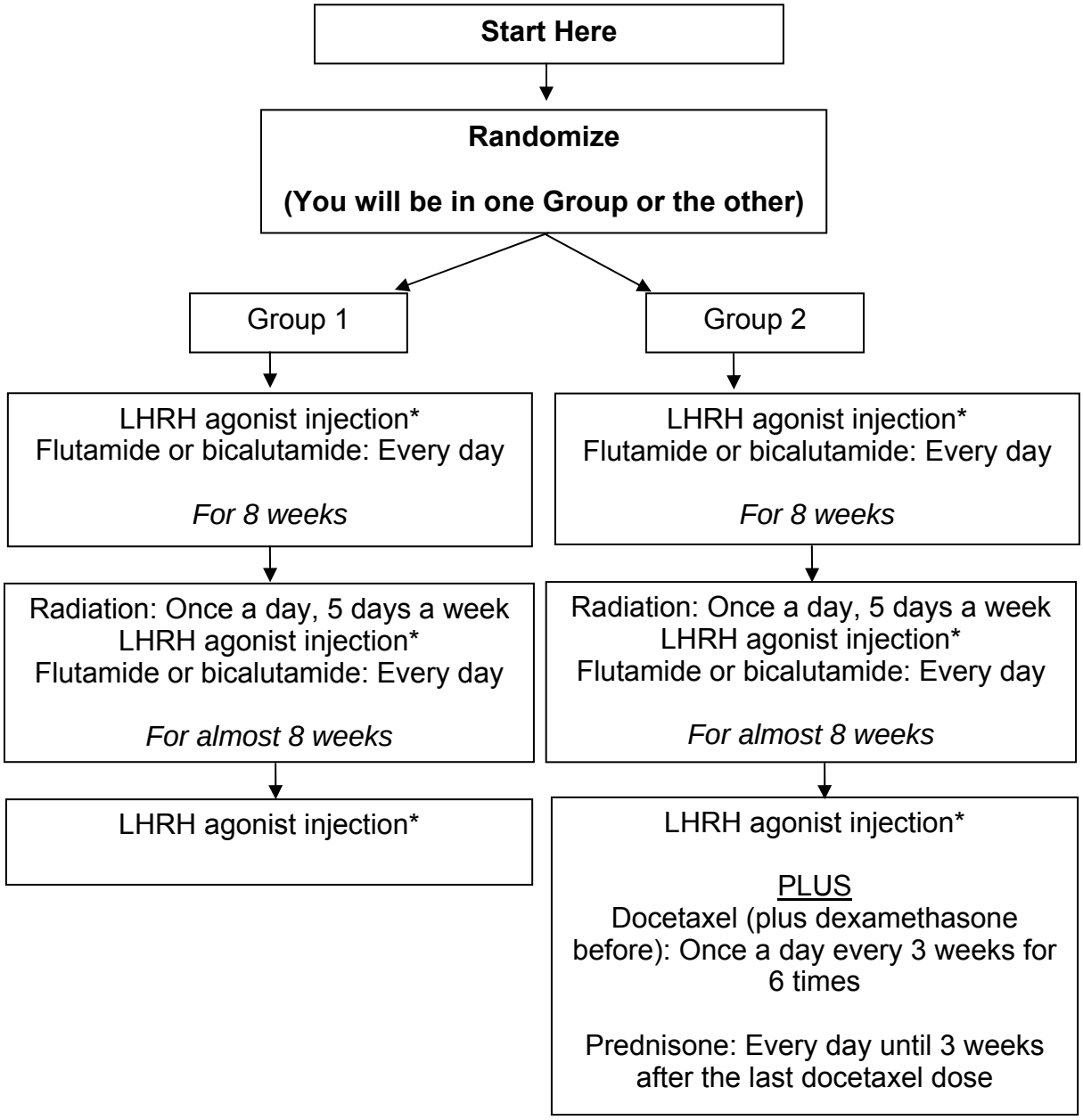
you will take prednisone until 21 days after the last docetaxel injection. These drugs will be given to you as an outpatient.

**When you are finished taking the hormone therapy and chemotherapy (if you are taking chemotherapy)… (04/27/07)**

You will be monitored with periodic examination of the prostate and PSA tests as well as testosterone blood tests to see when you recover from the effects of the hormone therapy. Starting with your entry into the study, the evaluations will be every 3 months for 2 years, then every 6 months for 3 years, then annually. This follow-up is standard for radiation therapy and hormone therapy. After treatment, if your digital rectal exam is abnormal or your PSA rises, your physician may request a needle biopsy to evaluate your disease status.

**Study Plan (10/4/06)**

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.




* LHRH agonist injection: a total amount equal to 2 years is given. It may be given every 4 or 12 or 16 weeks or once a year, depending on which drug is used.

**How long will I be in the study?**

GROUP 1:

You will be asked to take hormone therapy for a total of 24 months, and you will receive radiation therapy for about 8 weeks.

After you are finished taking the radiation treatments, the study doctor will ask you to visit the office for follow-up exams every 3 months for the first 2 years, then every 6 months for 3 years, then once a year.

GROUP 2:
You will be asked to take hormone therapy for a total of 24 months, and you will receive radiation therapy for about 8 weeks.

You will receive chemotherapy and prednisone for about 18 weeks, plus you will receive prednisone for another 3 weeks after you stop taking the chemotherapy.

After you are finished taking the radiation treatments, the study doctor will ask you to visit the office for follow-up exams every 3 months for the first 2 years, then every 6 months for 3 years, then once a year.

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

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

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

**What side effects or risks can I expect from being in the study?**
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the chemotherapy. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

**Risks and side effects related to Taxotere (docetaxel) include those that are (10/4/06):**

**Likely**

- Lowering of blood counts leading to increased risk of infection, weakness, or bleeding, which in rare cases could have fatal complications
- Hair loss
- Skin rash
- Changes to the nail beds
- Loss of appetite
- Taste changes

- Mouth sores
- Nausea and vomiting
- Diarrhea
- Constipation
- Fatigue
- Muscle aches and/or joint pain
- Decreased sensation, numbness, or tingling in the fingers and toes

**Less Likely**

- Sweating
- Fever and chills
- Headache
- Weight gain
- Muscle cramps
- Hives
- Local skin reactions
- Flushing
- Ulcers of the stomach or esophagus
- Abdominal pain
- Increased tearing
- Reactions of the infusion site that include redness of the skin, dryness of the skin, mild swelling of the vein, changes in skin color, leakage of IV solution into the skin

**Rare but Serious**

- Decreased vision, vision changes, or eye irritation
- Glaucoma and/or cataracts
- Dizziness
- Depression
- Seizures
- Confusion
- Muscle weakness
- Swelling in arms and legs
- Irritation of skin at sites of prior radiation
- Damage to skin at the site of injection in the vein
- Slow wound healing
- Blood in urine
- Allergic reaction including skin rash and difficulty breathing
- Low blood pressure
- Risk of developing leukemia requiring treatment
- Chest pain
- Slowing or irregular heart rhythm
- Heart damage, possibly including changes in rhythm and poor pumping of blood
- Liver and kidney damage
- Fluid build-up in the lungs
- Death from infection

- Bleeding into the stomach and/or intestines
- Obstruction of the intestines
- Changes in sensation in the nerves of the hands and feet
- Pulmonary embolism (a blockage of an artery in the lung)

Some prescribed or over-the-counter medicines, herbal products, and/or foods may affect how your body handles docetaxel. If you participate in this study, you should talk to the study doctor about this. If the study doctor feels it is in your best interests, he/she may recommend that you stop taking certain medicines or herbals or stop eating certain foods before and during treatment with docetaxel.

**Risks and side effects related to dexamethasone include those that are: (10/4/06)**

**Likely**

- Difficulty sleeping
- Increase in the sugar content of your blood
- Increased blood pressure

**Less Likely**

- Increase in appetite
- Weight gain
- Mood changes
- Impaired skin healing
- Increased risk of infection
- Osteoporosis

**Rare but Serious**

- Glaucoma and/or cataracts
- Addison's disease (a rare condition that develops when the adrenal glands are not able to produce enough of certain hormones)
- Muscle weakness
- Loss of muscle mass
- Blood clots

**Risks and side effects related to prednisone include those that are:**

**Likely**

- Fluid retention
- Wasting away of the skin (skin atrophy)

**Less Likely**

- Changes in appetite
- Changes in mood including feelings of elation or depression
- Nausea
- Sodium retention
- Impaired skin healing
- Increased risk of infection

- Osteoporosis
- Increased blood sugar (hyperglycemia)

**Rare but Serious**

- Glaucoma and/or cataracts
- Addison's disease (a rare condition that develops when the adrenal glands are not able to produce enough of certain hormones)
- Muscle weakness
- Loss of muscle mass
- Blood clots

## HORMONE THERAPY

**A. Risks and side effects related to LHRH agonists include those that are: (04/27/07)**

**Likely**

- Hot flashes or sweating episodes
- Impotence and loss of libido, which may be permanent
- Weight gain

**Less Likely**

- Dizziness
- Breast swelling or tenderness
- Diarrhea
- Unusual taste in the mouth
- Skin redness or hives
- Increased thirst and urination
- Anemia
- Loss of bone density
- Bone pain
- Thrombosis (clot within your blood vessel)
- Loss of strength
- Loss of the amount of muscle you have (muscle mass)
- Loss of penis length
- Decrease in the size of your testicles
- Increased cholesterol
- High blood pressure
- Worsening of diabetes (high blood sugar)
- Nausea
- Vomiting
- Changes in the texture of your hair
- Feelings of depression or other emotional changes

**Rare but Serious**

- Allergic generalized rash and difficulty breathing

**B. Risks and side effects related to Eulexin (flutamide) and Casodex (bicalutamide) include those that are:**

**Likely**

- Impotence
- Loss of libido
- Hot flashes
- Fatigue
- Diarrhea (for flutamide)

**Less Likely**

- Anemia
- Breast swelling and tenderness
- Diarrhea (for bicalutamide)
- Photosensitivity

**Rare but Serious**

- Liver function changes

**Risks and side effects related to radiation therapy include those that are:**

**Likely**

- Hair loss in the treatment area
- Temporary tiredness
- Diarrhea
- Abdominal cramps and rectal urgency
- Bladder irritation
- Infertility

**Less Likely**

- Reddening or tanning of the skin
- Permanent impotence
- Occasional rectal bleeding

**Rare but Serious**

- Bladder injury with bleeding
- Urethral scar tissue
- Severe rectal bleeding
- Urinary or bowel incontinence
- Injuries to the rectum, bowel, or urinary system that could result in colostomy (surgical creation of an artificial opening in the colon) or other major surgical procedures

**Risks and side effects related to blood draws for routine laboratory tests include those that are:**

**Likely**

- Minor pain or discomfort

**Less Likely**

- Bruising
- Infection

**Reproductive risks:** You should not father a baby while receiving treatment on this study because the drugs in this study can affect an unborn baby. If you are able to father a child, you must agree to use adequate birth control during treatment and for at least 3 months afterwards. Check with your study doctor about what kind of birth control methods to use. Some methods might not be approved for use in this study. Radiation for prostate cancer results in permanent infertility (you will not be able to father children).

**Other risks:** Because some of the drugs in this study may interact with a drug called aprepitant that is sometimes given for nausea or vomiting, you may not receive this drug while receiving treatment on this study. If you experience nausea or vomiting while you are on this study, your study doctor may give you with another anti-nausea/anti-vomiting drug instead.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. While doctors hope chemotherapy in addition to radiation therapy and hormone therapy will be more useful against prostate cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about chemotherapy as a treatment for prostate cancer. This information could help future cancer patients.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study; this could include the following options, either alone or in combination with each other:
    - Surgery
    - Radiation therapy
    - Chemotherapy
    - Hormones
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

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

**Will my medical information be kept private? (10/4/06) (11/14/06)**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be

given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

- The Radiation Therapy Oncology Group
- Qualified representatives of Sanofi Aventis, the company that makes taxotere
- The National Cancer Institute (NCI) and other government agencies involved in keeping research safe for people, like the Central Institutional Review Board (CIRB) and the Food and Drug Administration (FDA)
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials [for CTSU participants only]
- A Data Monitoring Committee (DMC) that regularly meets to monitor safety and other data related to this study

**What are the costs of taking part in this study? (11/14/06)**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. The drug Taxotere will be provided without cost to you by Sanofi Aventis, Inc., however, you or your health plan may need to pay for costs of the supplies and personnel who give you the drug.

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

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

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

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

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

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

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

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

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

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

**Who can answer my questions about the study?**

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

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

***You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).** *[*Only applies to sites using the CIRB.]*

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

*Consent Form for Use of Tissue for Research*

**About Using Tissue and Blood for Research (10/4/06) (04/27/07) (5/15/08)**
You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn

more about tissue research. This information sheet is available to all at the following web site: http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf

In addition, you will have blood tests before you start treatment and during treatment. We would like to keep about four teaspoons of blood for future research as well. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases. One specific test will analyze whether your blood contains certain genes and if the side effects you had on radiation are related to these genes. We will then try to see if these genes can help us learn about why some people get worse side effects than others.

Your tissue and blood may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About**
The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and blood. Then any tissue and blood that remains will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the Radiation Therapy Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and blood are used for genetic research (about diseases that are passed on in families). Even if your tissue and blood are used for this kind of research, the results will not be put in your health records.

Your tissue and blood will be used only for research and will not be sold. The research done with your tissue and blood may help to develop new products in the future.

***Benefits***

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

***Risks***

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

***Making Your Choice* (04/27/07)**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.

Yes No

2. My tissue may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

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

Yes No

4. My blood may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

5. My blood may be kept for use in future research to learn about the correlation between genes and radiation side effects.

Yes No

6. Someone may contact me in the future to ask me to take part in more research.

Yes No

**Where can I get more information?**

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

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

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

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

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

**Signature**

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

**Participant _____**

**Date _____**

## APPENDIX II

### ZUBROD PERFORMANCE SCALE

| | |
|---|---|
| 0 | Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100). |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80). |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60). |
| 3 | Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40). |
| 4 | Completely disabled. Cannot carry on self-care. Totally confined to bed (Karnofsky 10-20). |
| 5 | Death (Karnofsky 0). |

### KARNOFSKY PERFORMANCE SCALE

| | |
|---|---|
| 100 | Normal; no complaints; no evidence of disease |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 80 | Normal activity with effort; some sign or symptoms of disease |
| 70 | Cares for self; unable to carry on normal activity or do active work |
| 60 | Requires occasional assistance, but is able to care for most personal needs |
| 50 | Requires considerable assistance and frequent medical care |
| 40 | Disabled; requires special care and assistance |
| 30 | Severely disabled; hospitalization is indicated, although death not imminent |
| 20 | Very sick; hospitalization necessary; active support treatment is necessary |
| 10 | Moribund; fatal processes progressing rapidly |
| 0 | Dead |

## APPENDIX III

### AJCC STAGING SYSTEM
### PROSTATE, 6th Edition

**DEFINITION OF TNM**

**Primary Tumor, Clinical (T)**

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable or 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 with prostate*
- T2a Tumor involves one-half of one lobe or less
- T2b Tumor involves more than one-half of one lobe but not both lobes
- T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule**
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumor involves the seminal vesicle(s)

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

*Note: Tumor found in 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 classified not as T3, but as T2.

**Regional Lymph Nodes (N)**

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

**Primary Tumor, Pathologic (pT)**

pT2* Organ confined
- pT2a Unilateral, involving one-half of one lobe or less
- pT2b Unilateral, involving more than one-half of one lobe but not both lobes
- pT2c Bilateral disease

pT3 Extraprostatic extension
- pT3a Extraprostatic extension**
- pT3b Seminal vesicle invasion

pT4 Invasion of bladder, rectum

*Note: There is no pathologic T1 classification

**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

## AJCC STAGING SYSTEM
## PROSTATE, 6th Edition

**Distant Metastasis (M)***

| | | |
|---|---|---|
| MX | Presence of distant metastasis cannot be assessed (not evaluated by any modality) | |
| M0 | No distant metastasis | |
| M1 | Distant metastasis | |
| | M1a | Nonregional lymph node(s) |
| | M1b | Bone(s) |
| | M1c | Other site(s) with or without bone disease |

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

**Histopathologic Grade (G)**

| | |
|---|---|
| GX | Grade cannot be assessed |
| G1 | Well-differentiated (slight anaplasia [Gleason 2-4]) |
| G2 | Moderately differentiated (moderate anaplasia [Gleason 5-6]) |
| G3-4 | Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10]) |

***Stage Grouping***

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

## APPENDIX IV

## GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

| Pattern | Margins Tumor Areas | Gland Pattern | Gland Size | Gland Distribution | Stromal Invasion |
|---|---|---|---|---|---|
| 1 | Well defined | Single, separate, round | Medium | Closely packed | Minimal, expansile |
| 2 | Less definite | Single, separate rounded but more variable | Medium | Spaced up to one gland diameter, average | Mild, in larger stromal planes |
| 3 | Poorly defined | Single, separate more irregular | Small medium, or large | Spaced more than one gland diameter, rarely packed | Moderate, in larger or smaller stromal planes |
| **or** 3 | Poorly defined | Rounded masses of cribriform or papillary epithelium | Medium or large | Rounded masses with smooth sharp edges | Expansile masses |
| 4 | Ragged, infiltrating | Fused glandular masses or "hypernephroid" | Small | Fused in ragged masses | Marked, through smaller planes |
| 5 | Ragged, infiltrating | Almost absent, few tiny glands or signet ring | Small | Ragged anaplastic masses of epithelium | Severe between stromal fibers or destructive |
| **or** 5 | Poorly defined | Few small lumina in rounded masses of solid epithelium central necrosis | Small | Rounded masses and cords with smooth sharp edges | Expansile masses |

The Gleason Classification is a system of histologic grading based on over-all pattern of tumor growth at relatively low-magnification *(40 to 100x)*. Five patterns of growth are recognized and numbered in order of increasing malignancy. Because of histologic variation in the tumor, two patterns are recorded for each case, a primary or predominate pattern and a secondary or lesser pattern.
The Gleason Score is the sum of the primary and secondary pattern, If only one pattern is present, the primary and secondary pattern receive the same designation.
*(Primary = 2, Secondary = 1, Gleason = 3)*
*(Primary = 2. Secondary = 2, Gleason = 4)*

1. Gleason, D.F. et al: Prediction of prognosis for prostatic carcinoma by combined histologic grading and clinical staging. J Urol 111:58, 1974.

**APPENDIX V (1/24/07) (5/15/08)**

## CTSU LOGISTICS

### ADDRESS AND CONTACT INFORMATION FOR RTOG-0521

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data directly to the RTOG unless otherwise specified in the protocol:** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone - 1-888-823-5923<br>Fax – 215-569-0206 | CTSU Patient Registration<br>Voice Mail – 1-888-462-3009<br>Fax – 1-888-691-8039<br>Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)<br><br>[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.] | RTOG Headquarters<br>1818 Market Street, Suite 1600<br>Philadelphia, PA 19103<br><br>Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |
| **For patient eligibility questions:**<br>Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214.<br>**For treatment-related questions:**<br>Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page. | | |
| **For questions unrelated to patient eligibility, treatment, or data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Public Web site** is located at: www.ctsu.org<br><br>**The CTSU Registered Member Web site** is located at: http://members.ctsu.org | | |

### CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

**REGISTRATION/RANDOMIZATION**

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

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

All forms and documents associated with this study can be downloaded from the RTOG-0521 Web page on the CTSU registered member Web site (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

**Requirements for RTOG-0521 site registration:**

- **All patients MUST be treated with either 3DCRT or IMRT on this trial and all institutions must be pre-credentialed.** Credentialing requirements for 3DCRT and IMRT Treatment Approach are outlined in Section 5.1 of the protocol and on the Advanced Technology Consortium (ATC) web site at http://atc.wustl.edu. Submission of digital data to the Image-Guided Therapy Center (ITC) requires advanced request for an FTP account with the ITC (itc@castor.wustl.edu). The ITC will notify the registering institution when that institution is eligible to enter patients on study. The status of the credentialing review will be reflected on the RSS Site Registration Status screen http://members.ctsu.org/rss/
- **A Study Agent Shipment Form (SASF) must be processed before the institution is approved to receive Taxotere®.** Fax the completed form to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Institutions should **allow adequate time (7-10 days) for form processing before registering the first case.** Patient registration, not submission of the SASF, triggers the initial drug shipment. The SASF requires submission only once.

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

Note: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory From must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

**Pre-study requirements for patient enrollment on RTOG-0521**

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.

**CTSU Procedures for Patient Enrollment**

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG-0521 Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that RTOG registration hours end at 4:30 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG within the confines of RTOG's registration hours to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Androgen suppression must begin within 6 weeks after patient randomization.

**DATA SUBMISSION AND RECONCILIATION**

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0521 web page located on the CTSU registered member Web site (http://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU. See the Special Materials or Substudies section below for submission of dosimetry data.

3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the RTOG.

4. Please affix the RTOG study/case label to all source documentation and redact the patient's name.

**SPECIAL MATERIALS OR SUBSTUDIES**

**Radiation Therapy** (section 6.0)
**Dosimetry data for 3DCRT and IMRT must be submitted to the Image-Guided Therapy Center (ITC), either by digital transmission using the ITC-assigned FTP account or tape submission (contact ITC for acceptable tape types and format). Hard copy materials accompanying digital data should also be sent directly to the ITC. See section 12.2 for a complete inventory of dosimetry items to be submitted.**

Tissue/Specimen Submission– optional **(section 10.0)**

**1. With patient's consent, tumor tissue and blood will be collected. Submit specimens, pathology report, and RTOG Specimen Transmittal Form to the RTOG Biospecimen Resource at the University of San Francisco.**

**2. See protocol section 10.0 for detailed instructions on collection kits, preparation, and shipment of samples. All reports must include the protocol number and patient's case number (or RTOG label attached). Surgical pathology numbers and information must not be removed from the report; however, the patient's name and/or other identifying information should be redacted. Do not send specimens, forms, reports, or transmittals to the CTSU.**

**3. CTSU clinical sites qualify for specimen reimbursement in the amounts stated in section 10.3 of the protocol. Payments will be made in accordance with RTOG's pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.**

**SERIOUS ADVERSE EVENT (SAE) REPORTING**

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

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (http://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG-0521 web page.

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

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

**DRUG PROCUREMENT** (Section 7.0)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in section 7 of the protocol.

2. You may navigate to the drug forms on the CTSU Members' Web Site by selecting Pharmacy Forms from the document center drop down list on the RTOG-0521 web page.

3. Commercial agents:

Arm 1 – Androgen suppression agents (LHRH agonists and oral antiandrogen) at physician's discretion

Arm 2 – Androgen suppression agents (LHRH agonists and oral antiandrogen) at physician's discretion, plus docetaxel and prednisone

> Taxotere® (docetaxel) is being supplied free of charge to patients entered into this trial at U.S. institutions. The drug will be distributed by a vendor, Biologics, Inc., under contract to RTOG. The Study Agent Shipment Form (SASF) may be downloaded from the Pharmacy Forms section of the RTOG-0521 protocol page and must be sent to the CTSU Regulatory Office at time of site registration. **The SASF must be submitted prior to enrollment of the institution's first case (allow a 7-10 buffer for form processing).** Please see section 7.5.2.1 for details.

**REGULATORY AND MONITORING**

**Study Audit**

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

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

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

**Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

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

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

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

**APPENDIX VI (10/4/06) (04/27/07) (5/15/08) (7/28/09)**

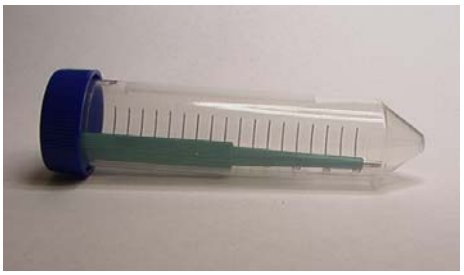
## Specimen Plug Kit* and Instructions

The Specimen Plug Kit contains a shipping tube and a dermal needle. **Note**: **Sites should not dispose of the Plug Kit.** Sites should ship the Plug Kit to the RTOG Biospecimen Resource to be used again.

**Step 1**
Place the dermal needle on the paraffin block over the selected tumor area. (*Ask a Pathologist to select area with tumor.*) Push the needle into the paraffin block. Twist the needle once around to separate the plug from the block. Then pull the needle out of the block. The needle should be filled with tissue sample.

**Step 2**
Label dermal needle with the pathology accession number, RTOG study and case numbers. **Do not try to remove specimen from needle.**

Use a separate dermal needle for every specimen. **Do not mix specimens.** Call or e-mail the RTOG Biospecimen Resource for questions or for additional specimen Plug Kits.



**Step 3**
Once specimen needle is labeled, place it in the shipping tube and mail to the address below.

The RTOG Biospecimen Resource will remove the specimen from the needle and embed it in a cassette, labeled with the specimen ID.

***NOTE**: If an institution is uncomfortable obtaining the plug but wants to retain the tissue block, the institution should send the entire block to the RTOG Biospecimen Resource. The Biospecimen Resource will sample a plug from the block and will return the remaining block to the institution. Institutions should indicate their request to perform the plug procedure and to return the block on the submission form.

Ship: Specimen Plug Kit, specimen in dermal needle, and all paper work to the address below:

**U. S. Postal Service Mailing Address: For Non-Frozen Specimens Only**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**Campus Box 1800**
**San Francisco, CA 94143-1800**

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**1657 Scott Street, Room 223**
**San Francisco, CA 94115**

**Questions: 415-476-RTOG (7864)/Fax 415-476-5271; E-mail: rtog@ucsf.edu**

**APPENDIX VII (04/27/07) (5/15/08) (7/28/09)**
**BLOOD COLLECTION KIT INSTRUCTIONS**

**Instructions** for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:

- Ten (10) 1 ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)

**Serum (if requested):**

- ❑ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. Aliquot a minimum of 0.5 ml serum (optimal 1ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected, and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at –70 to –80° Celsius.
5. Store serum at –70 to –80° Celsius until ready to ship.
6. Ship on dry ice.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

**Plasma (If requested):**

- ❑ Using three (3) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "plasma".

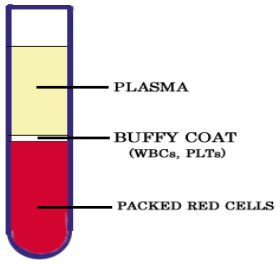
Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma (optimal 1 ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma".
5. Place cryovials into biohazard bag and immediately freeze at –70 to –80° Celsius.
6. Store plasma at –70 to –80° Celsius until ready to ship.
7. Ship on dry ice.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

**Buffy coat (if requested):**

*For a visual explanation of Buffy coat, please refer to diagram below.*




- ❑ Using one (1) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) "buffy coat".

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).
4. Remove the buffy coat cells carefully and place into cryovials labeled "buffy coat" (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date/time of collection and time point collected.
5. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
6. Store buffy coat samples frozen (-70 to -80° Celsius) until ready to ship.
7. Ship on dry ice.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

Shipping/Mailing:

- Ship specimens overnight **Monday-Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and buffy coats together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with dry ice (4-5lbs/2-2.5kg minimum). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.*
- Sites must submit the required documentation with specimens. All specimens will be shipped to:

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**1657 Scott Street, Room 223**
**San Francisco, CA 94115**

**For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail, phone, or fax the RTOG Biospecimen Resource: 415-476-RTOG (7864)/Fax 415-476-5271**
**rtog@ucsf.edu**

## APPENDIX VIII (11/15/06) (04/27/07) (5/15/08)

### RTOG 0521, Taxotere shipment

Taxotere (docetaxel) will be shipped only to institutions that have identified a single individual as responsible for receipt and accountability of shipments.

Sites must review Section 5.0 of the protocol to assure that all pre-registration requirements have been met before calling to register the first case. **U.S. institutions** must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) and fax it to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **International institutions** (non-Canadian institutions that submitted an approved LOI) must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution's first case.

The SASF must be processed before the institution is approved to receive drug. Institutions should allow adequate time (7-10 days) to process the form before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment.

**NOTE**: The SASF for U.S. and International institutions for this study is available on the RTOG web site, http://www.rtog.org, next to the protocol. The SASF for Canadian institutions is available in the Canadian Information Section on the RTOG web site:
http://www.rtog.org/members/CanadaInfo/0521/0521drug_request.html.